reports

MDPI

Article

Impacts of Different Modes of Bariatric Surgery on Plasma Levels of Hepassocin in Patients with Diabetes Mellitus

Wen-Chi Wu [1,†], Wei-Jei Lee [2,3], Chun Yeh [4,†], Shu-Chun Chen [5] and Chih-Yen Chen [6,7,*]

1 Department of Medicine, Taipei Veterans General Hospital, Taipei 11217, Taiwan; wcwu6@vghtpe.gov.tw
2 Department of Surgery, Min-Sheng General Hospital, Taoyuan 330, Taiwan; wjlee_obessurg_tw@yahoo.com.tw
3 Taiwan Society for Metabolic and Bariatric Surgery, Taipei 11031, Taiwan
4 Division of Gastroenterology, Department of Internal Medicine, Cheng-Hsin General Hospital, Taipei 112, Taiwan; ch6804@chgh.org.tw
5 Department of Nursing, Chang-Gung Institute of Technology, Guishan, Taoyuan 333, Taiwan; N002916@e-ms.com.tw
6 Division of Gastroenterology and Hepatology, Department of Medicine, Taipei Veterans General Hospital, Taipei 11217, Taiwan
7 Faculty of Medicine, National Yang-Ming University School of Medicine, Taipei 11221, Taiwan
* Correspondence: chency@vghtpe.gov.tw; Tel.:+886-2-2871-2121 (ext. 2050)
† These authors contributed equally to this work.

Received: 15 September 2019; Accepted: 30 September 2019; Published: 5 October 2019

Abstract: Background: Hepassocin is a liver-derived protein and its serum concentrations significantly increase in diabetes and fatty liver patients. Hepassocin is also a biomarker for diabetes and fatty liver; therefore, we aimed to investigate the impacts of different types of bariatric surgery on hepassocin plasma levels in obese patients with diabetes, and to determine if hepassocin could be a potential new marker for monitoring the effects of bariatric surgery and a treatment target. Methods: Overall, 12 patients undergoing gastric bypass (GB), 10 patients undergoing sleeve gastrectomy (SG) and 11 patients undergoing duodeno-jejunal bypass with sleeve gastrectomy (DJB-SG) were enrolled. Fasting hepassocin levels were measured at baseline, three, 12, and 24 months after surgery. Results: All the three groups significantly decreased their body mass index, waist-to-hip ratio, a body shape index (ABSI), triglycerides, fasting blood sugar, hemoglobin A1c, C-peptide levels and homeostasis model assessment of insulin resistance 24 months after surgery. There were no significant changes in hepassocin levels, even 24 months after the three surgeries. Hepassocin had a significant negative relationship with the ABSI ($p < 0.001$) 24 months after the SG. Conclusions: Neither GB, SG, nor DJB-SG altered plasma hepassocin levels in diabetic patients up to 24 months after surgery. The use of hepassocin in clinical settings requires more investigation.

Keywords: hepassocin; gastric bypass (GB); sleeve gastrectomy (SG); duodeno-jejunal bypass with sleeve gastrectomy (DJB-SG); type 2 diabetes mellitus (T2DM)

1. Introduction

The global incidence of type 2 diabetes mellitus (T2DM) has quadrupled over the past 30 years [1].Obesity (body mass index (BMI) >30 kg/m^2) has long been a well-known risk factor of T2DM [2,3]. In 2003, a systemic review already disclosed that bariatric surgery, including gastric bypass (GB) and gastric banding, was a more effective treatment with increased short-term weight loss and improvedglycemic control for obese patients with T2DM than conventional medical treatments [4].

Recent randomized trials demonstrated that bariatric surgery, including GB and sleeve gastrectomy (SG), is an effective treatment for non-morbidly obese Asian patients with T2DM at one and two years following the surgery [5,6]. Further studies even suggested that duodeno-jejunal bypass with sleeve gastrectomy (DJB-SG) might have better effects compared with those of GB or SG alone [7,8].

Hepassocin is a hepatic-derived humoral factor associated with the regulation of glucose homeostasis in the liver and insulin sensitivity in insulin-responsive tissues [9]. Hepassocin is also reported to be up-regulated in all patients with T2DM [10]. The plasma concentrations of hepassocin increased in parallel with plasma glucose levels [10]. Increased levels of hepassocin might interfere with extracellular signaling and consequently induce insulin resistance [11]. In a recent report, Ou et al. [12] showed a significant decrease in hepassocin concentration in 21 patients who presented a hyperglycemic crisis following treatments. A high hepassocin level leads to the increase of anti-oxidative stress proteins and results in hepatocellular protection against reactive oxygen species (ROS) [4]. The above characteristics of hepassocin, including its up-regulation in T2DM and obese patients and its further effects in reducing ROS levels, are similar to the ones of fibroblast growth factor (FGF)21—another hepatokine. FGF21 has been used as gene therapy for the treatment of obese animals or animals under long-term fat-rich diet [13]. Hepassocin might be a new treatment target such as FGF21 in T2DM.

Data comparing the three types of bariatric surgery, mini-GB, SG and DJB-SG, are still limited. We aim to demonstrate the efficacyof the three bariatric surgery procedures by directly comparing the changes in hepassocin and other parameters following surgery. To our knowledge, this is the first report to compare hepassocin levels in obese patients with T2DM undergoing the above three types of bariatricsurgery.

2. Methods

2.1. Participants

A hospital-based design was adapted for the present study. Patients with T2DM who had undergone mini-GB, SG, or DJB-SG procedures were enrolled in our study ((Institutional Review Board) IRB approval number: MSIRB2015020 (31/12/2015) and YM105004E (26/02/2016). The diagnostic and inclusive criteria were as follows: (i) T2DM discovered more than six months ago with hemoglobin A1c (HbA1c) > 8%, under the close monitoring and medical treatment including diet control, oral anti-diabetic agents, or insulin from an endocrinologist, (ii) BMI between 25 and 35 kg/m^2, (iii) willingness to receive additional therapy plus diet control and exercise, (iv) willingness to accept follow-up consultations, and (v) willingness to sign an informed consentform.

Candidates were excluded if they: (i) had experienced cancer within the last 5 years; (ii) had human immunodeficiency virus infection or active pulmonary tuberculosis; (iii) had experienced cardiovascular instability within the last six months, (iv) had pulmonary embolism or uncontrolled coagulopathy, (v) serum creatinine > 2.0 mg/dL, (vi) had chronic hepatitis B, C, liver cirrhosis, or inflammatory bowel diseases, (vii) had acromegaly or had received organ transplantation, (viii) had undergone any other bariatric surgery, (ix) were alcoholic or abused drugs, and (x) had other uncooperative conditions.

In total, 12 patients (aged 43.5 ± 8.9 years, three males and nine females) underwent mini-GB, 10 patients (aged 37.6 ± 9.1 years, six males and four females) underwent SG, and 11 patients (aged 44.8 ± 8.0 years, three males and eight females) underwent DJB-SG. Duration of T2DM in the mini-GB, SG and DJB-SG groups were 4.1 ± 2.1, 2.6 ± 2.2, and 4.6 ± 3.2 years, respectively.

2.2. Surgical Techniques

2.2.1. Laparoscopic GB (Mini-GB)

Laparoscopic GB leads to a digestive tract that bypasses the foregut, especially the duodenum and a thin, tube-like remnant stomach. The procedure was reported to result in encouraging weight loss and resolution of T2DM and metabolic syndrome [14]. Similar to the techniques reported in our previous study, a 5-trocar laparoscopic technique was conducted, and then a gastric tube approximately 2 cm wide was created along the lesser curvature. A type-II Biliroth procedure followed with the 120 cm small bowel distal to the ligament of Treitz was then performed. No drainage tube was left after thesurgery.

2.2.2. Laparoscopic Sleeve Gastrectomy (SG)

In short, an SG results in the reduction of the stomach. Under the standard 5-trocar laparoscopic technique, the pylorus was identified, and the greater curvature, which included the whole fundus, was resected from the distal antrum to the angle of His with the ransaction of the stomach, which was about 2cm wide along the lesser curvature. The procedure culminated in a tube-like stomach. The removed portion of the stomach was extracted from the peri-umbilical trocar site. A running absorbable suture was applied to reinforce the staple line to reduce the risk of hemorrhage and leakage [15].

2.2.3. Laparoscopic Duodeno-Jejunal Bypass with Sleeve Gastrectomy (DJB-SG)

The procedure was performed in the "French" position (surgeon between the patient's legs) through a standard 5-trocar laparoscopic technique. The whole greater curvature was mobilized from the omentum. A large portion of stomach was resected from the distal antrum. The staple line was routinely reinforced with a running suture using unabsorbable suture. The duodenum was dissected free of the lower and posterior wall. After the ligament of Treiz was identified, the length of the alimentary limb of the small bowel was decided according to the BMI value, with a 150 cm biliopancreatic limb for patients whose BMI were <35 kg/m^2.

The selected loop was ascended antecolically without dividing the omentum. A side-to-side duodeno-jejunal anastomosis was created. The stapler defect was closed with a two-layer absorbable running suture. At the end of the surgery, we performed an air leak test and left a drain [16].

Three bariatric surgery procedures were illustrated in Figure 1.

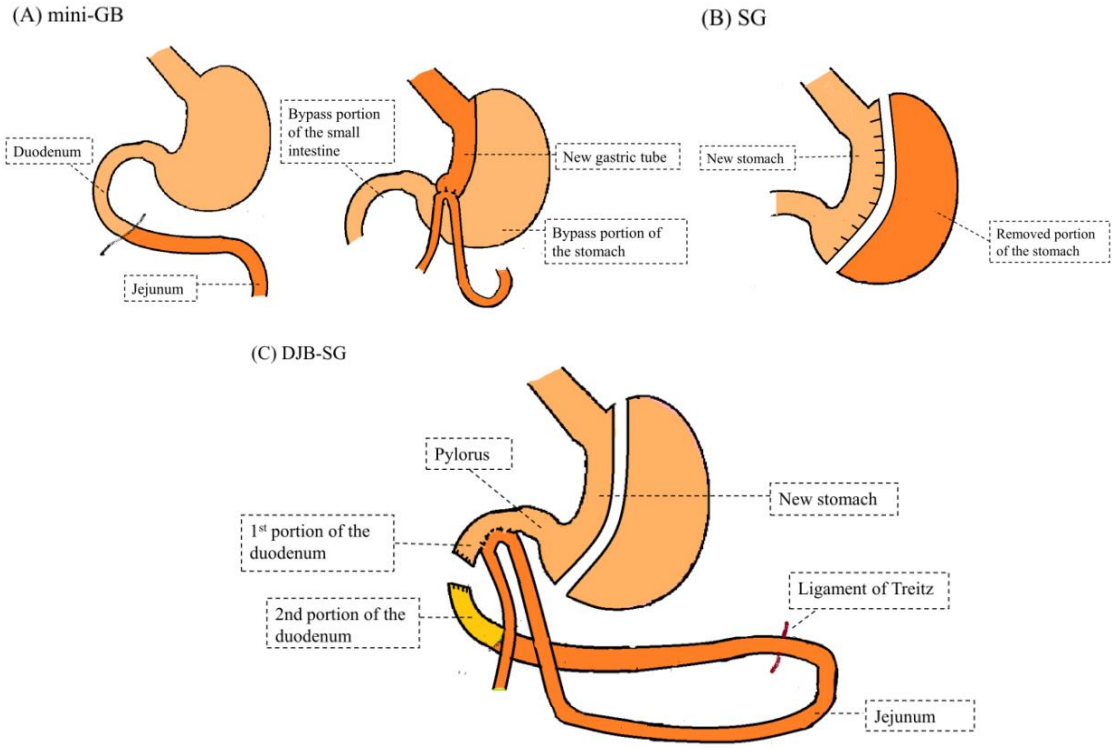

Figure 1. Different types of bariatric surgery. (**A**) Mini-gastric bypass (mini-GB). (**B**) Sleeve gastrectomy (SG). (**C**) Duodeno-jejunal bypass with sleeve gastrectomy (DJB-SG).

2.3. Blood Sampling

All participants were required to fast overnight before blood samples were taken from their median cubital veins between 8 a.m. and 11 a.m. on the following day. Samples were taken before the surgery, and three, 12 and 24 months after the surgery. Routine laboratory tests, including serum total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), fasting blood sugar (FBS), HbA1c, C-peptide, and hepassocin were performed on each day of the study. The homeostasis model assessment of insulin resistance (HOMA-IR) was calculated by multiplying plasma glucose (mmol/L) by insulin (μU/mL) [6]. An association of a body shape index (ABSI) was calculated as waist circumference ÷ the estimated allometric regression-adjusted weight and height circumference [17].

2.4. Assays of Plasma Hepassocin Levels

The blood sample taken following the protocol mentioned above was immediately injected into a test tube containing aprotinin (500 U/ mL). Plasma was separately dispensed into a polypropylene tube in aliquots after centrifugation at 300× *g* and was then stored at −20 °C. Enzyme immunoassays for hepassocin (USCN Business Co., Ltd., Wuhan, China) were carried out in a single batch and a blinded fashion.

2.5. Statistical Analysis

The Wilcoxon signed-rank test was used to compare baseline and post-operative variables. A Friedman's one-way repeated measures analysis of variance by ranks followed by a post hoc test was performed to analyze the differences among hepassocin plasma levels before the surgery, three, 12, and 24 months after the surgery. Correlations between the two parameters were examined by conducting a Spearman's correlation analysis. $p < 0.05$ was considered statistically significant. All analyses were conducted using the Statistical Packagefor Social Science, version 12.0 (SPSS, Inc., Chicago, Illinois, IL, USA).

3. Results

3.1. Effects of the Treatment 24 Months after Bariatric Surgery

BMI, waist-to-hip ratio, HbA1c, C-peptide, and TG decreased in all the three groups 24 months after surgery. C-peptide and HOMA-IR decreased in the mini-GB group 24 months after surgery. ABSI, insulin and HOMA-IR decreased and HDL-C levels increased in the SG group 24 months after surgery. FBS decreased in the DJB-SG group 24 months after surgery (Table 1).

Table 1. Characteristics of mini-GB, SG, and DJB-SG patients at the baseline of surgery (M0) and two years (M24) after surgery.

	mGB (*n* =12)		**SG (*n* =10)**		**DJB-SG (*n* =11)**	
	M0	**M24**	**M0**	**M24**	**M0**	**M24**
Age	43.5 ± 8.9		37.6 ± 9.1		44.8 ± 8.0	
Body weight (kg)	86.4 ± 14.0	64.6 ± 7.2 ***	98.0 ± 14.9	77.6 ± 19.3 ***	91.5 ± 13.1	71.7 ± 8.7 ***
Weight loss (kg)		18.3 ± 6.4		21.9 ± 5.3		19.9 ± 7.1
BMI (kg/m^2)	33.0 ± 4.2	26.2 ± 3.2 ***	34.9 ± 2.5	27.0 ± 4.0 ***	34.2 ± 5.0	26.9 ± 3.6 ***
Waist-hip ratio	0.96 ± 0.04	0.88 ± 0.06 ***	0.94 ± 0.07	0.86 ± 0.06 **	0.90 ± 0.07	0.86 ± 0.05 *
ABSI	0.08 ± 0.00	0.08 ± 0.01 ***	0.08 ± 0.00	0.07 ± 0.00 **	0.08 ± 0.01	0.08 ± 0.00
TC (mg/dL)	190.3 ± 44.2	169.7 ± 23.8	182.3 ± 49.7	184.9 ± 35.3	190.0 ± 36.3	184.3 ± 41.9
TG (mg/dL)	171.3 ± 62.6	91.3 ± 31.7 **	189.6 ± 132.7	96.6 ± 51.2 **	211.7 ± 111.9	132.7 ± 66.5 **
HDL-C (mg/dL)	43.0 ± 5.8	47.6 ± 7.7	39.2 ± 6.8	50.5 ± 12.6 **	46.6 ± 10.0	49.5 ± 12.4
LDL-C (mg/dL)	122.5 ± 34.1	111.3 ± 26.5	112.6 ± 35.9	115.1 ± 25.6	113.9 ± 38.1	110.7 ± 33.1
FBS (mg/dL)	164.1 ± 44.7	116.9 ± 6.5 *	127.4 ± 43.7	88.8 ± 7.1 *	158.0 ± 46.4	122.7 ± 33.1 *
HbA1c (%)	9.0 ± 1.6	6.7 ± 1.6 **	8.0 ± 1.5	5.6 ± 0.3 **	8.9 ± 1.6	6.6 ± 1.4 **
Insulin (μU/mL)	15.1 ± 8.7	4.5 ± 2.3 ***	11.9 ± 5.7	6.4 ± 2.8 *	19.1 ± 20.0	11.9 ± 23.1
C-peptide (ng/mL)	3.0 ± 1.4	1.3 ± 0.7 ***	3.3 ± 1.6	1.9 ± 0.7 *	2.2 ± 0.8	1.4 ± 0.4 **
HOMA-IR	5.9 ± 3.4	1.8 ± 1.8 ***	3.7 ± 1.8	1.4 ± 0.6 **	6.7 ± 5.5	4.5 ± 10.3

mGB—mini-gastric bypass; SG—sleeve gastrectomy; DJB-SG—duodeno-jejunal bypass with sleeve gastrectomy; BMI—body mass index; ABSI—a body shape index; TC—total cholesterol; TG—triglycerides; HDL-C—high-density lipoprotein cholesterol; LDL-C—low-density lipoprotein cholesterol; FBS—fasting blood sugar; HbA1c—hemoglobin A1c; HOMA-IR—homeostatic model assessment for insulin resistance. Expressed values are means ± SD. *indicates statistical difference between groups compared before and after surgery. *$p< 0.05$; **$p< 0.01$; ***$p< 0.001$.

3.2. Changes in Hepassocin Levels 12 and 24 Months after Bariatric Surgery

There were no significant changes in hepassocin at three, 12 and 24 months after any of the three types of surgery (Figure 2, $p > 0.05$).

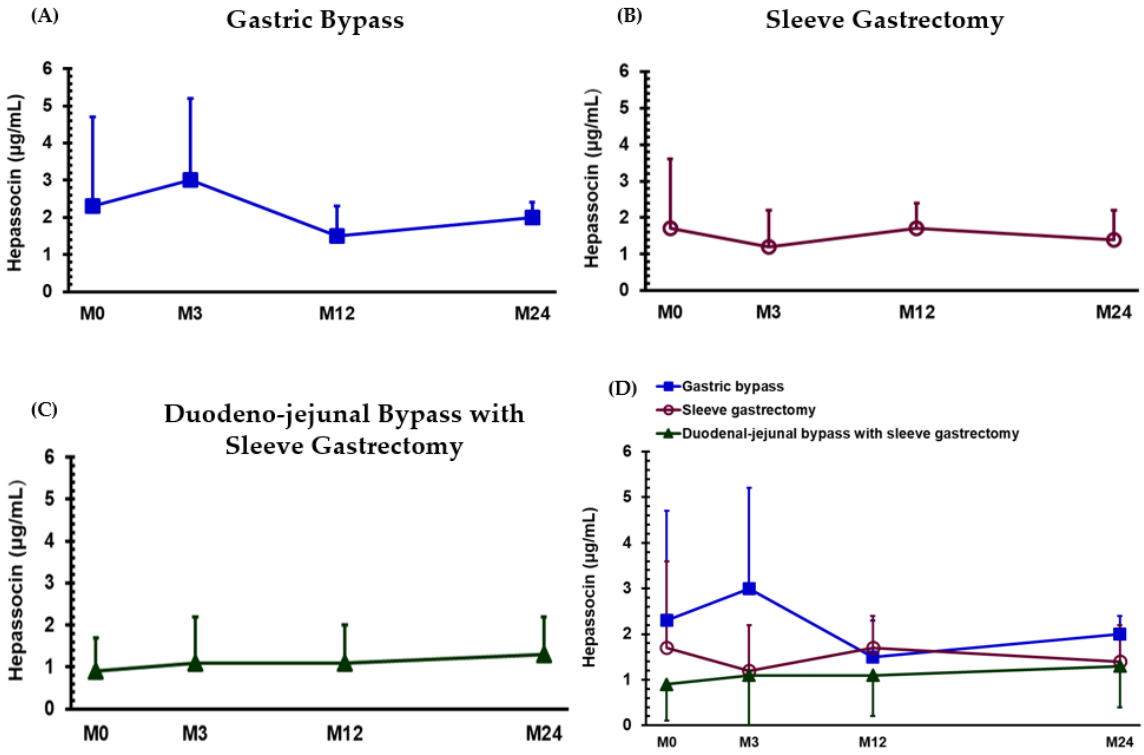

Figure 2. The serum concentration of hepassocin at the baseline of surgery (M0), three (M3), 12 (M12) and 24 months (M24) after bariatric surgery. (**A**) Mini-gastric bypass group, n = 12. (**B**) Sleeve gastrectomy group, n = 10. (**C**) Duodeno-jejunal bypass with sleeve gastrectomy group, n = 11. (**D**) Merging different hepassocin concentrations between the three different surgeries.

3.3. Relationship between Hepassocin and Clinical Parameters before Surgery and 24 Months after Surgery

Before surgery, there were no significant relationships between hepassocin and any demographic or biochemical parameters in the mini-GB and DJB-SG groups. However, there was a significant positive relationship between hepassocin and HDL-C levels (p = 0.0427) (Table 2).

Table 2. Relationship between hepassocin levels and various parameters at baseline before surgery.

	mGB (n = 12)		**SG (n = 10)**		**DJB-SG (n = 11)**	
	rho	***p***	**Rho**	***p***	**rho**	***p***
Body weight	−0.0699	0.817	−0.176	0.607	−0.355	0.270
BMI	0.0769	0.800	−0.200	0.559	−0.591	0.0510
Waist-hip ratio	−0.287	0.352	−0.590	0.0665	−0.0545	0.860
ABSI	−0.0839	0.783	0.0545	0.865	0.236	0.467
TC	0.112	0.716	−0.491	0.137	−0.382	0.233
TG	0.0420	0.886	−0.292	0.384	−0.436	0.168
HDL-C	0.00353	0.974	−0.632	0.0427	−0.369	0.245
LDL-C	0.186	0.542	−0.491	0.137	−0.136	0.673
FBS	−0.126	0.683	−0.515	0.116	0.345	0.283
HbA1c	−0.295	0.340	−0.103	0.759	−0.330	0.310
Insulin	−0.0140	0.956	0.345	0.309	0.200	0.538
C-peptide	0.0350	0.904	−0.297	0.384	−0.0364	0.903
HOMA-IR	−0.0140	0.956	−0.0424	0.892	0.218	0.502

mGB—mini-gastric bypass; SG—sleeve gastrectomy; DJB-SG—duodeno-jejunal bypass with sleeve gastrectomy; BMI—body mass index; ABSI—a body shape index; TC—total cholesterol; TG—triglycerides; HDL-C—high-density lipoprotein cholesterol; LDL-C—low-density lipoprotein cholesterol; FBS—fasting bloodsugar; HbA1c—hemoglobin A1c; HOMA-IR—homeostatic model assessment for insulin resistance.

Twenty-four months after the surgery, hepassocin had no significant relationships with any demographic or biochemical parameters in the mini-GB and DJB-SG groups. Additionally, there was a significant negative relationship between hepassocin and ABSI levels ($p < 0.0001$) (Table 3).

Table 3. Relationship between hepassocin levels and various parameters two years after surgery.

	mGB (n = 12)		SG (n = 10)		DJB-SG (n = 11)	
	rho	***p***	**Rho**	***p***	**rho**	***p***
Body weight	−0.460	0.123	0.347	0.309	−0.200	0.538
BMI	−0.309	0.317	0.158	0.631	−0.400	0.210
Waist-hip ratio	0.108	0.733	0.552	0.0892	0.178	0.575
ABSI	0.0877	0.766	0.924	0.000	0.500	0.109
TC	0.0989	0.749	0.000	1.000	0.210	0.520
TG	0.561	0.0547	0.256	0.446	0.355	0.270
HDL-C	0.164	0.603	0.0547	0.865	0.0729	0.818
LDL-C	0.00879	0.974	0.0518	0.865	−0.0909	0.776
FBS	0.540	0.0663	−0.105	0.759	0.282	0.384
HbA1c	0.337	0.273	0.0686	0.838	0.164	0.614
Insulin	−0.0756	0.800	0.261	0.446	0.0320	0.903
C-peptide	−0.382	0.206	0.332	0.327	0.0364	0.903
HOMA-IR	−0.0599	0.834	0.152	0.656	0.291	0.369

mGB—mini-gastric bypass; SG—sleeve gastrectomy; DJB-SG—duodeno-jejunal bypass with sleeve gastrectomy; BMI—body mass index; ABSI—a body shape index; TC—total cholesterol; TG—triglycerides; HDL-C—high-density lipoprotein cholesterol; LDL-C—low-density lipoprotein cholesterol; FBS—fasting bloodsugar; HbA1c—hemoglobin A1c; HOMA-IR—homeostatic model assessment for insulin resistance.

4. Discussion

In our current study, we found BMI, waist-to-hip ratio, TG, HbA1c and C-peptide levels significantly decreased 24 months after any of the three surgeries, which strongly indicated the important role of bariatric surgery in controlling weight, metabolic syndrome, glucose levels, and insulin resistance in obese patients with T2DM. However, none of the individuals who underwent mini-GB, SG, or DJB-SG procedures demonstrated any changes in hepassocin levels before and 12 or 24 months after surgery.

The liver plays a role in maintaining glucose homeostasis by secreting hepatokines to regulate insulin-responsive tissues and by secreting glucose generated from gluconeogenesis and glycogenesis [9,18–20]. Hepassocin is one type of hepatokines [9]. Previously, hepassocin was found to be involved in liver proliferation. It is over-expressed in hepatocytes in patients with non-alcoholic fatty liver disease (NAFLD) and results in oleic acid-induced lipid accumulation [21].

It is also generally accepted that hepassocin was up-regulated in all patients with poorly-controlled T2DM—whether they had a fatty liver or not [21]. The level of hepassocin is significantly positively related to plasma glucose concentration. Some studies showed that high plasma glucose levels induce the secretion of hepassocin and that hepassocin plays a vital role in hepatic protection. The level of hepassocin decreased once the plasma glucose level began to normalize [12]. The complex relationships between hepassocin, NAFLD and T2DM were thoroughly examined by Lu et al. [10]. They demonstrated that both NAFLD and T2DM are independently associated with hepassocin. Besides, they found that the serum TG level was significantly positively related to the serum hepassocin level [10].

Ou et al. [12] published a report about the decrease of hepassocin concentration in patients who presented a hyperglycemic crisis after intensive medical treatment. Hepassocin levels before and after the crises were 6.80 ± 5.74 and 2.70 ± 1.99 μg/mL, correspondingly. In our study, the mean levels of serum hepassocin ranged from 0.9 to 3.0 μg/mL, which were compatible with their study. These results further suggested the high accuracy of the hepassocin measurement in our study. However, in their study, hepassocin levels dropped as the plasma glucose level improved. On the other hand, HbA1c, insulin, C-peptide and BMI decreased in our study; while hepassocin concentration

did not. We considered this was mainly due to the liver status of the patients, which had not been evaluated in our study. From previous researches, we already knew that hepassocin expression would be up-regulated in patients with a fatty liver. Differences in liver conditions might have played a role in our hepassocin results. Second, in their study, the volume of plasma was relative depleted when a hyperglycemic crisis occurred. It was therefore uncertain whether it was the expanded plasma volume that caused the hepassocin concentration to decrease, or if it was the improvement in plasma glucose levels.

In our study, plasma hepassocin concentration had a negative correlation with ABSI 24 months after the SG procedure. ABSI is derived from waist circumference and BMI [17]. It represented body shape and was considered to be a significant risk factor for early death rather than BMI and waist circumstance [17,22]. However, there was no significant relationship between plasma hepassocin and waist circumference or BMI. We cannot explain this phenomenon, although it is an interesting finding from the current study. Further study is needed.

There are some limitations in our study. First, the size of the study population is small. More women received bariatric surgery than men. Second, the duration of the follow-up phase might not have been long enough. Third, a type 2 statistical error might occur due to the selected study populations. Furthermore, the liver function of the patients was not thoroughly investigated, which might affect the results of the hepassocin level. Differential regulation of bile acid and FGF 19 has been recently demonstrated in T2DM remission and fatty liver improvement after SG [23]. The importance of glucagon-like peptide-1 has been elucidated after bariatric surgery [6]. Due to focusing discussion, we did not include bile acids, FGF 19, and glucagon-like peptide-1 in the current study [24]. Last but not least, the single-centered, open-labeled nature of the study is a limitation as well.

To sum up, real-world data of clinical use of hepassocin is still limited. To our knowledge, this is the first study regarding changes in hepassocin levels in obese T2DM patients undergoing any of the three different types of bariatric surgery: mini-GB, SG, and DJB-SG. To date, bariatric surgery has been widely accepted as an essential management procedure for body weight and glycemic control, and the reduction of cardiovascular morbidity and mortality in obese patients with T2DM [4,25–27]. However, hepassocin levels did not change significantly after any of the three types of bariatric surgery. The possible use of hepassocin as a therapeutic marker requires more investigation.

Author Contributions: Conceptualization, C.-Y.C.; investigation, W.-J.L, S.-C.C., and C.-Y.C.; project administration, C.Y. and C.-Y.C.; operation, W.-J.L.; writing—original draft preparation, W.-C.W. and C.-Y.C.; writing—review and editing: W.-C.W. and C.-Y.C. W.-C.W. and C.Y. contributed equally to this work.

Funding: This work was supported with grants awarded by the Min-Sheng General Hospital, Taoyuan, the Taiwan Ministry of Science and Technology (MOST 104-2314-B-010-005-) and the Cheng Hsin General Hospital-National Yang-Ming University Joint Research Program (CY10517, CY10618, CY10717 and CY10824) in Taipei, Taiwan.

Acknowledgments: We sincerely acknowledge the grants from the Min-Sheng General Hospital, the Taiwan Ministry of Science and Technology, and the Cheng Hsin General Hospital–National Yang-Ming University Joint Research Program. Parts of the content have been invited to be presented at The 24th World International Federation for the Surgery of Obesity and Metabolic Disorders (IFSO) Congress held in Madrid, Spain, on September 5, 2019. We would like to thank the Clinical Research Core Laboratory of Taipei Veterans General Hospital for providing experimental space and facilities.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Zheng, Y.; Ley, S.H.; Hu, F.B. Global aetiology and epidemiology of type2 diabetes mellitus and its complications. *Nat. Rev. Endocrinol.* **2018**, *14*, 88–98. [CrossRef] [PubMed]
2. Chan, J.M.; Rimm, E.B.; Colditz, G.A.; Stampfer, M.J.; Willett, W.C. Obesity, fatdistribution, and weight gain as risk factors for clinical diabetes in men. *Diabetes Care* **1994**, *17*, 961–969. [CrossRef] [PubMed]
3. Colditz, G.A.; Willett, W.C.; Stampfer, M.J.; Manson, J.E.; Hennekens, C.H.; Arky, R.A.; Speizer, F.E. Weight as a risk factor for clinical diabetes in women. *Am. J. Epidemiol.* **1990**, *132*, 501–513. [CrossRef]

4. Maggard-Gibbons, M.; Maglione, M.; Livhits, M.; Ewing, B.; Maher, A.R.; Hu, J.; Li, Z.; Shekelle, P.G. Bari atric surgery forweight loss and glycemic control in nonmorbidly obese adults with diabetes: Asystematic review. *JAMA* **2013**, *309*, 2250–2261. [CrossRef] [PubMed]
5. Lee, W.J.; Almulaifi, A.; Tsou, J.J.; Ser, K.H.; Lee, Y.C.; Chen, S.C. Laparoscopic sleeve gastrectomy for type 2 diabetes mellitus: Predicting the success by ABCD score. *Surg. Obes. Relat. Dis.* **2015**, *11*, 991–996. [CrossRef] [PubMed]
6. Lee, W.J.; Chen, C.Y.; Chong, K.; Lee, Y.C.; Chen, S.C.; Lee, S.D. Changes in postprandial gut hormones after metabolic surgery: A comparison of gastric bypass and sleeve gastrectomy. *Surg. Obes. Relat. Dis.* **2011**, *7*, 683–690. [CrossRef]
7. Huang, C.K.; Tai, C.M.; Chang, P.C.; Malapan, K.; Tsai, C.C.; Yolsuriyan wong, K. Loop duodenojejunal bypass with sleeve gastrectomy: Comparative study with Roux-en-Y gastric bypass in type 2 diabetic patients with a BMI <35 kg/m(2), first year results. *Obes. Surg.* **2016**, *26*, 2291–2301.
8. Zachariah, P.J.; Chen, C.Y.; Lee, W.J.; Chen, S.C.; Ser, K.H.; Chen, J.C.; Lee, Y.C. Compared to sleeve gastrectomy, duodenal-jejunal bypass with sleeve gastrectomy gives better glycemic control in T2DM patients, with a lower β-cell response and similar appetite sensations:mixed-meal study. *Obes. Surg.* **2016**, *26*, 2862–2872. [CrossRef]
9. Iroz, A.; Couty, J.P.; Postic, C. Hepatokines: Unlocking the multi-organ network in metabolic diseases. *Diabetologia* **2015**, *58*, 1699–1703. [CrossRef]
10. Lu, F.H.; Ou, H.Y.; Wu, H.T.; Hung, H.C.; Yang, Y.C.; Chang, C.J. Serum hepassocin concentrations in diabeticpatients with or without nonalcoholic fatty liver disease. *Diabetes Manag.* **2014**, *4*, 255–261. [CrossRef]
11. Wu, H.T.; Ou, H.Y.; Hung, H.C.; Su, Y.C.; Lu, F.H.; Wu, J.S.; Yang, Y.C.; Wu, C.L.; Chang, C.J. Anovelhepatokine, HFREP1, plays a crucial role in the development of insulin resistance and type 2 diabetes. *Diabetologia* **2016**, *59*, 1732–1742. [CrossRef] [PubMed]
12. Ou, H.Y.; Wu, H.T.; Lin, C.H.; Du, Y.F.; Hu, C.Y.; Hung, H.C.; Wu, P.; Li, H.Y.; Wang, S.H.; Chang, C.J. The hepatic protection effects of hepassocinin hyperglycemic crisis. *J. Clin. Endocrinol. Metab.* **2017**, *102*, 2407–2415. [CrossRef] [PubMed]
13. Jimenez, V.; Jambrina, C.; Casana, E.; Sacristan, V.; Muñoz, S.; Darriba, S.; Rodó, J.; Mallol, C.; Garcia, M.; León, X.; et al. FGF21 gene therapy as treatment forobesity and insulin resistance. *EMBO Mol. Med.* **2018**, *10*, e8791. [CrossRef] [PubMed]
14. Lee, W.J.; Hur, K.Y.; Lakadawala, M.; Kasama, K.; Wong, S.K.; Chen, S.C.; Lee, Y.C.; Ser, K.H. Predicting success of metabolic surgery: Age, body mass index, C-peptide, and duration score. *Surg. Obes. Relat. Dis.* **2013**, *9*, 379–384. [CrossRef]
15. Huang, H.H.; Yeh, C.; Chen, J.C.; Lee, T.H.; Chen, S.C.; Lee, W.J.; Chen, C.Y. Does bariatric surgery influence plasma levels of fetuin-A and leukocyte cell-derived chemotaxin-2 in patients with type 2 diabetes mellitus? *PeerJ* **2018**, *6*, e4884. [CrossRef]
16. Lee, W.J.; Lee, K.T.; Kasama, K.; Seiki, Y.; Ser, K.H.; Chun, S.C.; Chen, J.C.; Lee, Y.C. Laparoscopic single-anastomosis duodenal-jejunal bypass with sleeve gastrectomy (SADJB-SG): Short-term result and comparison with gastric bypass. *Obes. Surg.* **2014**, *24*, 109–113. [CrossRef]
17. Bertoli, S.; Leone, A.; Krakauer, N.Y.; Bedogni, G.; Vanzulli, A.; Redaelli, V.I.; DeAmicis, R.; Vignati, L.; Krakauer, J.C.; Battezzati, A. Association of body shape index (ABSI) with cardio-metabolic risk factors: A cross-sectional study of 6081 Caucasian adults. *PLoS ONE* **2017**, *12*, e0185013. [CrossRef]
18. Lautt, W.W. The HISS story overview: A novel hepatic neurohumoral regulationof peripheral insulin sensitivity in health and diabetes. *Can. J. Physiol. Pharmacol.* **1999**, *77*, 553–562. [CrossRef]
19. Petersen, K.F.; Tygstrup, N. A liver factor increasing glucose uptake in rathindquarters. *J. Hepatol.* **1994**, *20*, 461–465. [CrossRef]
20. Hwang, J.H.; Stein, D.T.; Barzilai, N.; Cui, M.H.; Tonelli, J.; Kishore, P.; Hawkins, M. Increased intrahepatic triglyceride is associated with peripheral insulin resistance: In vivo MR imaging and spectroscopy studies. *Am. J. Physiol. Endocrinol. Metab.* **2007**, *293*, E1663–E1669. [CrossRef]
21. Wu, H.T.; Lu, F.H.; Ou, H.Y.; Su, Y.C.; Hung, H.C.; Wu, J.S.; Yang, Y.C.; Wu, C.L.; Chang, C.J. The role of hepassocin in the development of non-alcoholic fatty liver disease. *J. Hepatol.* **2013**, *59*, 1065–1072. [CrossRef] [PubMed]
22. Krakauer, N.Y.; Krakauer, J.C. A new body shape index predicts mortality hazard independently of body mass index. *PLoS ONE* **2012**, *7*, e39504. [CrossRef] [PubMed]

23. Huang, H.H.; Lee, W.J.; Chen, S.C.; Chen, T.F.; Lee, S.D.; Chen, C.Y. Bile acid and fibroblast growth factor 19 regulation in obese diabetics, and non-alcoholic fatty liver disease after sleeve gastrectomy. *J. Clin. Med.* **2019**, *8*, E815. [CrossRef] [PubMed]
24. Condello, G.; Chen, C.Y. Fostering the acupuncture practice for health outcomes research: The perspective from Taiwan. *J. Chin. Med. Assoc.* **2019**, *82*, 603–604. [CrossRef]
25. Schauer, P.R.; Kashyap, S.R.; Wolski, K.; Brethauer, S.A.; Kirwan, J.P.; Pothier, C.E.; Thomas, S.; Abood, B.; Nissen, S.E.; Bhatt, D.L. Bariatric surgery versus intensive medical therapy in obese patients with diabetes. *N. Engl. J. Med.* **2012**, *366*, 1567–1576. [CrossRef]
26. Sandoval, D.A. Mechanisms for the metabolic success of bariatric surgery. *J.Neuroendocr.* **2019**, *31*, e12708. [CrossRef]
27. Dixon, J.B.; Zimmet, P.; Alberti, K.G.; Rubino, F. International diabetes federation task force on epidemiology and prevention. Bariatric surgery: An IDF statement for obese type 2 diabetes. *Surg. Obes. Relat. Dis.* **2011**, *7*, 433–447. [CrossRef]