A STUDY ON THE METABOLIC OUTCOME OF PATIENTS WHO UNDERWENT BARIATRIC SURGERY IN HOSPITAL UNIVERSITI SAINS MALAYSIA

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May Allah bless you all.

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LIST OF ABBREVIATIONS

ALT	Alanine Transaminase
AST	Aspartate Transaminase
BP	Blood Pressure
BMI	Body Mass Index
CI	Confidence Interval
DBP	Diastolic Blood Pressure
DM	Diabetes Mellitus
HDL-Cholesterol	High Density Lipoprotein Cholesterol
HbA1c	Glycosylated Haemoglobin A1c
iu	International Unit
LDL-Cholesterol	Low Density Lipoprotein Cholesterol
NASH	Non-Alcoholic Steatohepatitis
NAFLD	Non-Alcoholic Fatty Liver Disease
OHA	Oral Hypoglcaemic Agent
RR	Relative Risk
RYGB	Roux-en-Y Gastric Bypass
SBP	Systolic Blood Pressure
SD	Standard Deviation
TC	Total Cholesterol
TG	Triglycerides

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LIST OF SYMBOLS

>	More Than
≥	Greater Than or Equal To
<	Less Than
≤	Less Than or Equal To
=	Equal To
%	percentage
iu	International Unit
kg	Kilogram
kg/m^2	Kilogram Per Meter Square
mmHg	Milimeter Mercury
mmol/l	Milimol Per Liter
n	Number of Participants

ABSTRAK (BAHASA MELAYU)

Latar belakang: Hospital Universiti Sains Malaysia adalah satu-satunya hospital yang menawarkan pembedahan bariatrik di Pantai Timur Malaysia sejak Oktober 2016. Pembedahan bariatrik ini bukan sahaja menghilangkan berat badan, bahkan menurunkan tekanan darah dan mengurangkan paras glukosa darah. Namun begitu, maklumat berkaitan kesan metabolik pembedahan metabolik dan bariatrik di pusat ini masih lagi belum diketahui.

Kaedah: Kajian retrospektif ini menggunakan data yang diperolehi daripada rekod perubatan pesakit yang menjalani pembedahan 'pemotongan perut' (sleeve gastrectomy) dan 'pintasan gastrik' (gastric bypass) di Hospital Universiti Sains Malaysia bermula dari Oktober 2016 sehingga Julai 2019. Kami menganalisa berat, tekanan darah dan parameter biokimia sebelum dan 6 bulan selepas menjalani pembedahan menggunakan *student paired t-test*. *McNemar test* digunakan untuk menentukan perubahan pada jumlah bilangan oral anti-diabetik dan/atau jumlah dos insulin, jumlah bilangan ubatan darah tinggi dan jumlah bilangan ubatan kolesterol.

Dapatan: Seramai 39 pesakit telah dianalisa. Min penurunan berat adalah sebanyak 29.14 (95% CI = 24.75, 33.53) kg, manakala min penurunan tekanan darah sistolik sebanyak 17.87 (95% CI = 11.17, 24.58) mmHg and min penurunan tekanan darah diastolik sebanyak 7.18 (95% CI = 3.21, 11.15) mmHg. Min penurunan HbA1c adalah 3.13 (95% CI = 2.07, 4.19) %, dan min penurunan *triglycerides* sebanyak 0.29 (95% CI = 0.12, 0.47) mmol/L. Selepas 6 bulan pembedahan, 16 pesakit (61%) berjaya sembuh dari penyakit darah tinggi dan 41% pesakit dapat mengurangkan jumlah bilangan ubatan darah tinggi. Lapan pesakit (40%) sembuh dari penyakit kencing manis dan seramai 4 pesakit (20%)

yang sebelum ini mengidap penyakit kencing manis bertukar status ke pra-kencing manis. Hanya seramai 4 pesakit memerlukan ubatan oral anti-diabetik dan/atau 3 pesakit memerlukan rawatan insulin. Jumlah dos insulin menurun dengan dos median 148 (34) iu ke 24 (34) iu sahaja selepas pembedahan. Lima pesakit (25%) menunjukkan bacaan darah kolesterol pada paras normal dan tidak memerlukan ubatan.

Kesimpulan: Pembedahan bariatrik untuk pesakit obesiti di Hospital Universiti Sains Malaysia menghasilkan perubahan metabolik yang baik yang mana ia adalah setara dengan di pusat-pusat lain di Asia.

ABSTRACT (ENGLISH)

Background: Hospital Universiti Sains Malaysia is the only centre in East Coast of Malaysia who offered bariatrics surgery services since October 2016. Bariatric surgery confers benefits to obese in terms of weight, blood pressure reduction and normalisation of blood sugars. However, the information on the effect of bariatric surgery in this centre is lacking.

Methods: This retrospective study involving review of medical records of all patients underwent sleeve gastrectomy or Roux-en-Y gastric bypass in Hospital Universiti Sains Malaysia between October 2016 until July 2019. We analyse weight, blood pressure and biochemical parameters at baseline and 6 months post-surgery using student paired t-test. McNemar test is used to determine change in oral hypoglycaemic agents and/or total insulin dose, total number of anti-hypertensives and total number of anti-lipids.

Result: A total of 39 patients were analysed. Mean weight reduction was 29.14 (95% CI = 24.75, 33.53) kg, SBP mean reduction was 17.87 (95% CI = 11.17, 24.58) mmHg and DBP mean reduction was 7.18 (95% CI = 3.21, 11.15) mmHg. Mean HbA1c reduction was 3.13 (95% CI = 2.07, 4.19) %, triglycerides mean reduction of 0.29 (95% CI = 0.12, 0.47) mmol/L. At 6 months post-surgery, 16 participants (61%) had remission in hypertension, 41% had reduction in number of antihypertensive. Eight patients (40%) had remission of diabetes and 4 patients (20%) who were diabetics becoming pre-diabetes. Only 4 patients were on oral hypoglycaemic agents and/or 3 patients were able to off insulin. Total insulin dose were markedly reduced, with median dose of 148 (34) iu to 24 (34) post-operatively. Five patients (25%) had normalisation of lipid profile and were able to off anti-lipids.

Conclusion: Bariatric surgery among our patients with obesity confers significant metabolic benefits which is comparable to other centres.

KEYWORDS: *bariatrics surgery, early outcome, weight changes, blood pressure changes, HbA1c changes, total cholesterol changes, triglycerides changes, LDL-cholesterol changes, HDL-cholesterol changes, alanine transaminase, aspartate transaminases, total number of glucose lowering drugs, total insulin dose, total number anti-hypertensives, total number anti-lipids.*

CHAPTER 1

INTRODUCTION

1.1 EPIDEMIOLOGY, AETIOLOGY AND IMPACT OF OBESITY

The dramatic increment of prevalence of overweight and obesity has been a great concern globally. (Finucane et al., 2011, Ng et al., 2014). This is estimated to be the cause of more than 3.4 million deaths, 4% of years of life lost and at least 4% disability-adjusted life years all around the world. (Ng et al., 2014).

Overweight and obesity are defined as abnormal or excessive fat accumulation that may impair health (WHO, 2018). Worldwide obesity has nearly tripled since 1975. WHO estimated that in 2016, more than 1.9 billion adults and older, were overweight. 39% of adults aged 18 years and over were overweight (39% of men and 40% of women). About 13% of the world's adult population were obese in 2016 (WHO, 2020). Prevalence of obesity in Malaysia is higher than the world prevalence of 13.0% in 2014 (NHMS 2015). Malaysia has the highest rate of obesity and overweight among Asian countries with 64% of male and 65% of female population being either obese or overweight (NHMS 2015).

The cause of obesity is complex and multifactorial (Yanovski and Yanovski, 2002, Haslam and James, 2005). At the simplest level, obesity develops as a result of a period of chronic energy imbalance and is maintained by a continued elevated energy intake sufficient to maintain the acquired higher energy needs of the obese state. Complex interactions between biological (including genetic and epigenetic), behavioural, social and environmental factors (including chronic stress) are involved in regulation of energy balance and fat stores (Farooqi and O'Rahilly, 2006, Kyrou et al., 2006). The rapid

increase in the prevalence of obesity over the past 30 years is mainly a result of cultural and environmental influences. High energy density diet, increased portion size, low physical activity and adoption of a sedentary lifestyle as well as eating disorders are considered as important risk factors for the development of obesity (Branca et al., 2007). These behavioural and environmental factors lead to alterations in adipose tissue structure (hypertrophy and hyperplasia of adipocytes, inflammation) and secretion for example adipokines (Ailhaud, 2006, Tilg and Moschen, 2006). Weight loss surgery has proven to be a convenient and proper research tool facilitating insights into the pathogenesis of obesity as well as regulation of hunger and satiation. Gut hormones communicate information from the gastrointestinal tract to the regulatory appetite centres within the CNS via the so-called 'gut-brain axis' (Buhmann et al., 2014, Holtmann and Tally, 2014). Obesity is associated with changes in the composition of the intestinal microbiota. Products of intestinal microbes may induce beneficial metabolic effects through enhancement of mitochondrial activity, prevention of metabolic endotoxaemia and activation of intestinal gluconeogenesis via different routes of gene expression and hormone regulation (Gerard, 2015, Tilg and Adolph, 2015).

Co-morbidities related to overweight and obesity include cancers (cancers of breast, endometrial, ovarian, colorectal, oesophageal, kidney, pancreatic, prostate), Type 2 diabetes, hypertension, stroke, Coronary Artery Disease, Congestive Heart Failure, asthma, chronic back pain, osteoarthritis, pulmonary embolism, gallbladder disease, and also an increased risk of disability. All this leads to more than three million deaths worldwide annually. (Kelishadi et al., 2007, Guh et al., 2009)

It is estimated that in industrialized countries, disability due to obesity-related cardiovascular diseases will increase, under an increasing trend. (Visscherr and Seidell, 2001). Body Mass Index, BMI itself, even without considering the other anthropometric measures (e.g., waist circumference, waist-to-hip ratio), is a strong predictor for overall mortality. This estimation includes both values, above and below the expected level of about 22.5-25 kg/m^2. Above this defined range the progressive increase in mortality is mainly related to cardiovascular disease. At the range of 30-35 kg/m^2, mostly, median survival is reduced by 2-4 years; whereas at 40–45 kg/m^2, it is reduced by 8-10 years. The expected increase in mortality below 22·5 kg/m^2 is not clearly explained. (Flegal et al., 2004).

Relationship between obesity and mental health disorders is not clear. (Birmingham et al., 1999). However, overweight is a stigma and the obesity discrimination can lead to some mental disorders. Scientific evidence lays emphasize on an increasing risk of low self-esteem, mood disorder, motivational disorders, eating problems, impaired body image, interpersonal communication problems and all these directly or indirectly affect the quality of life. (PiScott et al., 2009, Scott et al., 2008). Obese individuals, attribute this to their appearance and their weight, and encounter frequent difficulties in their sexual activities. Sexual activity and sexual health outcomes such as sexual satisfaction, unintended pregnancy, and abortion have been mentioned as relevant issues. (Kaneshiro et al., 2008). As the number of people with obesity increases, the nation is now facing upward surge of non-communicable diseases such as diabetes and cardiovascular disease (Mohamad W et al., 1996).

1.2 CALCULATING BODY MASS INDEX AND CLASSIFICATION OF OBESITY

Obesity is a chronic disease characterised by an increase of body fat stores. In clinical practice, the body fatness is usually estimated by Body Mass Index (BMI). BMI formerly called the Quatelet index, is a measure for indicating nutritional status in adults. It is defined as a person's weight in kilograms divided by the square of height in meters. (WHO, 2018).

In adults (age over 18 years) obesity is defined by a BMI 30 kg/m^2 and overweight (also termed pre-obesity) by a BMI between 25 and 29.9 kg/m^2 (WHO 1997). However, lower BMI cut-off points apply for some ethnic groups for instance Southeast Asians ethnicity (WHO, 2000). Malaysian CPG Management of Obesity 2003 classify obesity as follows:

- Underweight: BMI <18.5 kg/m^2
- Normal: BMI ranging 18.5 – 22.9 kg/m^2
- Pre-obese: BMI ranging 23.0 – 27.4 kg/m^2
- Obese I: BMI ranging 27.5 – 34.9 kg/m^2
- Obese II: BMI ranging 35.0 – 39.9 kg/m^2
- Obese III: BMI ≥40 kg/m^2

This classification is helpful in guiding clinicians in choosing the best treatment approach to treat obesity namely lifestyle (diet, physical activity, behavioural therapy) and/or pharmacotherapy and/or surgery (NIH Clinical Guidelines Obesity 1998).

1.3 MANAGEMENT OF OBESITY

Appropriate goals of weight management emphasise realistic weight loss to achieve a reduction in health risks and should include promotion of weight loss, maintenance and prevention of weight regain (Yamuk et al., 2015). Significant clinical benefits may be achieved even by modest weight loss (i.e. 5–10% of initial body weight), and lifestyle modification for instance improving nutritional content of the diet and modest increment in physical activity and fitness (Yamuk et al., 2014, Slentz et al., 2004).

Management of co-morbidities, improving quality of life and well-being of obese patients are also included in treatment aims. Appropriate management of obesity complications in addition to weight management should include management of dyslipidaemia, optimising glycaemic control in type 2 diabetic patients, normalising blood pressure in hypertension, management of pulmonary disorders such as sleep apnoea syndrome (SAS), attention to pain control and mobility needs in osteoarthritis, management of psychosocial disturbances including affective disorders, eating disorders, low self-esteem and body image disturbance (Schwarz et al., 2008, Hainer et al., 2008).

Pharmacotherapy can help patients to maintain compliance, ameliorate obesity-related health risks and improve quality of life. It can also help to prevent the development of obesity co-morbidities. Current drug therapy is recommended for patients with a BMI $\geq$ 30 kg/m^2 or a BMI $\geq$ 27 kg/m^2 with an obesity-related disease (e.g. hypertension, type 2 diabetes mellitus, sleep apnoea (Yamuk et al, 2015). Orlistat, Lorcaserin, Liraglutide, Phentermine/Topiramate and Bupropion/Naltrexone are the drugs approved by United States Food and Drug Administration for the treatment of obesity. The efficacy of pharmacotherapy should be evaluated after the first 3 months. If weight loss achieved is

satisfactory (>5% weight loss in non-diabetic and >3% in diabetic patients), treatment should be continued (Hainer et al., 2008, Toplak et al., 2014, Pucci and Finer, 2015, Apovian et al., 2015). Unfortunately, these drugs is not widely available in Malaysia.

Surgery is the most effective treatment for morbid obesity in terms of long-term weight loss, improvements of co-morbidities and quality of life and decreases of overall mortality (Pories 2008, Sjostrom, 2013, Berrington et al., 2013, Neovius et al. 2012).

Rome Diabetes Surgery Summit used the term bariatric surgery is used for body mass index of 35 and more and gastrointestinal metabolic surgery for body mass index below 35 (Rubino et al., 2010). Bariatric surgery is an option of treatment for obesity in people with Asian ethnicity with BMI more than 35kg/m^2 with or without comorbidities. Bariatric surgery is an option of treatment for obesity in people with Asian ethnicity with BMI more than 32kg/m^2 with comorbidities (Lakdawa et al., 2010). There are 4 types of surgery in the treatment of type 2 diabetes namely Roux-en Y Gastric Bypass, Vertical Sleeve Gastrectomy, Laparoscopic Adjustable Gastric Banding and Biliopancreatic diversion (Rubino et al., 2016).

1.4 LITERATURE REVIEW

Obesity is associated with an increased risk of type 2 diabetes, hypertension, dyslipidemia, cardiovascular disease, osteoarthritis, numerous cancers and increased mortality. Effects of bariatric surgery on the components of metabolic syndrome (hyperglycemia, hyperlipidemia and hypertension), weight loss, perioperative morbidity

and mortality, and the long-term impact on cardiovascular risk and mortality. (Corcelles et al., 2016). Metabolic changes after surgery occur because of the impact on the gut, brain, adipose tissue, liver, muscle, pancreas, kidney, and bone. Many secondary benefits arise through the downstream effects on organs and organ systems from the primary metabolic improvements, thus creating an inter-reliant chain reaction of effects that on the whole have a positive impact on health. (Sinclair et al., 2018).

The first line therapy for the treatment for type 2 diabetes mellitus, hypertension and obesity is weight loss with lifestyle modification such as diet and exercise. (ADA Standard of Care 2019). The first five cases of laparoscopic gastric bypass surgery were performed in 1993-1994 (Wittgrove et al.,1994). Following that, several gastrointestinal operations, including partial gastrectomies and bariatric procedures promote dramatic and, durable improvement of type 2 diabetes. (F Rubino et al., 2016).

Early identification of weight loss could allow earlier provision of postoperative behavior and intensive lifestyle intervention and maximise weight loss. (Manning et al., 2015). Roux-en Y Gastric Bypass group achieved 31.0±7.1 kg weight loss compared to Vertical Sleeve Gastrectomy Group who achieved 27.1 ±7.1 kg. (Yang et al., 2015). Among patients with morbid obesity, there was no significant difference in excess BMI loss between laparoscopic sleeve gastrectomy and laparoscopic Roux-en-Y gastric bypass at 5 years of follow-up after surgery (Peteril et al.2018).

Bariatric surgery can significantly reduce weight and 83% of type 2 diabetes mellitus patients, and 98% of patients with impaired glucose tolerance experience postoperative normalisation of blood sugar, serum insulin and glycosylated haemoglobin and long-term

stabilisation of diabetes mellitus type 2 control (ADA Standard of Care 2019). Glycosylated haemoglobin level reduced from 6.7% to 5.8% post bariatric surgery in patients with diabetes. (Ahmed AA et al., 2018). 87.5% reduction in total daily insulin dose was seen by day two post bariatric surgery (Diemer DM et al., 2017).

Remission of hypertension was achieved in 51% of patients who underwent bariatric surgery. Total number of antihypertensives medications were reduced more than thirty percent while maintaining controlled blood pressure. (CA Schiavon et al., 2018). A systematic review by Buchwald et al. found overall 63% resolution of hypertension, with procedure-specific percentages of 68%, 43%, and 83% for Roux-en Y gastric bypass, adjustable gastric binding, and biliopancreatic diversion with duodenal switch, respectively. (Buchwald et al., 2004). Another systematic review reported a 63% resolution or improvement of hypertension over a mean follow-up time of five years. (Vest et al., 2012). Analogous results were obtained in a meta-analysis in which the authors found a 64% resolution or improvement of hypertension after metabolic surgery. (Sarkhosh et al., 2012).

Sleeve gastrectomy produced superior response in high density lipoprotein cholesterol and Apolipoprotein A1 quantity compared to Roux-en Y gastric bypass at 6 months post bariatric surgery (Heffron SP et al., 2017). Low density lipoprotein cholesterol level decreased 36% after 24 hours of bariatric surgery and 30% at 12 months compared to baseline. (Boyer M et al. 2017)

Bariatrics surgery also leads to a complete resolution of steatosis, inflammation, ballooning and fibrosis in 66%, 50% and 76% and 40% of patients. (Yung Lee et al.,

2019). It also decreases in Non-Alcoholic Fatty Liver Disease (NAFLD) fibrosis scores, ratio of aminotransferase (AST) to alanine aminotransferase (ALT), AST-to-platelet ratio index (APRI), and BARD score for NAFLD. (Nickel et al., 2017)

Beyond improving glycemia, metabolic surgery has been shown to confer additional health benefits including substantial reductions in cardiovascular disease risk factors (F Rubino et al., 2016), reductions in incidence of microvascular disease (RO Brien et al., 2018) and enhancement in quality of life (RV Cohen et al. 2012, PR Schauer et al., 2014).

Bariatric procedures are generally safe and effective, but can be associated with devastating complications, some of which may be fatal if not addressed quickly. Early complications include leaks, stenoses, bleeding, and venous thromboembolic events (VTE). Roux-en Y gastric bypass results in permanent alteration of anatomy, which provides both the potential for unique complications namely gallstone disease, marginal ulceration, perforation, small bowel obstruction and internal hernia (Lim et al., 2018).

Sleeve gastrectomy is primarily a restrictive procedure for weight loss. The perioperative and postoperative mortality rates are 0.29% and 0.34%, respectively, with complication rates of 13% (Chang et al., 2014, Triantafyllidis et al., 2011). Rare complications occur in the early postoperative period after sleeve gastrectomy; however, serious complications include difficult-to-remedy proximal leaks (4.9%) and bleeding from the long gastric staple line (2.4%). (Himpens et al., 2010, Topart et al., 2012). The majority of complications associated with sleeve gastrectomy occur in the late postoperative period. These include gastroesophageal reflux (23%), vomiting (18%), gastric tube stricture (2.3%), stenosis (2.4%), leak (2.4%), incisional hernia (2.4%), gastrocutaneous fistula, and weight regain. (Hamdan et al., 2011, Triantafyllidis et al., 2011, Himpens et al.,

2010). Nutritional deficiencies are less common after sleeve gastrectomy compared with operations that cause more drastic diet alterations or involve intestinal bypass; however, these deficiencies do occur with enough frequency that postoperative monitoring is mandatory. Despite the lack of a malabsorptive component, deficiencies in iron (43%), vitamin D (39%), folic acid (15%), vitamin B1 (11%), and vitamin B12 (9%) have been observed after sleeve gastrectomy (Aarts et al., 2011).

Roux-en Y gastric bypass has been the most common weight-loss procedure performed in the United States with rates of perioperative and postoperative mortality are 0.38% and 0.72%, respectively (Chang et al., 2014). Early postoperative serious complications are the minority and include leak, ileus, obstruction, and GI tract haemorrhage (Carucci and Turner, 2019, Podnos et al., 2003). Dumping syndrome results from patients' inability to regulate gastric emptying of simple carbohydrates or other osmotic loads and it is an expected complication after Roux-en Y gastric bypass (Swanson et al., 2012) with a reported prevalence of severe symptoms as high as 24.3% (Padaoin et al., 2009, McMahon et al., 2006). The most common late complication of Roux-en Y gastric bypass is gallstone formation with incidence ranging from 22% to 71% (Bult et al., 2008, Wudel et al., 2002, Villegas et al., 2004). Nutritional deficiencies that occur with gastric bypass are the result of a partial malabsorptive anatomy, bypass of the stomach, and a prolonged starvation state. Vitamin B12 deficiency is common in the absence of supplementation, as well as deficiencies in thiamine (vitamin B1), iron, calcium, copper, and vitamin D. (Aillis et al., 2008, Saltzman and Karl, 2013). Obinwanne et al. reported that 51.3% of patients developed iron deficiency within 1 year after surgery and 22.7% developed iron deficiency anemia (Obinwanne et al. 2014).

1.5 PROBLEM STATEMENT & STUDY RATIONALE

While there were many prior studies looking into the efficacy of metabolic surgery, there is scarcity of published information to date with regards to metabolic effect (blood pressure changes, blood sugar level changes, cholesterol level changes as well as liver function changes) particularly in Malaysia. Majority of published data came from western and more developed nation.

Hospital Universiti Sains Malaysia started bariatrics and gastrointestinal metabolic surgery services in 2016. This study was conducted to assess the outcome of bariatrics and metabolic surgery as a new service for obesity and metabolic management for East Coast of Malaysia.

CHAPTER 2: OBJECTIVE OF THE STUDY

2.1 General Objective

To evaluate the metabolic outcome of patients who underwent bariatric surgery (sleeve gastrectomy and Roux-en-Y gastric bypass) in Hospital Universiti Sains Malaysia.

2.2 Specific Objectives

1. To determine the change of weight and blood pressure before and 6 months post-surgery.
2. To correlate the change in weight with blood pressure changes 6 months post-surgery.
3. To determine the change of glycosylated haemoglobin (HbA1c), total cholesterol, triglycerides, Low-Density Lipoprotein cholesterol, High-Density Lipoprotein cholesterol, Aspartate Transaminase and Alanine Transaminase before and 6 months post-surgery.
4. To determine change of number of glucose lowering drugs and/or total insulin dose, anti-hypertensives and lipid lowering drugs before and 6 months post-surgery

CHAPTER 3: MANUSCRIPT

Title page

OUTCOME OF OBESE PATIENTS WHO UNDERWENT BARIATRIC SURGERY IN HOSPITAL UNIVERSITI SAINS MALAYSIA.

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ABSTRACT

Background: Hospital Universiti Sains Malaysia is the only centre in East Coast of Malaysia who offered bariatrics surgery services since October 2016. Bariatric surgery confers benefits to obese in terms of weight, blood pressure reduction and normalisation of blood sugars. However, the information on the effect of metabolic effects of bariatric surgery on patients with obesity in this centre is lacking.

Methods: This retrospective study involving review of medical records of all patients underwent sleeve gastrectomy or Roux-en-Y gastric bypass in Hospital Universiti Sains Malaysia between October 2016 until July 2019. We analyse weight, blood pressure and biochemical parameters at baseline and 6 months post-surgery using student paired t-test. McNemar test is used to determine change in oral hypoglycaemic agents and/or total insulin dose, total number of anti-hypertensives and total number of anti-lipids.

Result: A total of 39 patients were analysed. Mean weight reduction was 29.14 (95% CI = 24.75, 33.53) kg, SBP mean reduction was 17.87 (95% CI = 11.17, 24.58) mmHg and DBP mean reduction was 7.18 (95% CI = 3.21, 11.15) mmHg. Mean HbA1c reduction was 3.13 (95% CI = 2.07, 4.19) %, triglycerides mean reduction of 0.29 (95% CI = 0.12, 0.47) mmol/L. At 6 months post-surgery, 16 participants (61%) had remission in hypertension, 41% had reduction in number of antihypertensive. Eight patients (40%) had remission of diabetes. Only 4 patients were on oral hypoglycaemic agents and/or 3 patients were on insulin. Five patients (25%) had normalisation of lipid profile and were able to off anti-lipids.

Conclusion: Bariatrics surgery among our patients confers significant benefits which is comparable to other centres.

KEYWORDS: *bariatrics surgery, metabolic surgery, early outcome, weight changes, blood pressure changes, HbA1c changes, total cholesterol changes, triglycerides changes, LDL-cholesterol changes, HDL-cholesterol changes, alanine transaminase, aspartate transaminases, total number of glucose lowering drugs, total insulin dose, total number anti-hypertensives, total number anti-lipids.*

INTRODUCTION

Overweight and obesity are defined as abnormal or excessive fat accumulation that may impair health (1). Worldwide obesity has nearly tripled since 1975. WHO estimated that in 2016, more than 1.9 billion adults and older, were overweight. 39% of adults aged 18 years and over were overweight (39% of men and 40% of women). About 13% of the world's adult population were obese in 2016 (2). Prevalence of obesity in Malaysia is higher than the world prevalence of 13.0% in 2014 (3). Malaysia has the highest rate of obesity and overweight among Asian countries with 64% of male and 65% of female population being either obese or overweight (3). As the number of people with obesity increases, the nation is now facing upward surge of non-communicable diseases such as diabetes and cardiovascular disease. Trends of overweight, obesity and abdominal obesity continue to rise compared to National Health & Morbidity Survey (NHMS) 2011 (29.4%, 15.1%, 45.4%) and 2015 (30.0%, 17.7%, 48.6%) findings (4).

There are not many drugs approved for the weight loss medications. The rationale for weight-loss medications is to help patient to more consistently adhere to low calorie diets and to reinforce lifestyle changes. Metabolic surgery is an option to treat type 2 diabetes mellitus in obese patients who do not achieve durable weight loss and improvement in comorbidities (5). Diabetics were more obese than normal person and had higher prevalence of hypercholesterolemia (6).

Rome Diabetes Surgery Summit used the term bariatric surgery is used for body mass index of 35 and more and gastrointestinal metabolic surgery for body mass index below 35 (7). Bariatric surgery is an option of treatment for obesity in people with Asian ethnicity with BMI more than 35kg/m^2 with or without comorbidities. Bariatric surgery is an option of treatment for obesity in people with Asian ethnicity with BMI more than 32kg/m^2 with comorbidities (8).

The first line therapy for the treatment for type 2 diabetes mellitus, hypertension and obesity is weight loss with lifestyle modification such as diet and exercise. (5). The first five cases of laparoscopic gastric bypass surgery were performed in 1993-1994 (9).

Following that, several gastrointestinal operations, including partial gastrectomies and bariatric procedures promote dramatic and, durable improvement of type 2 diabetes (10). There are 4 types of metabolic surgery in the treatment of type 2 diabetes namely Roux-en Y Gastric Bypass, Vertical Sleeve Gastrectomy, Laparoscopic Adjustable Gastric Banding and Biliopancreatic diversion (10).

Early identification of weight loss could allow earlier provision of postoperative behavior and intensive lifestyle intervention and maximise weight loss (11). Roux-en Y Gastric Bypass group achieved 31.0±7.1 kg weight loss compared to Vertical Sleeve Gastrectomy Group who achieved 27.1 ±7.1 kg. (12). Among patients with morbid obesity, there was no significant difference in excess BMI loss between laparoscopic sleeve gastrectomy and laparoscopic Roux-en-Y gastric bypass at 5 years of follow-up after surgery (13).

Bariatric surgery can significantly reduce weight and 83% of type 2 diabetes mellitus patients, and 98% of patients with impaired glucose tolerance experience postoperative normalisation of blood sugar, serum insulin and glycosylated haemoglobin and long-term stabilisation of diabetes mellitus type 2 control (5). Glycosylated haemoglobin level reduced from 6.7% to 5.8% post bariatric surgery in patients with diabetes. (14). 87.5% reduction in total daily insulin dose was seen by day two post bariatric surgery (15).

Remission of hypertension was achieved in 51% of patients who underwent bariatric surgery. Total number of antihypertensives medications were reduced more than thirty percent while maintaining controlled blood pressure. (16). In another study; bariatrics surgery offered more than 30% reduction in total number of antihypertensive medications while maintaining controlled office blood pressure <140/90mmHg after bariatrics surgery. (17).

Sleeve gastrectomy produced superior response in high density lipoprotein cholesterol and Apolipoprotein A1 quantity compared to Roux-en Y gastric bypass at 6 months post bariatric surgery (18). Low density lipoprotein cholesterol level decreased 36% after 24 hours of bariatric surgery and 30% at 12 months compared to baseline. (19).

Bariatrics surgery also leads to a complete resolution of liver steatosis, inflammation, ballooning and fibrosis in 66%, 50% and 76% and 40% of patients. (20). It also decreases

in Non-Alcoholic Fatty Liver Disease (NAFLD) fibrosis scores, ratio of aminotransferase (AST) to alanine aminotransferase (ALT), AST-to-platelet ratio index (APRI), and BARD score for NAFLD. (21)

Beyond improving glycemia, metabolic surgery has been shown to confer additional health benefits including substantial reductions in cardiovascular disease risk factors (10), reductions in incidence of microvascular disease (22) and enhancement in quality of life (23, 24).

This study will focus on metabolic effects in terms of changes in weight, blood pressure, glycosylated haemoglobin (HbA1c), lipids profile as well as aspartate transferase, alanine transferase and total bilirubin before and 6 months post-surgery.

M**ETHODOLOGY**

Hospital Universiti Sains Malaysia started its bariatrics and gastrointestinal metabolic surgery services in 2016. This study was conducted at Endocrinology Unit and Surgical Specialist Clinic Hospital Universiti Sains Malaysia which is tertiary referral centre for bariatric surgery in East Coast of Malaysia i.e Kelantan and Terengganu. Bariatric or gastrointestinal metabolic surgery was offered to patients with BMI more than 35kg/m^2 with or without comorbidities and to those with with BMI more than 32kg/m^2 with comorbidities. Operated patients will be followed-up initially two weeks after surgery and every three months thereafter for a year. Data of patients that underwent bariatric surgery at Hospital Universiti Sains Malaysia from October 2016 until July 2019 were obtained from medical record at Hospital Universiti Sains Malaysia's Medical Record Unit. Only patient who underwent sleeve gastrectomy and Roux-en-Y gastric bypass will be included in this study. Patient who underwent surgery, but was loss to follow-up and who

underwent other different types of surgery were excluded from this study. The sample size to determine the change of weight and blood pressure were calculated using web sample size calculator (Arifin W.N., 2020). Conventionally, the power of the study is set at 80% with $\sigma = 0.05$. The calculated sample size was 33. There were 57 patients who underwent bariatric surgery, however after excluding the patient who did not full-fill the exclusion criteria, only 39 patients were included in the study. Data on demographic (age, sex and ethnicity) and parameters before and after surgery were collected using proforma checklist provided (Appendix 1). Data were prepared in Microsoft Excel file.

Ethical approval

The study was conducted according to the principles outlined in the Declaration of Helsinki and ethical approval was obtained from the Human Research and Ethics Committee, Universiti Sains Malaysia for the purpose of audit and publications.

Statistical analysis

Data obtained in the Microsoft Excel format were imported in SPSS Software version 26 for analysis. Data were explored for missing entry and distribution of numerical data. Descriptive statistics were used to summarize the socio-demographic and clinical characteristics of subjects. Numerical data were presented as mean (SD) or median (IQR) based on their normal distribution. Categorical data were presented as frequency (percentage). Paired sample t-test was used to compare the weight and blood pressure changes pre and post-surgery. The biochemistry changes (HbA1c and cholesterol level was also analysed using paired sample t-test. Due to the skewed distribution of data,

Wilcox Signed Rank Test was used to compare the AST and ALT changes pre and post-surgery. McNemar test was used to compare changes in number of glucose lowering agents, number of insulin, anti-hypertensives as well as anti-lipids.

RESULT

From October 2016 until July 2019, there were 57 bariatrics or gastrointestinal metabolic surgery. However only 39 patients were eligible for this study. 18 patients were excluded due to operation done beyond the scope of this study and a patient was excluded due to missing data (no documentation of post-operative weight at six months).

Demographic and Baseline Measurement

Out of 39 participants, the mean (SD) for age were 41.62 (8.83) years old. Two third of them were female patient. The mean (SD) for weight of the participant was 129.45 (33.41) kg while the mean (SD) for BMI was 49.90 (12.31) kg/m^2. Most of the patients had sleeve gastrectomy (n = 27, 69.2%). The demographic information of the participants was summarised in Table 1.

Most the participants were diabetics (n = 20, 51.3%), hypertensives (n = 26, 66.7%), had normal Total Cholesterol (n = 20, 51.3%), low HDL (n = 25, 64.1%), high LDL (n = 29, 74.4%), normal triglyceride (n = 30, 76.9%) and all of them had dyslipidaemia (n = 39, 100.0%). The mean (SD) for HbA1c of the participant was 9.09% (2.35), while the mean (SD) for SBP was 140.44 (14.95) mmHg, mean (SD) for DBP was 80.23 (10.50) mmHg, mean (SD) for Total Cholesterol was 5.08 (1.11) mmol/L, mean (SD) for HDL was 1.13 (0.25) mmol/L, mean (SD) for LDL was 3.34 (0.96) mmol/L, mean (SD) for triglyceride

was 1.43 (0.64) mmol/L, while median (IQR) for AST was 32 (29) mmol/l and median (IQR) for ALT was 40 (37) mmol/L. The baseline measurements of the participants were summarised in Table 2.

Most of the participants were not on any glucose lowering agent (n = 23, 59.0%), not on insulin (n = 30, 76.9%), not on any antihypertensive agent (n = 20, 51.3%) and not on any anti-lipid agent (n = 22, 56.4%). Among those with insulin, the mean (SD) for insulin dose was 132.22 (51.26) i.u. The medications taken by the participants are summarised in Table 3.

Pre and Post-Surgical Procedure Comparison

There was significant different between pre and post-surgery for weight with mean reduction was 29.14 (95% CI = 24.75, 33.53) kg, SBP with mean reduction was 17.87 (95% CI = 11.17, 24.58) mmHg and DBP with mean reduction was 7.18 (95% CI = 3.21, 11.15) mmHg. The detail of the difference in physical parameters are summarised in Table 4. The was no correlation between weight changes and blood pressure changes. The detail of relationship between weight and blood pressure changes are summarised in Table 5.

Some of the biochemistry parameters of the participants were statistically significant reduced, which include HbA1c with mean reduction of 3.13 (95% CI = 2.07, 4.19) %, Triglyceride with mean reduction of 0.29 (95% CI = 0.12, 0.47) mmHg, AST and ALT, while the other parameters (total cholesterol, HDL-cholesterol and LDL-cholesterol)

were no statistically significant changes. The details of the difference in biochemistry parameter of the participants are summarised in Table 6.

Except for the number of participants taking insulin, there were statistically different in number of medications taken by the participants for glucose lowering agent [χ^2-stat (df) = 13 (6), p = 0.043] in which 13 participants (33.3%) had reduction in the number of oral hypoglycaemic agent taken, antihypertensive agent [χ^2-stat (df) = 16 (6), p = 0.014] in which 16 participants (41.0%) had reduction in number of antihypertensive agent taken and anti-lipid agent [χ^2-stat (df) = 8 (3), p = 0.046] in which 8 participants (20.5%) had reduction in number of anti-lipid agent taken. Otherwise, there was significant different of insulin dose among participant on insulin [Median (IQR) = 148 (34) iu vs 24 (34) iu, z-score (df) = - 2.67, p = 0.008]. The changes of medication among the participants are summarised in Table 7, Table 8, Table 9, Table 10 and Table 11 respectively.

DISCUSSION

We conducted retrospective study through medical record review of 39 obese patients who underwent bariatrics surgery in Hospital Universiti Sains Malaysia. Mean age for our study was 41.62 (8.83) years which is comparable with other studies by Peterli et al. (13), Sciavon et al. (16), and Rajan et al. (25). Our patient's baseline weight of 129.45 (33.41) kg were also comparable to study by Peterli et al. (13) and Boyer et al. (19).

Pre and Post-Surgical Procedure Comparison

Weight Changes

The main goal of bariatric surgery is to help obese patients achieve a desired body weight. Studies have shown that sleeve gastrectomy benefits the obese adults by both weight loss

and decreasing their obesity-related co-morbidities in a mid-term follow-up period and that efficacy of sleeve gastrectomy is similar to that of a Roux-en-Y gastric bypass. (29,30). It has also been noted that despite favourable 5-year outcomes of sleeve gastrectomy, a major lifestyle modification is necessary for this method to be most effective (31). In this study, mean weight loss after 6 months post-surgery were 29.14 kg (24.75,33.53) which is comparable to weight loss found by Arsenovic et al. (32) which showed weight loss of (29.80 ± 13.27 kg) after 6 months of Roux-en-Y gastric bypass surgery. This is lower compared to study by Keleidari et al. (33) who reported weight loss of 42±18.5 kg at 6 months post-surgery. These early outcome of weight changes however did not translate into long term suppression of weight loss as found by Yang et al. (34) who compared the weight loss between the sleeve gastrectomy versus Roux-en-Y gastric bypass surgery.

Blood Pressure Changes

The GATEWAY (Gastric Bypass to Treat Obese Patients With Steady Hypertension) trial (16) has shown reduction of 4.6 mmHg in systolic blood pressure and 3.6mmHg reduction in diastolic blood pressure. Our study showed mean reduction of 17.87 (11.17, 24.58) mmHg in systolic and 7.18 (3.21, 11.15) mmHg in diastolic blood pressure. This is similar findings with Sjöström et al. (35) that showed at the first 6 months post-surgery, SBP was reduced by 11.4±19.0 mmHg and DBP was reduced by 7.0±11.0 mmHg.

Blood pressure reduction translates into risk reduction of cardiovascular events. Bundy et al. (36) showed that linear association between the magnitudes of SBP reduction and the risk of CVD and all-cause mortality. For example, by lowering SBP by 10 mm Hg to

achieve the treatment goal of 120 to 124 mm Hg, the risk of CVD was reduced by 29% (95% CI, 17%-40%), by lowering SBP by 20 mm Hg, the risk of CVD was reduced by 42% (95% CI, 28%-52%), by lowering SBP by 30 mm Hg, the risk of CVD was reduced by 54% (95% CI, 37%-66%), and by lowering SBP by 40 mm Hg or more, the risk of CVD was reduced by 64% (95% CI, 49%-74%). Ettehad et al. (37) also showed similar findings i.e. for every 10 mm Hg systolic blood pressure reduction significantly reduced the risk of major cardiovascular disease events (RR 0·80, 95% CI 0·77–0·83), coronary heart disease (0·83, 0·78–0·88), stroke (0·73, 0·68–0·77), heart failure (0·72, 0·67–0·78), and all-cause mortality (0·87, 0·84–0·91).

Beyond risk reduction, the number of pills taken to achieve BP control was also reduced. At baseline, there were 26 patients (66%) were hypertensives and 19 of them require anti-hypertensives. At 6 months, 16 participants (61%) had remission in hypertension and not requiring any anti-hypertensives. 41% had reduction in number of antihypertensive taken after 6 months post-surgery. These findings were consistent with Salminen et al. (38) and Sciavon et al. (16) which showed 51% and more than 30% of anti-hypertensive were discontinued post-surgery.

HbA1c changes

At baseline, 7 patients (18%) were pre-diabetes and 20 patients (51%) were diabetics. Amongst diabetics, 16 patients (61%) were on glucose lowering agents and/or insulin with mean insulin dose of 132 (51.26) units. The mean reduction of HbA1c were 3.13 (2.-8,4.19)%, p-value <0.001. After 6 months post-surgery, 8 patients (40%) had remission of diabetes, 5 patients (25%) were pre-diabetes and 7 patients (35%) remained diabetics.