International Journal of Pharmaceutical Science Invention
ISSN (Online): 2319 – 6718, ISSN (Print): 2319 – 670X
www.ijpsi.org Volume 2 Issue 6‖ June2013 ‖ PP.26-34

Gastric Banding Reduces Weight through Ghrelin and Adiponectin Plasma Concentration in Obese Rat Models

Koernia Swa Oetomo [1], Hidayat Sujuti,[2] Mochammad Rasjad Indra[3], Kuntoro[4], Askandar Tjokroprawiro[5] And Djanggan Sargowo[6],

[1]*Departement of Surgery Hajj Hospital, Surabaya Indonesia*
[2,3,]*Department of Biochemistry Medical Faculty of Brawijaya University Malang Indonesia*
[4]*Department of Biostatistic Public Health Faculty of Airlangga University Surabaya Indonesia*
[5]*Department of Internal Medicine Medical Faculty of Airlangga University Surabaya Indonesia*
[6]*Department of Cardiology Medical Faculty of Brawijaya University Malang Indonesia*

ABSTRACT :*Obesity is caused by an imbalance of food intake and body expenditure. Obesity is often defined as a condition of abnormal or excess fat in adipose tissue that seriously damages the health. A national survey conducted in 2009 showed that from all provincial capitals in Indonesia, 8.1% of adult males (≥ 18 years) were overweight (BMI 25-27) and 6.8% were obese, 10.5% of females adults were overweight and 13.5% were obese. In the group age of 40-49 years, overweight or obese reached its peak of 24.4% and 23% in men, 30.4% and 43% in women. From body Mass Index 23.0 to 24.9, obese I (25.0 to 29.0) and obese II (≥ 30) indicate the risk of metabolic syndrome in Indonesian people and LAGB procedure should be considered. On the obesity condition, ghrelin and adiponectin decrease. On previous studies, it is known that there is a relationship between adiponectin, glucose, insulin, lipid parameters in both overweight / obese women and men. Ghrelin is secreted by the stomach into the blood circulation. Treatment of obesity can be done with diet regulation strategies, behavior, drugs and physical exercise, but the success rate is still low. Bariatric surgery technique was developed and has been known to reduce obesity by about 30%. The success of bariatric surgery in obesity is to lose weight about 20-40 kg of initial body weight and BMI reduction of about 10-15 kg/m2. The purpose of this study was to determine the influence of gastric banding (GB) on weight loss through an increase in ghrelin and adiponectin.The research was carried out in vivo in obese mice models by means of a purely experimental research conducted in the laboratory with a factorial design. This study examines the influence of gastric banding (GB)factors, and time(duration) against the dependent variable. Ghrelin and adiponectin levels were measured in plasma by ELISA method.There is a decrease in weight of about 27.87% on day 8 and 38.87% on day 16 after GB. The results of statistical analysis showed that theweight loss percentage decreasedsignificantly (p = 0.0001). An increase in ghrelin and adiponectin levels were measured on days 0, 8, and 16. After receiving treatment, the ghrelin serum in the GB group is higher and it has a stable value over the control group. The results of pathway analysis showed that the GB indirectly affects body weight through ghrelin and adiponectin.Gastric banding affects the weight loss through an increase in ghrelin and adiponectin. Gastric banding not only reduces obesity, but also fixes adiposopathy through the increased adiponectin in obese mice models. Time (duration) of GB is associated with weight loss through the increased ghrelin and adiponectin levels.*

KEYWORDS : *obesity, gastric banding, ghrelin, adiponectin*

I. INTRODUCTION

Obesity is caused by an imbalance of food intake compared to body expenditure. Obesity is often defined as a condition of abnormal or excess fat in adipose tissue that seriously damages the health [1]. WHO 1995 defines obesity on BMI ≥ 30 for men and, ≥28.6 for women [2]. The definition is then developed on BMI, ≥ 25 for overweight and BMI, ≥30 as obese. Obesity class III classification is based on modification of BMI according to Strum (2007) [3]. It is classified as the underweight when BMI is <18.5, as normal when BMI is 18.5 - 24.9, and as overweight when BMI is 25 - 29.9, and grade 1 obesity is reached when BMI is 30 - 34.9, grade 2 obesity is reached when BMI is 35 - 39.9 and severe obesity is reached when BMI is over 40. Severe obesity is divided into three, namely severe obesity with a BMI over 40, morbid obesity with BMI 40 - 44.9 and super obese with BMI over 50.From the results of 33 studies in the United States in 2008, medical costs per person reached $266 on overweight, while obesity reached $1.723. Nationally, the cost of treatment for overweight and obesity were $113.9 billion [4]. Obesity is caused by many factors such as diet, lifestyle habit, genetic, pollutant, infection and endocrine agent. For that we need to understand the pathophysiological mechanisms of obesity, especially the mechanisms that explain the relationship between obesity and other risk

factors. Food intake control is important in relation to obesity, because fat tissue is largely concentrated in the stomach which then becomes visceral obesity. Control of food intake involves biochemical processes including the involvement of several hormones and cytokines that determine hunger and fullness. Controlling food intake involves central and peripheral nervous system [5]. If there is no energy balance of food intake, it will cause dysfunction of adipocytes that will be the background that causes adiposopathy. Adiposopathy ("sick fat") is defined as a change in pathogenicity of the anatomy of adipose tissue that occurs because there is no balance of calories, resulting in the pathophysiology of endocrine and immune responses that can lead to metabolic diseases [6].

Ghrelin, which circulates in the blood vessel has two forms, namely acylated (or n-octanoylated) and unacylated ones. Ghrelin acylation works through GHSR1a to increase food intake and adiposity. Peripheral ghrelin reduces energy use and increases the appetite by activating neuropeptide Y and AGRP neurons that inhibit the expression of anorexigenic neuromodulator. Neuromodulator affects MC4R melanocortin and suppresses appetite (apeptite) thereby increasing peripheral energy expenditure [7]. Ghrelin is secreted by the stomach trough the blood circulation and increases appetite resulting in weight gain.Adiponectin increases insulin sensitivity, stimulates fatty acid oxidation, glucose and lactic acid production in muscle cells (rhabdomyocytes). Adiponectin stimulates hepatic fatty acid oxidation and reduces gluconeogenesis [8]. Until now, adiponectin is one of the best adipokines with a great potential for development of some diseases therapy. Other than insulin-sensitizing, adiponectin also acts as anti-inflammatory, anti-atherogenic, anti-diabetic, anti-obesity, anti-fibrotic and anti-cancer [9]**.** The results of Torigoe et al (2007) research reported that plasma adiponectin levels can predict endothelial dysfunction before further becoming vascular disease. High molecular weight adiponectin are better used as a marker of endothelial dysfunction than total adiponectin [10].Control of obesity can also be done with medicine. Medicinal therapy in obese is indicated if the BMI≥ 30 kg/m2 or BMI 27.0 to 29.9 kg/m2 with obesity comorbid (e.g., hypertension, diabetes, obstructive sleep apnea). However, all efforts mentioned above are less optimal, that is why it is necessary to do other therapies that may be more effective in reducing obesity such as bariatric surgery procedure. Weight loss and weight maintenance can be accomplished by reducing energy intake. This is the best management with a combination of a reduction in total fat intake, the reduction of portion sizes, the reduction of the energy density, and the intake of fruit and vegetable. Physical exercise with duration of 90-120 minutes a day combined with energy-dense diet low in calories consumed constantly showed a weight loss of 7 to 8 kg [11]. A good exercise in obese patients done for 30-60 minutes each day per week in a long-term is very good at weight maintenance but has no effect in weight loss when it is not accompanied by diet changes [12, **13].** The purpose of this research is to analyze gastric banding (GB) on weight loss through the increased ghrelin and adiponectin in obese mice models.

II. METHODS

This study is a pure experimental research conducted in the laboratory with a factorial design. This study examined the influence of GB and the time (duration) compared with the dependent variable. Mice were weighed, fasted and anesthetized with 10 mg / kg ketamine 1000 mg/10 mL (KTM-100, Indonesia) via intraperitoneal. The initial step was a midline incision made in the abdominal wall ± 2 cm. Surgical techniques for gastric banding was performed by placing a band, diameter 6 mm with a width of 2 mm made of prolene mesh surrounding the glands of the gastric fundus or the bottom of the esophagogastric junction to divide the stomach into upper pockets and lower pockets . To keep the band dislocation, two stitches then were placed in the anterior abdominal wall, one near the greater curvature and the other near the larger curvature. Abdominal wall then was sewn back with prolene 30 and then given with antiseptic alcohol 70% and the wound was covered with sterile gauze [14**].**All rats were returned to the cage after being conscious for ± 2 hours, after that food and water were given ad libitum. Weight loss was monitored daily after the surgery. Body weight and food intake ofthe rats were observed every day by weighing. Food intake of the rats were obtained from the difference between the initial feed and the final feed. Weight gain was calculated based on the difference of the final body weight (before surgery) with initial body weight. Weight loss was measured by the difference in weight after obesity with the weight loss after surgery. Samples(blood) of control and GB mice were taken at day-0, 8 and 16 under anesthesia ketamine 10 mg/kg body weight and fasted for 2 hours. Measurement of body weight, levels of ghrelin, obestatin levels, the ratio of ghrelin/obestatin, adiponectin levels and A-FABP levels were measured on days 0, 8, and 16on both control group and GB.

III. THE MEASUREMENT LEVELS OF GHRELIN, OBESTATIN, THE RATIO OF GHRELIN/OBESTATIN, ADIPONECTIN ANDA-FABP IN RAT PLASMA

3.1.Ghrelin measurement method

Ghrelin measurement method refers to the rat Ghrelin ELISA Kit Catalog EK-030-87 [**15] (**Phoenix Lab, USA). Material and standard were placed into room temperature. 100μL standard, Standard, blank and the sample were dissolved in the dilution and placed into the wells and incubated for 3hour sat room temperature. Suspense was washed with PBS for 4 times. Conjugate was added at 200μL per well. A serum sample was incubated for 2 hours to eat at room temperature. The suspense was washed with washing buffer up to 4 times and then added with 200μL substrate solution per well and incubated 30 min at room temperature. Stop solution was added per well and read 450 nm for 30 min and read at a wavelength of 540 nm.

3.2.Adiponectin measurement methods

Adiponectin measurement method refers to the rat adiponectin ELISA Kit Catalog SK00010-03 [**16]** (Adipobioscience, USA). All ingredients were prepared before the work performed ELISA. Calibrator obestatin was dissolved in 1 mL of buffer solution. The preparation of wash solution was done with 500 mL of wash solution concentrate mixed with de-ionized water. Reagents were ready for use. Obestatin measurement steps are as follows. All the reagents were placed in 20-30oC temperature before the use. Each well was added with the 0:35 mL/well wash solution and left for 30 seconds and then the aspiration was done. Each well was washed twice. A total of 50 μ L solution of the labeled antigen was taken and added to the solution of calibrators (31.25; 62.5; 125: 250: 500; 1000; 2000 pg/mL) or sample and 50 μ L antibody mouse / rat obestatin was added to each well. It was closed with a seal plate and incubated for 18-20 hours (overnight). After the incubation of 4° C, the seal plate was washed with washing solution for 3 times with 0.35mL/well as much. SA-HRP solution was inserted into the well of 100 μ L / well and incubated for 1 h at room temperature. Plate was covered with a seal, and after incubation well was washed with washing buffer for 5 times. TMB solution was added, as much as 100 μ L per well and incubated with 100 μL and incubated for 30 min at room temperature. 100 μ L stop solution was given into each well and incubated for 30 min at room temperature. The reaction was read by ELISA reader at a wavelength of 450 nm.

IV. RESULTS

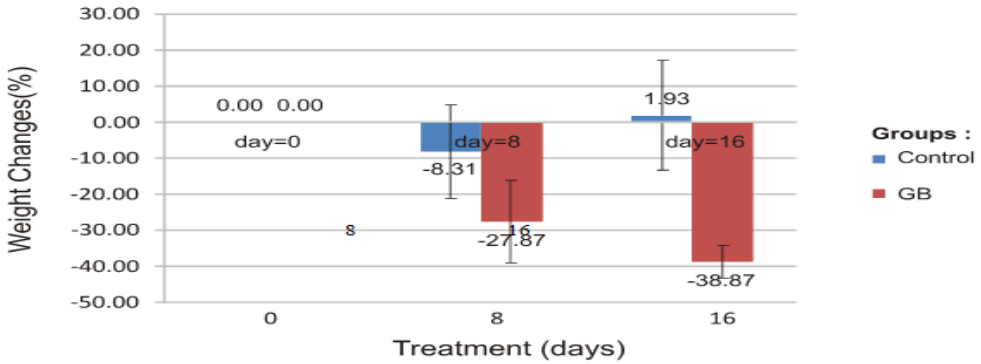
4.1.The Percentage of Weight Loss

Animal weight data (white mice) is normally distributed in each group ($p > 0.05$, see Appendix). The test of homogeneity of variance with Levene's test showed the group is homogeneous ($p > 0.05$). Because the data is normally distributed and all groups are homogeneous, variance (ANOVA) one way analysis is conducted.

Table 1. Changes in an animalweightin eachtreatment group

Groups	N	Body Weight (%)			
		$\bar{x}$	SD	Min	Max
Control 0 day	7	0,00			
Control 8th day	7	-8,31	13,07	-34,59	8,18
Control 16th day	7	1,93	15,22	-27,36	16,67
GB 0 day	7	$0,00^{a}$			
GB 8th day	7	$-27,87^{b}$	11,50	-19,50	-11,47
GB 16th day	7	$-38,87^{c}$	4,54	-45,11	-33,01

There is no difference between the control group a, b, c. Different superscript indicates the difference between the groups GB (based on the test). The results of analysis with one-way ANOVA showed significant results indicating that at least there is difference between a pair of treatment groups($p < 0.05$).Further analysis with Tukey's Multiple Comparisons method found no difference in weight gain among all groups of controls and GB group day-0, there is a difference in weight between the control group with the GB group treated until day16.



*based on t test

Figure 2: The percentage of animal weight in each treatment group

The picture above shows the weight loss of about 27.87% on day 8 and 38.87% on day 16 after GB. The results of statistical analysis showed the significant weight reduction percentage (p =0.0001).

4.2.Serum ghrelin

The data of ghrelin serum levels of experimental animals (white mice) is normally distributed in each group (p>0.05, see Appendix). Test of homogeneity of variance with Levene's test showed he group is not homogeneous (p <0.05). Because the data is normally distributed and the group is not homogeneous, statistical analysis of Brown-Forsythe is conducted.

Table 2. Ghrelin serum levels of experimental animals in each treatment group

Groups	n	Serum Ghrelin (ng/mL)				**Brown-Forsythe**
		x̄	**SD**	**Min**	**Max**	
Control 0 day	7	385,83[a]	89,27	202,17	452,17	F=10,252
Control 8th day	7	470,37[b]	34,51	424,78	522,61	p=0,001*
Control 16th day	7	426,18[a]	32,12	380,87	470,43	
GB 0 day	7	511,83[cd]	8,30	502,17	525,00	
GB 8th day	7	503,98[c]	11,61	488,26	518,70	
GB 16th day	7	523,66[d]	15,15	498,26	536,96	

Description:

* Significant at α=0.05

a,b and c: Different superscript indicates a difference between groups by t-test independent.

The analysis showed minimal differences between the pair of treatment groups(p <0.05). Further analysis with independent t test showed a difference between the control group (both of which are treated up to day-0, 8, or16) with the GB, while the GB groups obtained pairs of different groups are groups that are treated with GB up to day to-8 and day-to-16.

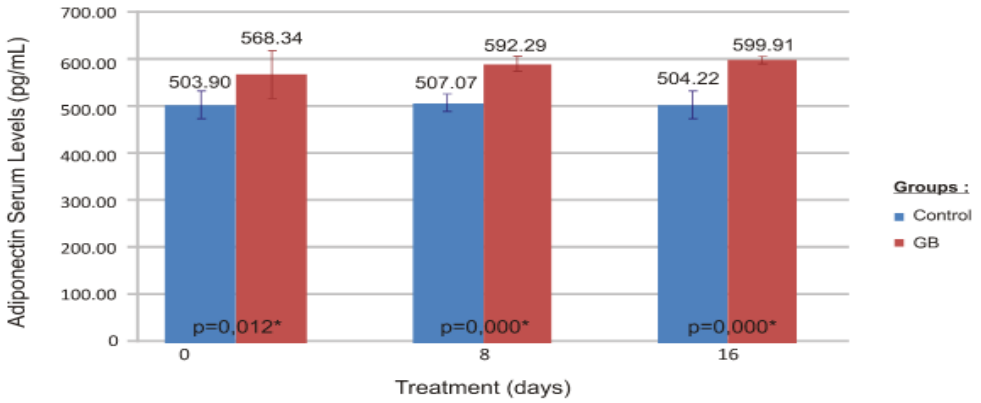


Figure 3 . Serum ghrelin levels of experimental animals in each treatment group

The picture above shows that after receiving the treatment, the serum ghrelin levels of GB group get higher and have a stable value over the control.

4.3.Adiponectin

The data of serum adiponectin levels of experimental animals (white mice) is normally distributed in each group (p>0.05,see Appendix).

Table . Levels of serum adiponectin experimental animals in each treatment group

Groups	N	Serum Adiponectin				**Brown-Forsythe**
		$\bar{x}$	**SD**	**Min**	**Max**	
Control 0 day	7	503,90[a]	29,36	466,98	534,92	F=17,653
Control 8th day	7	507,07[a]	17,88	474,29	531,11	p=0,000*
Control 16th day	7	504,22[a]	29,12	466,98	534,92	
GB 0 day	7	568,34[b]	49,89	474,29	606,98	
GB 8th day	7	592,29[b]	14,90	569,84	606,98	
GB 16th day	7	599,91[b]	7,30	591,75	608,25	

Note: *significant atα=0.05

a,b Different superscript indicates a difference between groups by independent t test

The test of homogeneity of variance with Levene's test showed the group is not homogeneous (p <0.05). Because the data is normally distributed and the group is not homogeneous, statistical analysis of Brown-Forsythe is conducted. The analysis showed minimal differences between the pair of treatment groups (p <0.05). Further analysis with independent t test showed a difference in serum adiponectin levels with the control group GB. Between the control group (treated up today-0, 8, and16) there is no differences in serum adiponectin levels, as well as inter-group GB (treated up today-0, 8, and 16).

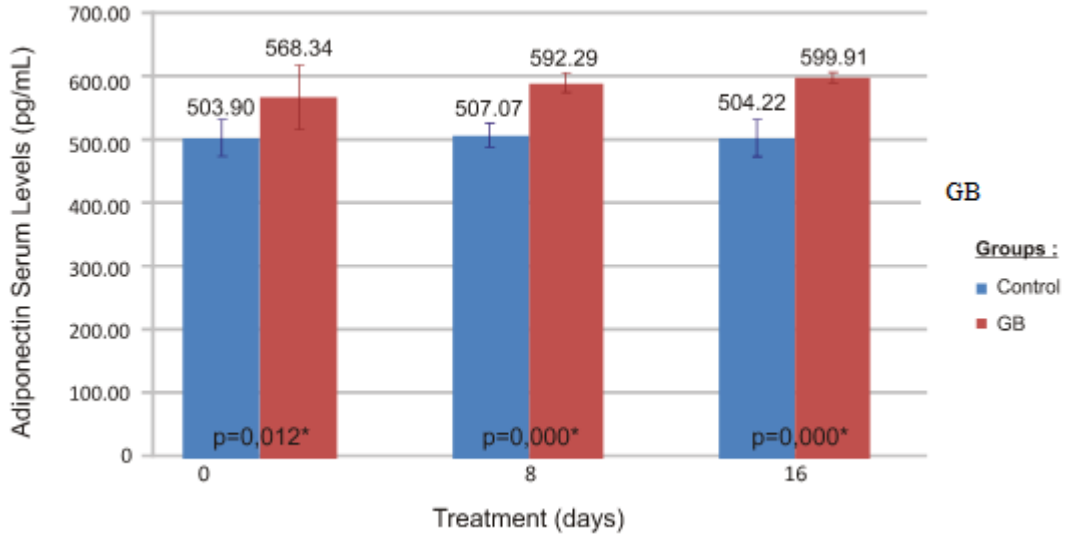


Figure 4 . Adiponectin serum levels of experimental animals in each treatment group showed serum adiponectin levels in all groups of G Bis higher than the control levels in all groups.

V. DISCUSSION

This study aims to determine the effect of gastric banding (GB) on weight loss, the increased ghrelin, the decreased obestatin, the increased ratio of ghrelin / obestatin, the increased adiponectin and the decreased A-FABP. Successful evaluation of GB was observed on day 0, 8 and 16. This evaluation of success is adapted to the rat with age of 3 months 8 days that is comparable to human age of 13.5 years and the age of 3 months 16 days is comparable to 14 years in human age [**17].** Selection of post-operative duration was based on the fact that because over 2 years human post-operative period weight loss was significant. 2 year old human is equivalent to 8 days interval and 8-year-old man is equivalent to 16 days post-surgery interval in rats. 8 days after surgery in mice of new GB is studied because it can decrease nitrogen balance resulting in weight loss [**14, 18, 19].** The analysis showed an association between the variables of weight, serum levels of Ghrelin, Obestatin levels, the ratio of Ghrelin / Obestatin, Adiponectin levels and A-FABP11 [**17**].Bariatric surgery procedures to date, is getting better and the only option to lose weight significantly that will stay for a long time [**20,21,22].** Laparoscopic Gastric Banding in a randomized trial involved 100 patients.

LGB data showed 58.9% weight loss for 3 years [**23]** . From GB procedures in mice the occurance of percentage weight loss can be seen compared with the control group. The results of this study indicate that weight loss of about 27.87% on day 8 and 38.87% on day 16 after GB. The same study conducted by [**24]** suggested that the treatment of gastric banding is able to reduce weight on obese Zucker rats [**25]**. Surgical methods are expected to increase weight loss [**26, 27, 28 ,29].**The decrease in average weight gain after GB is approximately 28% [**26,27].** GB mechanism in contributing to the greater efficacy remains unclear. Recent data suggest that the mechanism of function of adipocytes, neural and hormonal systems may contribute to the success of the GB in weight loss in obese [**30, 31**]. Bariatric surgery peripheral results in the decreased lipogenesis due to the reduced food intake resulting in reduced total energy expenditure [**32].**Shah *et al.,* (2006) states that GB can lose weight significantly during the 6 to 12 months of 24 patients [**33].** The results of Colles et al. (2008) also states that GB can lose weight for 4 to 12 months from 85 subjects [**34].** Phillips *et al.,* (2005) showed that LGB significantly reduces weight, waist circumference, plasma free fatty acid, the subcutaneous abdominal and visceral fat, in obese non-diabetic women 12 weeks after LGB because there is a significant improvement in insulin sensitivity [**35]**.Ghrelin is a peptide having 28 amino acid secreted by gastric endocrine cells and induces weight gain by stimulating appetite in mammals. This study showed that after GB treatment, the increased levels of ghrelin are higher with a stable value over the control group. Ghrelin is a hormone secreted by cells in the fundus A stomach. Ghrelin modulates the secretion of hormones in addition to functioning as well as regulating appetite, food intake, energy use and intestinal motility [**36]**. In mice, the administration of ghrelin stimulates feeding, increases body weight, and reduces the use of fat [**37].** The report showed Ghrelin levels after surgery did not differ compared to the patients with no surgery and some studies have found that ghrelin levels were stable after 6 months of operation [**25**]. Plasma ghrelin concentrations rise before meals and fall rapidly after meals to produce an increase in plasma glucose concentration or insulin. In general, ghrelin increases in a state of negative energy balance, but decreases in a state of positive energy balance **[25].**The mechanism that explains the mechanism of the decreased ghrelin from GB is still unclear. In contrast to the results of the study it is shown that gastric banding (GB) in human can lose weight through a decrease in leptin, the increased adiponectin, ghrelin and the decreased PYY but the mechanism of the changes in food intake is still unknown **[38].**

PYY and GLP-1 is a satiety signal released by L cells in the gastric fundus. In humans, plasma PYY levels increase during fasting and post-prandial for 6 and 12 months after bariatric surgery. Cumming (2008) explains that ghrelin levels rose about 53% after eight months of LGB. This is because there is activity of ghrelin secretion that is affected by the vagus nerve **[39].** In the LGB there is the occurrence of a reduction in esophageal relaxation that increases satiety and reduces hunger, causing long-term reduction in caloric intake resulting in hunger arousal again. This condition will increase the levels of ghrelin **[40]**. Leptin system is one system that meets the set hypothesis point in weight control with the media of leptin hormone that is mainly produced in adipocytes. Leptin binds to specific receptors which are mainly located in the hypothalamus, and also found in other tissues such as adipose and pancreas. Leptin is secreted into the circulation of white adipose tissue, penetrating brain blood vessels, and bound by membrane cell receptors of specific brain areas. Leptin receptor is superfamily with GH and prolactin receptors associated with signal transduction pathways JAK-STAT3 **[17, 41]**. Leptin administration decreases your appetite, while increasing metabolism rate, body temperature and physical activity level **[42].** Under conditions of less fat deposits after food intake limit and fat burning due to activity, blood leptin levels drop so that α-MSH in the hypothalamus is reduced. This situation triggers hunger centers in hypothalamus neurons releasing agouti related protein (AGRP) in which synthesis is suppressed by leptin through bonding with its receptors. AGRP stimulates appetite through a mechanism of α-MSH antagonist of the MC4-R. Furthermore, the reduction in the synthesis of α-MSH from POMC suppresses catabolism of fat into fat deposits in adipocytes replenished as a result of a combination of these effects with feeding behavior. When fat stores are adequate, the control mechanism returns to the inhibition of appetite and increases the use of energy so the weight can be maintained on a limited range of years **[43,44].**The role of stress in the regulation of appetite is affecting appetite satiety center in the hypothalamus. In the acute situation, CRH causes anorexia, whereas NPY, which is orexiogenic, stimulates the secretion of CRH, via the Y1 receptor. At the same time, NPY inhibits the LC system / NE-sympathetic and parasympathetic systems causing a decrease in thermogenesis and helps the digestive system and nutrient storage. On the other hand, leptin, contributes stimulation to satiety hormone and inhibits the secretion of NPY in the hypothalamus. This mechanism will stimulate arcuate nucleus POMC neurons to release α-MSH, a powerful thermogenic anorexiogen and peptides, which gives effect through specific melanocortin receptor type 4 (MC4) resulting in the feeling of satiety [44,45**].**

The results of path analysis showed that the GB affects indirectly on body weight through Ghrelin. These results equals to the results of the research conducted by Benedix *et al.,* (2011). Gastric banding does not decrease the production of ghrelin because ghrelin is produced by the oxyntic cells of gastric fundus and salivary glands, so in a state of hunger the levels of ghrelin increase due to GB **[46].** The results of another study revealed that the increased ghrelin due to weight loss in this study affects the metabolism in the periphery. Ghrelin conditions that increase due to GB are not followed by proper intake therefore the central influence declines but the influence is more salient to the peripheral processes resulting in the impaired glukogenesis and lipogenesis. Glucose needs by body can be met with a reverse mechanism process of lipolysis that becomes weight loss **[25,32].** Ghrelin affects the physiology of the cardiovascular system.mRNA expression and Ghrelin receptor can be observed on the heart and blood vessels through the increase in GHS affinity. Ghrelin affects on systemic vasodilation and may involve peripheral and central mechanisms. Giving intravenous ghrelin in humans can significantly lower arterial pressure but doesn't alter heart rate. Ghrelin increases coronary perfusion pressure in rat heart using a Langendorf system and myogenic tone significantly in coronary arteries. Ghrelin effect on vasoactive is mediated by activation of GHS-R1a. In the microcirculation, ghrelin also increases the flow of blood vessels [**46,47,48,49].**Adiponectin is secreted from adipose tissue and circulates in multimeric forms ranging from trimers, hexamer (low molecular weight, ~ 180kDa) to high molecular weight oligomers containing 12-18 subunits of the complex (high molecular weight, ~ 400 kDa) **[8,50,51].**The results showed serum adiponectin levels in all groups of GB are higher than the control levels in all groups on days 8 and 16. Adiponectin levels are associated with weight gain. The results of path analysis showed that the GB affects indirectly via Adiponectin on body weight. The result of this research is comparable to the research conducted by Diker (2006) and Benedix., (2011). Gastric banding affects weight loss, while weight loss alone results in the increased insulin sensitivity and decreased glucogenesis resulting in a reduction in the number of fat cells. This decrease in fat cells results in the increased plasma adiponectin levels **[46,52].**Adiponectin increases insulin sensitivity, stimulates fatty acid oxidation, glucose uptake and lactate production in muscle cells (rhabdomyocytes). Adiponectin stimulates hepatic fatty acid oxidation and reduces gluconeogenesis [8]. This is consistent with results of other studies that adiponectin mRNA levels in adipose tissue of obese patients is lower compared to the lean subjects, and lower in visceral adipose tissue compared to subcutaneous. Adiponectin is adipocytes specific protein that decreases in obesity, and involved in the repair process of inflammation, insulin resistance and metabolic syndrome **[53,54]**.Adiponectin is a hormone produced mainly by adipose tissue. The study reveals the role of adipokines in the pathophysiology of insulin resistance and metabolic syndrome **[53]**. The results also showed an increase in body mass index (BMI) and waist-hip ratio, total and visceral adipocytes associated with the decreased plasma adiponectin concentration. Adiponectin is a peptide produced and secreted into the circulation exclusively by adipose tissue. Different levels of leptin, and adiponectin in plasma remain relatively constant throughout the day and are not affected by food intake **[55]**. Because GB can increase adiponectin and the is associated with weight loss then the GB is one method to improve the function of adipocytes [**45,52**].

VI. CONCLUSION

Gastric banding(GB) proved to lose weight through the increased ghrelin in mice models with obesity, Gastric appeal (GA) is not directly related to weight loss through the increased ghrelin in mice models with obesity, Gastric appeal(GA) proved to lose weight through the increased levels of adiponectin in mice models with obesity, Time (duration) GA is associated with weight loss through an increase in ghrelin, and the increased levels of adiponectin.

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