Available online at www.sciencedirect.com
ScienceDirect
Metabolism Clinical and Experimental 58 (2009) 1400–1407
Metabolism
Clinical and Experimental
www.metabolismjournal.com

Serum bile acid along with plasma incretins and serum high–molecular weight adiponectin levels are increased after bariatric surgery

Hiroshi Nakatani[a], Kazunori Kasama[b], Takashi Oshiro[b], Mitsuhiro Watanabe[a], Hiroshi Hirose[a,c,*], Hiroshi Itoh[a]

[a]*Department of Internal Medicine, Keio University School of Medicine, Tokyo 160-8582, Japan*
[b]*Yotsuya Medicalcube Hospital, Tokyo 102-0084, Japan*
[c]*Health Center, Keio University, Tokyo 160-8582, Japan*

Received 24 February 2009; accepted 7 May 2009

Abstract

Bariatric surgery has been shown to improve glucose tolerance, although the mechanism has not been fully elucidated. Animal studies have suggested important roles of bile acid (BA) as a regulator of energy homeostasis and glucose metabolism. However, little is known about its role in humans. We investigated the longitudinal changes of BA, incretins, and adipokines after significant weight reduction in 34 Japanese adults with morbid obesity who underwent laparoscopic bariatric surgery. In subjects who underwent malabsorptive or restrictive surgery, body mass index had markedly decreased from 43.0 ± 6.5 (SD) to 37.8 ± 5.7 kg/m^2 and from 45.3 ± 11.2 to 41.5 ± 10.5 kg/m^2, respectively, at 1 month after surgery. Glycated hemoglobin decreased from 6.1% ± 1.5% to 5.2% ± 0.4% and from 6.2% ± 1.3% to 5.4% ± 0.7%, and total BA level increased from 3.1 ± 3.5 to 7.2 ± 5.3 μmol/L and from 3.2 ± 2.6 to 9.4 ± 10.0 μmol/L, respectively. At baseline, serum concentration of primary BA was positively correlated with plasma gastric inhibitory polypeptide level (r = 0.548, P = .001); and change in primary BA level was positively correlated with changes in plasma gastric inhibitory polypeptide (r = 0.626, P = .001) and serum immunoreactive insulin level (r = 0.592, P = .002) at 1 month after surgery. Furthermore, plasma glucagon-like peptide–1 and serum high–molecular weight adiponectin levels increased in both surgeries. These hormonal changes might explain the mechanism(s) of improved glucose tolerance after bariatric surgery in morbidly obese subjects.

1. Introduction

Type 2 diabetes mellitus (T2DM) is a major global health problem, causing a number of complications including microangiopathy and cardiovascular disease. It is now clear that strict control of hyperglycemia in patients with T2DM can attenuate the development of such complications. At present, several hypoglycemic agents are available, such as sulfonylureas, metformin, thiazolidinediones, α-glucosidase inhibitors, and insulin. Because these agents are mainly intended to reduce hyperglycemia itself and have limited efficacy, further approaches are needed for the treatment of T2DM.

One of the most important contributors to the pathogenesis of T2DM is obesity. In patients with morbid obesity, bariatric surgery is currently the most effective treatment to achieve long-term weight reduction. It is also reported that long-term total mortality is significantly reduced after gastric bypass surgery, particularly death from heart disease, cancer, and diabetes [1,2]. Most interestingly, resolution of T2DM has been reported after bariatric surgery [3]; and amelioration of glycemic control often occurs before significant weight reduction [4], suggesting that the improvement in glycemic control might be related to a direct effect of bariatric surgery rather than weight reduction. A clear understanding of the short-term improvement in glycemic control after bariatric surgery might lead to a new strategy for the treatment of T2DM. It has been proposed that the incretins [5] and/or adiponectin [6] may be key mediators of the antidiabetic effects of bariatric surgery. However, the mechanism has not been fully elucidated.

* Corresponding author. Department of Internal Medicine, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan. Tel.: +81 (3) 3353 1211; fax: +81 (3) 5269 3219.
E-mail address: hhirose@hc.cc.keio.ac.jp (H. Hirose).

0026-0495/$ – see front matter © 2009 Elsevier Inc. All rights reserved.
doi:10.1016/j.metabol.2009.05.006

Recently, we have reported that bile acid (BA) lowers the triglyceride (TG) level [7] and, moreover, induces energy expenditure by promoting intracellular thyroid hormone activation in mice [8]. Although BA has long been known to be essential for dietary lipid absorption and cholesterol catabolism, an important role of BA as a regulator of energy homeostasis has emerged. We hypothesized that bariatric surgery might change the concentration of BA and that this may be related to the mechanism for amelioration of T2DM, at least in part.

The purpose of the present study was to clarify the association between BA and metabolic parameters. We measured serum BA concentration in 34 patients with morbid obesity and investigated its correlation with metabolic parameters, adipokines, and incretins. Furthermore, we studied the longitudinal change in BA, adipokines, and incretins after laparoscopic bariatric surgery.

2. Methods

2.1. Subjects

Sixteen male and 18 female morbidly obese patients (aged 39 ± 9 years) undergoing laparoscopic bariatric surgery at Yotsuya Medicalcube Hospital (Tokyo, Japan) were recruited. We defined laparoscopic Roux-en-Y gastric bypass surgery (LRYGB) and laparoscopic sleeve gastrectomy with duodenal jejunal bypass surgery (LSG/DJB) as *malabsorptive procedures* (MP), and laparoscopic sleeve gastrectomy (LSG) and laparoscopic adjustable gastric

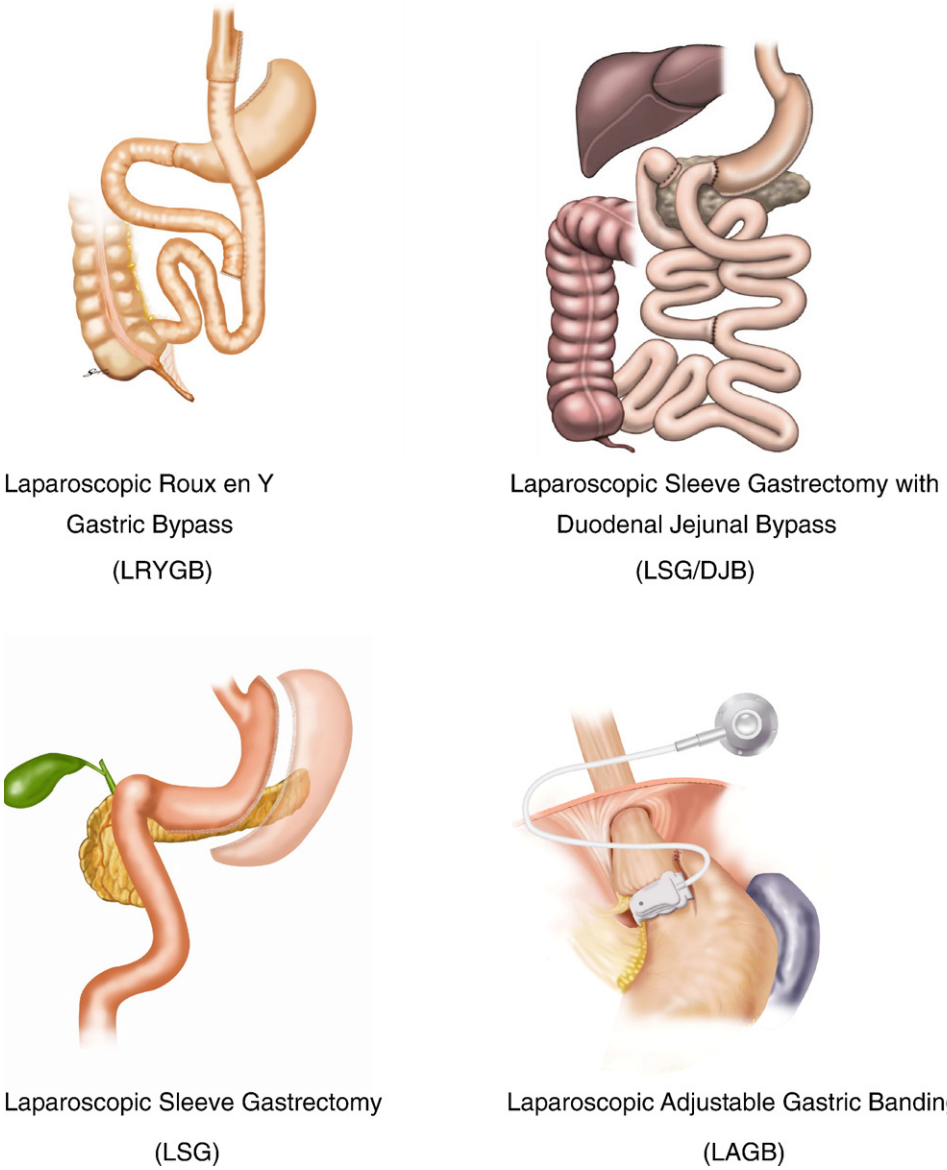

Fig. 1. Procedures of laparoscopic bariatric surgery: LRYGB and LSG/DJB were defined as *MP*, and LSG and LAGB were defined as *RP*.

banding (LAGB) as *restrictive procedures* (RP). Four men and 15 women (aged 36 ± 7 years) underwent MP surgery, and 12 men and 3 women (aged 42 ± 10 years) underwent RP surgery. In patients undergoing MP, 3 subjects had normal glucose tolerance, 12 had impaired glucose tolerance (IGT), and 4 had T2DM. In patients undergoing RP, 5 subjects had normal glucose tolerance, 5 had IGT, and 5 had T2DM. Patients were studied before and 1 and 3 months after surgery.

The present study was conducted according to the principles expressed in the Declaration of Helsinki. Informed consent was obtained from each subject after a full explanation of the purpose, procedures, and risks of the study. The protocol was approved by the ethics review committee of Yotsuya Medicalcube Hospital (Tokyo, Japan).

2.2. Laparoscopic bariatric surgery (Fig. 1)

The protocol of each surgery is described by Kasama et al [9]. In brief, 13 patients underwent LRYGB with a 15-mL gastric pouch, 50- to 100-cm afferent limb, and 120- to 200-cm Roux limb. Six patients underwent LSG/DJB, which is an alternative procedure to LRYGB for patients at risk of remnant gastric cancer, such as those with *Helicobacter pylori* infection or a family history of gastric cancer. After performing LSG, DJB with 50 to 100 cm of afferent limb and 150 to 200 cm of Roux limb was done. Nine patients underwent LSG, and 6 patients underwent LAGB.

Table 1
Baseline clinical characteristics of 34 patients and correlation coefficients (r) with BA

	Mean ± SD	r with BA		r with primary BA	
		r	P	r	P
Age (y)	39 ± 9	0.163	NS	0.123	NS
Height (cm)	165.9 ± 10.3	−0.045	NS	0.052	NS
Body weight (kg)	122.2 ± 31.0	−0.040	NS	−0.080	NS
BMI (kg/m^2)	44.0 ± 8.8	−0.014	NS	−0.117	NS
FPG (mg/dL)[a]	122 ± 58	−0.063	NS	−0.069	NS
Insulin (μU/mL)[a]	20.8 ± 13.8	0.196	NS	0.156	NS
HOMA-IR[a]	6.3 ± 4.9	0.175	NS	0.192	NS
HbA_{1c} (%)	6.2 ± 1.4	−0.139	NS	−0.102	NS
LDL-C (mg/dL)	128 ± 32	0.070	NS	0.109	NS
HDL-C (mg/dL)	48 ± 10	0.124	NS	0.036	NS
TG (mg/dL)[a]	162 ± 185	−0.071	NS	0.033	NS
Leptin (ng/mL)[a]	30.8 ± 15.8	0.029	NS	−0.034	NS
Adiponectin (μg/mL)[a]	3.2 ± 2.7	−0.250	NS	−0.323	.06
GLP-1 (pmol/L)[a]	3.1 ± 2.3	0.190	NS	0.200	NS
GIP (pg/mL)[a]	43.0 ± 28.0	0.548	.001	0.616	<.001
Ghrelin (fmol/mL)	1.9 ± 2.1	−0.101	NS	−0.127	NS
Total BA (μmol/L)[a]	3.2 ± 3.1	–	–	0.92	<.001
Primary BA (μmol/L)[a]	2.1 ± 2.5	0.92	<.001	–	–
Secondary BA (μmol/L)[a]	1.1 ± 0.9	0.746	<.001	0.466	.006

Data are expressed as mean ± SD. LDL-C indicates low-density lipoprotein cholesterol; NS, $P \geq .05$.
[a] Analyzed after logarithmic transformation.

Table 2
Longitudinal changes in various parameters before and after MP (n = 19) and RP (n = 15)

		Before surgery	1 mo after surgery		3 mo after surgery	
BMI (kg/m^2)	MP	43.0 ± 6.5	37.8 ± 5.7	†	34.9 ± 5.5	†
	RP	45.3 ± 11.2	41.5 ± 10.5	†	39.0 ± 10.4	†
FPG (mg/dL)[a]	MP	126 ± 67	106 ± 14		101 ± 11	*
	RP	117 ± 46	107 ± 26		114 ± 44	
Insulin (μU/mL)[a]	MP	18.9 ± 10.0	16.6 ± 10.1		9.1 ± 4.4	†
	RP	23.3 ± 17.5	20.0 ± 13.8		16.4 ± 15.0	
HOMA-IR[a]	MP	6.0 ± 4.7	4.4 ± 2.6		2.3 ± 1.2	†
	RP	6.6 ± 5.3	5.3 ± 3.8		4.6 ± 4.2	
HbA_{1c} (%)	MP	6.1 ± 1.5	5.2 ± 0.4	*	4.9 ± 0.3	†
	RP	6.2 ± 1.3	5.4 ± 0.7	*	5.5 ± 1.0	*
LDL-C (mg/dL)	MP	131 ± 35	122 ± 35		122 ± 40	
	RP	125 ± 28	118 ± 32		121 ± 24	
HDL-C (mg/dL)	MP	49 ± 12	41 ± 7	†	48 ± 10	
	RP	48 ± 7	42 ± 10	*	53 ± 12	*
TG (mg/dL)[a]	MP	190 ± 241	118 ± 56		92 ± 39	*
	RP	127 ± 60	124 ± 73		103 ± 67	*
Leptin (ng/mL)[a]	MP	36.7 ± 16.7	15.7 ± 9.0	†	12.7 ± 7.3	†
	RP	23.4 ± 11.3	15.6 ± 13.1	†	16.0 ± 13.1	†
Adiponectin (μg/mL)[a]	MP	3.3 ± 3.3	5.6 ± 4.1	†	5.8 ± 2.9	†
	RP	3.2 ± 1.9	4.3 ± 1.7	†	5.8 ± 2.1	†
GLP-1 (pmol/L)[a]	MP	2.8 ± 1.9	4.5 ± 3.2	*	4.5 ± 2.4	†
	RP	3.4 ± 2.7	5.1 ± 3.1	*	6.1 ± 6.1	*
GIP (pg/mL)[a]	MP	48.4 ± 31.2	57.1 ± 45.2		58.3 ± 42.6	
	RP	36.1 ± 22.5	88.4 ± 54.1	†	71.7 ± 52.5	†
Ghrelin (fmol/mL)	MP	2.2 ± 2.9	2.0 ± 1.8		1.7 ± 0.9	
	RP	1.5 ± 0.0	1.5 ± 0.0		1.5 ± 0.0	
Total BA (μmol/L)[a]	MP	3.1 ± 3.5	7.5 ± 5.3	†	9.0 ± 9.0	*
	RP	3.2 ± 2.6	9.4 ± 10.0	*	12.6 ± 19.0	†
Primary BA (μmol/L)[a]	MP	2.2 ± 2.9	2.8 ± 2.1		4.5 ± 4.5	*
	RP	2.0 ± 2.0	5.7 ± 5.8	*	6.5 ± 7.8	†
Secondary BA (μmol/L)[a]	MP	0.9 ± 0.9	4.7 ± 3.9	†	4.5 ± 6.8	
	RP	1.2 ± 1.0	3.6 ± 4.5	†	6.0 ± 11.7	†

Data are expressed as mean ± SD.
[a] Analyzed after logarithmic transformation.
* $P < .05$ by general linear models for repeated-measurements design.
† $P < .005$ by general linear models for repeated-measurements design.

2.3. Clinical variables

Height was measured to the nearest 0.1 cm. Weight was measured in light indoor clothing with shoes removed. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared.

2.4. Biochemical measurements

All patients were asked to fast overnight before blood sampling. Fasting plasma glucose (FPG) and lipids were assayed by routine automated laboratory methods. Serum immunoreactive insulin (IRI) was measured by an enzyme immunoassay using a commercially available kit. The insulin resistance index was calculated based on homeostasis model assessment (HOMA-IR). Total, primary, and secondary BA levels were calculated from BA components measured by high-performance liquid chromatography.

Serum high–molecular weight (HMW) adiponectin level was measured with a commercially available enzyme-linked immunosorbent assay (ELISA) kit (Fujirebio, Tokyo, Japan) [10] with intra- and interassay coefficients of 4.8% to 4.9% and 3.3% to 6.8%, respectively. Serum leptin level was measured using a radioimmunoassay kit (Linco Research, St Charles, MO) with intra- and interassay coefficients of 3.4% to 8.3% and 3.0% to 6.2%, respectively. Plasma active glucagon-like peptide–1 (GLP-1) level was measured with an ELISA kit (Linco Research) with intra- and interassay coefficients of 6% to 9% and 1% to 13%, respectively. Plasma gastric inhibitory peptide (GIP) level was measured using an ELISA kit (Linco Research) with intra- and interassay coefficients of 3.0% to 8.8% and 1.8% to 6.1%, respectively. To measure GLP-1 and GIP, dipeptidyl peptidase–4 inhibitor had been added to sample collection tubes. Plasma ghrelin level was also measured with an ELISA kit (Mitsubishi Kagaku Iatron, Tokyo, Japan).

Before surgery, a standard 75-g oral glucose tolerance test was performed in each patient to assess the glycemic status.

2.5. Statistical analysis

All statistical analyses were performed using the SPSS program for Windows (version 13.0; SPSS, Chicago, IL). Relationships among metabolic and endocrine parameters at baseline and changes in parameters after surgery were analyzed by simple correlations. General linear models for repeated-measurements design were used to compare parameters before and 1 and 3 months after surgery and to compare differences in longitudinal changes in parameters between MP and RP. Because IRI, HOMA-IR, TG, HMW adiponectin, leptin, GLP-1, GIP, and BA levels were normally distributed after log-transformation, the logarithms of these data were used for analysis. All data are expressed as mean ± SD unless otherwise specified, and P less than .05 was considered statistically significant.

3. Results

3.1. Baseline clinical characteristics and relationships between BA and clinical parameters

Relationships between BA and anthropometric and metabolic parameters, adipokines, and incretins in the 34 patients are shown in Table 1. Serum total BA level was 3.2 ± 3.1 μmol/L (range, 0.4-15.5 μmol/L). Total and primary BA levels were positively correlated with plasma GIP level. These correlations were significant even after adjustment for BMI (r = 0.549, P = .001 and r = 0.613, P < .001, respectively).

Among endocrine parameters measured, HMW adiponectin was negatively correlated with both HOMA-IR (r = −0.395, P = .021) and TG (r = −0.530, P = .001), and was positively correlated with high-density lipoprotein cholesterol (HDL-C) (r = 0.425, P = .012). Neither GLP-1 nor GIP was correlated with IRI or other metabolic parameters.

3.2. Longitudinal changes in parameters after surgery and comparison between MP and RP

Changes in BMI and metabolic parameters, adipokines, and incretins in the 34 patients who underwent bariatric surgery are shown in Table 2. Differences in longitudinal changes in parameters between MP and RP are shown in Fig. 2.

At both 1 and 3 months after surgery, BMI and glycated hemoglobin (HbA_{1c}) had significantly decreased with both procedures; and a greater decrease in BMI was observed with MP. Immunoreactive insulin and HOMA-IR were significantly decreased 3 months after MP, but did not significantly decrease after RP.

Leptin had significantly decreased 1 and 3 months after surgery with both procedures, and a greater decrease was observed with MP. High–molecular weight adiponectin had significantly increased 1 and 3 months after both procedures.

At both 1 and 3 months after surgery, total BA had significantly increased with both procedures; and primary BA had significantly increased 3 months after both procedures. No significant difference in BA was observed between the procedures. Similarly, GLP-1 had significantly increased 1 and 3 months after both procedures; but no significant difference was observed between the procedures. GIP had increased 1 and 3 months after surgery with RP, but did not show a significant change with MP.

3.3. Relationships among changes in metabolic and endocrine parameters after surgery

Relationships among changes in metabolic and endocrine parameters at 1 and 3 months after surgery are shown in Table 3. Change in primary BA was positively correlated with change in GIP at both 1 (r = 0.626, P = .001) and 3 months (r = 0.540, P = .004) after surgery. These correlations were significant even after adjustment for change in BMI (r = 0.628, P = .001 and r = 0.552, P = .004, respectively). Change in primary BA was positively correlated with change in IRI at 1 month after surgery (r = 0.592, P = .002), but did not correlate at 3 months after surgery. Change in GIP was also positively correlated with change in IRI 1 month after surgery (r = 0.574, P = .003), but did not correlate at 3 months after surgery. No significant relationship was observed between change in BA and change in FPG or HbA_{1c} either at 1 or 3 months after surgery.

Change in HMW adiponectin was negatively correlated with change in BMI (r =−0.419, P = .033), IRI (r = −0.465, P = .019), HOMA-IR (r = −0.516, P = .008), HbA_{1c} (r = −0.396, P = .045), and TG (r = −0.648, P < .001) and was positively correlated with change in HDL-C (r = 0.440, P = .025) at 3 months after surgery. Furthermore, these correlations with changes in HOMA-IR and TG were still

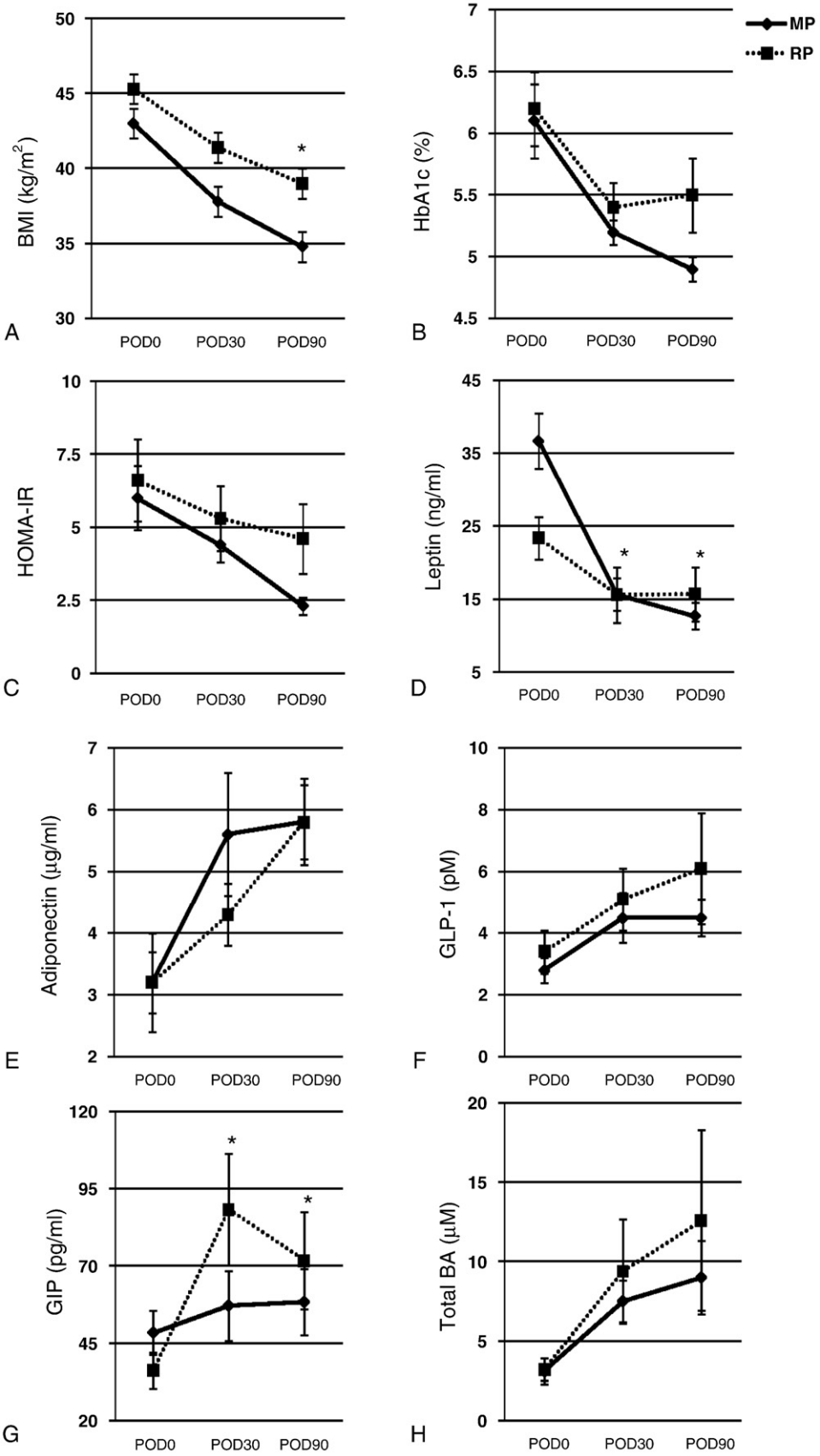
MP
RP
A
BMI (kg/m2)
50
45
40
35
30
POD0
POD30
POD90
*
B
HbA1c (%)
7
6.5
6
5.5
5
4.5
C
HOMA-IR
10
7.5
5
2.5
0
D
Leptin (ng/ml)
45
35
25
15
5
E
Adiponectin (μg/ml)
7
6
5
4
3
2
F
GLP-1 (pM)
10
8
6
4
2
0
G
GIP (pg/ml)
120
95
70
45
20
H
Total BA (μM)
20
15
10
5
0

Table 3
Relationships among changes in metabolic and endocrine parameters 1 month (A) and 3 months (B) after surgery

(A)

	r with Δ primary BA		r with Δ adiponectin		r with Δ GLP-1		r with Δ GIP	
	r	P	r	P	r	P	r	P
Δ BMI	−0.149	NS	−0.169	NS	−0.218	NS	−0.036	NS
Δ FPG[a]	0.306	NS	−0.059	NS	0.082	NS	0.425	.034
Δ IRI[a]	0.592	.002	−0.27	NS	0.23	NS	0.574	.003
Δ HOMA-IR[a]	0.607	.001	−0.253	NS	0.225	NS	0.624	.001
Δ HbA_{1c}	0.317	NS	−0.105	NS	0.191	NS	0.391	NS
Δ LDL-C	0.468	.018	−0.224	NS	−0.071	NS	0.075	NS
Δ HDL-C	0.105	NS	−0.144	NS	−0.202	NS	0.043	NS
Δ TG[a]	0.375	NS	−0.143	NS	0.226	NS	0.356	NS
Δ Leptin[a]	0.266	NS	−0.298	NS	0.156	NS	0.609	.001
Δ Primary BA[a]	–		−0.308	NS	0.058	NS	0.626	.001
Δ Adiponectin[a]	−0.308	NS	–		0.420	.037	−0.118	NS
Δ GLP-1[a]	0.058	NS	0.420	.037	–		0.366	NS
Δ GIP[a]	0.626	.001	−0.118	NS	0.366	NS	–	

(B)

	r with Δ primary BA		r with Δ adiponectin		r with Δ GLP-1		r with Δ GIP	
	r	P	r	P	r	P	r	P
Δ BMI	0.065	NS	−0.491	.033	−0.292	NS	0.319	NS
Δ FPG[a]	−0.126	NS	−0.276	NS	0.459	.018	−0.005	NS
Δ IRI[a]	0.157	NS	−0.465	.019	0.316	NS	0.376	NS
Δ HOMA-IR[a]	0.097	NS	−0.516	.008	0.446	.026	0.346	NS
Δ HbA_{1c}	−0.126	NS	−0.396	.045	0.295	NS	0.110	NS
Δ LDL-C	−0.020	NS	−0.077	NS	−0.221	NS	−0.034	NS
Δ HDL-C	0.148	NS	−0.006	NS	−0.130	NS	0.44	.025
Δ TG[a]	−0.003	NS	−0.648	<.001	−0.002	NS	0.182	NS
Δ Leptin[a]	0.114	NS	−0.498	.008	0.081	NS	0.250	NS
Δ Primary BA[a]	–		−0.231	NS	0.067	NS	0.540	.004
Δ Adiponectin[a]	−0.231	NS	–		−0.006	NS	−0.321	NS
Δ GLP-1[a]	0.067	NS	−0.006	NS	–		0.129	NS
Δ GIP[a]	0.540	.004	−0.321	NS	0.129	NS	–	

[a] Analyzed after logarithmic transformation.

significant after adjustment for change in BMI ($r = -0.454$, $P = .026$ and $r = -0.581$, $P = .003$, respectively).

4. Discussion

In this study, we have shown that (1) serum BA, serum HMW adiponectin, and plasma GLP-1 levels were increased after both MP and RP; (2) plasma GIP level increased after RP; (3) serum primary BA level was positively correlated with plasma GIP level, and the change in BA level after surgery was positively correlated with the changes in GIP level (at both 1 and 3 months) and IRI (at 1 month) after surgery; and (4) the change in HMW adiponectin was negatively correlated with the change in HOMA-IR after adjustment for the change in BMI.

We showed that the serum level of BA was increased after bariatric surgery in the present study. In patients who underwent MP, alteration of enterohepatic circulation of BA might have a role in the increase in BA level after surgery: BA is synthesized in the liver and released into the small intestine, and most BA is reabsorbed at the terminal ileum and returned to the liver. Malabsorptive procedures might decrease the enterohepatic circulation of BA, followed by increased conversion of cholesterol to BA. We do not know, however, the mechanism of the increased level of BA in RP, although there is a possibility that decreased intake of cholesterol after surgery might increase cholesterol biosynthesis and accelerate conversion of cholesterol to BA.

Next, we showed that the plasma level of GLP-1 increased after both MP and RP and that GIP increased

Fig. 2. Longitudinal changes in BMI, HbA_{1c}, and endocrine parameters after MP and RP: BMI (A), HbA_{1c} (B), HOMA-IR (C), leptin (D), adiponectin (E), GLP-1 (F), GIP (G), and total BA (H). Data are expressed as mean ± SE. Endocrine parameters and HOMA-IR were analyzed after log-transformation. *$P < .05$ for changes in parameters between MP and RP by general linear models for repeated-measurements design. POD indicates postoperation day.

after RP. GLP-1 is an incretin hormone that stimulates insulin secretion and suppresses glucagon secretion, inhibits gastric emptying, and reduces appetite and food intake. Clinical trials with the incretin mimetics exenatide and liraglutide showed a reduction in HbA_{1c} by 1% to 2% [11]. Previous studies have shown that bariatric surgery was accompanied by improvement of glycemic control and an increased level of GLP-1. Guidone et al [12] have reported an increase in fasting and glucose-stimulated GLP-1, as well as improvement of insulin sensitivity and β-cell glucose sensitivity after biliopancreatic diversion. Our results are in line with those of the previous reports. The mechanism by which GLP-1 level increases after bypass surgery is not fully elucidated, but could be explained by the following mechanism: After gastric bypass, the distal ileum, where most of the GLP-1–secreting enteroendocrine L cells exist, might be rapidly and directly exposed to ingested nutrients; and GLP-1 secretion might increase. However, the reason for the increased GLP-1 level in RP remains unclear. Verdich et al [13] have reported that weight reduction by a low-calorie diet increased GLP-1 level; and GLP-1 might be affected by weight reduction itself, although Laferrere et al [14] have reported that diet-induced weight reduction did not increase fasting or stimulated GLP-1 level. This discrepancy might be related to subject characteristics: Our study subjects included not only those with T2DM, but also those with IGT and normal glucose tolerance; and the study subjects of Verdich et al did not include patients with T2DM. On the other hand, the study subjects of Laferrere et al included only T2DM patients. In our study, the sample size was too small to separate the subjects by glycemic status.

Contrary to GLP-1, reported data on GIP level after bariatric surgery are inconsistent, showing either a decrease [15] or an increase [16]. In the present study, GIP level increased only with RP; and this might be related to weight reduction. Verdich et al [13] also showed that weight reduction by a low-calorie diet increased GIP secretion. In patients who undergo MP, ingested nutrients might bypass the proximal small intestine where many of the GIP-secreting K cells exist; and GIP secretion does not increase. Interestingly, we showed that BA level was positively correlated with GIP level before surgery; and we also showed a positive correlation between changes in BA and GIP levels at 1 and 3 months after surgery. Furthermore, we showed a positive correlation between changes in BA level and IRI 1 month after surgery. Our findings suggest that BA might enhance GIP secretion, which in turn would increase insulin secretion. Change in BA, however, was not associated with change in IRI at 3 months after surgery. This may have been due to the marked improvement in insulin sensitivity due to considerable weight reduction 3 months after surgery. Although Katsuma et al [17] have reported that BA promoted GLP-1 secretion through a G protein–coupled receptor, TGR5, in a murine enteroendocrine cell line, there is no report that showed BA stimulates GIP secretion. Further studies will be needed to clarify this issue.

Previously, we showed that BA lowers the TG level via a pathway involving the farnesoid X receptor, short heterodimer partner, and sterol regulatory element–binding protein–1c [7], and increases energy expenditure in brown adipose tissue by inducing a cyclic adenosine monophosphate–dependent thyroid hormone–activating enzyme, type 2 iodothyronine deiodinase, preventing obesity and insulin resistance [8]. Although BA has been known to be essential for dietary lipid absorption and cholesterol catabolism, these findings indicate that BA has important roles as signaling molecules in glucose and lipid metabolism. In the present study, we showed that the serum level of BA was increased after bariatric surgery. Thus, our observations suggest that BA might have an important role as a regulator of energy and glucose homeostasis not only in mice, but also in humans. It has been reported that colesevelam HCl, a specifically engineered BA sequestrant, improves glycemic control in patients with T2DM receiving sulfonylurea [18] or insulin therapy [19]. These findings suggest that therapy aimed at modulating downstream pathways of BA might be effective to improve glycemic control. In the present study, however, we were not able to find a significant correlation between the change in BA level and that in HbA_{1c} value. There are several possible reasons: First, we investigated only the fasting state of the plasma BA level. Because the plasma concentration of BA increases after a meal [20], postprandial BA level might be more important. Second, the weight reduction after surgery was too dramatic to detect the effect of BA on glucose metabolism. Further investigations are needed to clarify these points.

We also showed that the serum level of HMW adiponectin increased after MP and RP. Among the many known adipokines, adiponectin plays a key role as an insulin-sensitizing cytokine. We [21] and other groups [22,23] have reported that serum adiponectin level was negatively correlated with adiposity variables and insulin resistance. Prospective studies have shown that a low adiponectin level predicts progression to type 2 diabetes mellitus [24,25] and cardiovascular disease [26]. Recent studies have revealed that the HMW form is the active form of adiponectin [25,27], so we measured HMW adiponectin in the present study. Swarbrick et al [6] have shown that HMW adiponectin concentration was increased 1 month after Roux-en-Y gastric bypass surgery, and our results are in line with this report. Among endocrine parameters measured in the present study, the change in HMW adiponectin level was negatively correlated with the changes in BMI, IRI, HOMA-IR, HbA_{1c}, and TG and was positively correlated with the change in HDL-C after surgery. Furthermore, correlations with changes in HOMA-IR and TG were still significant after adjustment for change in BMI. These observations support favorable effects of adiponectin on improved glucose metabolism after bariatric surgery, although no significant difference was observed concerning increase in adiponectin level between MP and RP.

A limitation of this study is that the sample size was small, and the sex ratio and glucose tolerance status differed between MP and RP.

To summarize, the present study showed that serum BA level, along with plasma incretins and serum HMW adiponectin levels, increased after bariatric surgery. It is suggested that these hormonal changes might explain the mechanism(s) of improved glucose tolerance after bariatric surgery in morbidly obese subjects. Further clinical and laboratory studies are needed to clarify the importance of BA in glucose metabolism in humans.

Acknowledgment

We are particularly grateful to all the individuals who participated in this study. This study was supported in part by research grants (to M.W. and H.H.) from the Ministry of Education, Culture, Sports, Science and Technology of Japan.

References

[1] Sjostrom L, Narbo K, Sjostrom CD, Karason K, Larsson B, Wedel H, et al. Effects of bariatric surgery on mortality in Swedish obese subjects. N Engl J Med 2007;357:741-52.

[2] Adams TD, Gress RE, Smith SC, Halverson RC, Simper SC, Rosamond WD, et al. Long-term mortality after gastric bypass surgery. N Engl J Med 2007;357:753-61.

[3] Buchwald H, Avidor Y, Braunwald E, Jensen MD, Prories W, Fahrbach K, et al. Bariatric surgery: systematic review and meta-analysis. JAMA 2004;292:1724-37.

[4] Mingrone G, DeGaetano A, Greco AV, Capristo E, Benedetti G, Castagneto M, et al. Reversibility of insulin resistance in obese diabetic patients: role of plasma lipids. Diabetologia 1997;40:599-605.

[5] Laferrere B, Heshka S, Wang K, Khan Y, McGinty J, Teixeira J, et al. Incretin levels and effect are markedly enhanced one month after Roux-en-Y gastric bypass surgery in obese patients with type 2 diabetes. Diabetes Care 2007;30:1709-16.

[6] Swarbrick MM, Austrheim-Smith TA, Stanhope KL, Van Loan MD, Ali MR, Wolfe BM, et al. Circulating concentrations of high-molecular-weight adiponectin are increased following Roux-en-Y gastric bypass surgery. Diabetologia 2006;49:2552-8.

[7] Watanabe M, Houten SM, Wang L, Moschetta A, Mangelsdorf DJ, Heyman RA, et al. Bile acids lower triglyceride levels via a pathway involving FXR, SHP, and SREBP-1c. J Clin Invest 2004;113:1408-18.

[8] Watanabe M, Houten SM, Mataki C, Christoffolete MA, Kim BW, Sato H, et al. Bile acids induce energy expenditure by promoting intracellular thyroid hormone activation. Nature 2006;439:484-9.

[9] Kasama K, Tagaya N, Kanahira E, Umezawa A, Kurosaki T, Oshiro T, et al. Has laparoscopic bariatric surgery been accepted in Japan? The experience of a single surgeon. Obes Surg 2008;18:1473-8.

[10] Nakano Y, Tajima S, Yoshimi A, Akiyama H, Tsushima M, Tanioka T, et al. A novel enzyme-linked immunosorbent assay specific for high-molecular-weight adiponectin. J Lipid Res 2006;47:1572-82.

[11] Drucker JD, Nauck MA. The incretin system: glucagon-like peptide–1 receptor agonists and dipeptidyl peptidase–4 inhibitors in type 2 diabetes. Lancet 2006;368:1696-705.

[12] Guidone C, Manco M, Valera-Mora E, Iaconelli A, Gniuli D, Mari A, et al. Mechanisms of recovery from type 2 diabetes after malabsorptive bariatric surgery. Diabetes 2006;55:2025-31.

[13] Verdich C, Toubro S, Buemann B, Madsen JL, Holst JJ, Astrup A. The role of postprandial releases of insulin and incretin hormones in meal-induced satiety—effect of obesity and weight reduction. Int J Obes 2001;25:1206-14.

[14] Laferrere B, Teixeira J, McGinty J, Tran H, Egger JR, Colarusso A, et al. Effect of weight loss by gastric bypass surgery versus hypocaloric diet on glucose and incretin levels in patients with type 2 diabetes. J Clin Endocrinol Metab 2008;93:2479-85.

[15] Clements RH, Gonzales QH, Long CI, Wittert G, Laws HL. Hormonal changes after Roux-en-Y gastric bypass for morbid obesity and the control of type-II diabetes mellitus. Am Surg 2004;70:1-4.

[16] Naslund E, Backman L, Holst JJ, Theodorsson E, Hellstrom PM. Importance of small bowel peptides for the improved glucose metabolism 20 years after jejuno-ileal bypass for obesity. Obes Surg 1998;8:253-60.

[17] Katsuma S, Hirasawa A, Tsujimoto G. Bile acids promote glucagon-like peptide–1 secretion through TGR5 in a murine enteroendocrine cell line STC-1. Biochem Biophys Res Commun 2005;329:386-90.

[18] Fonseca VA, Rosenstock J, Wang AC, Truitt KE, Jones MR. Colesevelam HCl improves glycemic control and reduces LDL cholesterol in patients with inadequately controlled type 2 diabetes on sulfonylurea-based therapy. Diabetes care 2008;31:1479-84.

[19] Goldberg RB, Fonseca VA, Truitt KE, Hones MR. Efficacy and safety of colesevelam in patients with type 2 diabetes mellitus and inadequate glycemic control receiving insulin-based therapy. Arch Intern Med 2008;168:1531-40.

[20] Everson GT. Steady-state kinetics of serum bile acids in healthy human subjects: single and dual isotope techniques using stable isotopes and mass spectrometry. J Lipid Res 1987;28:238-52.

[21] Yamamoto Y, Hirose H, Saito I, Tomita M, Taniyama M, Matsubara K, et al. Correlation of the adipocyte-derived protein adiponectin with insulin resistance index and serum high-density lipoprotein–cholesterol, independent of body mass index, in the Japanese population. Clin Sci 2002;103:137-42.

[22] Weyer C, Funahashi I, Tanaka S, Hotta K, Matsuzawa Y, Pratley RE, et al. Hypoadiponectinemia in obesity and type 2 diabetes: close association with insulin resistance and hyperinsulinemia. J Clin Endocrinol Metab 2001;86:1930-5.

[23] Tschritter O, Fritsche A, Thamer C, Haap M, Shirkavand F, Rahe S, et al. Plasma adiponectin concentrations predict insulin sensitivity of both glucose and lipid metabolism. Diabetes 2003; 52:239-43.

[24] Spranger J, Kroke A, Moehling M, Bergmann MM, Ritow M, Boeling H, Pfeiffer FH. Adiponectin and protection against type 2 diabetes mellitus. Lancet 2003;361:226-8.

[25] Nakashima R, Kamei N, Yamane K, Nakanishi S, Nakashima A, Kohno N. Decreased total and high molecular weight adiponectin are independent risk factors for the development of type 2 diabetes in Japanese-Americans. J Clin Endocrin Metab 2006;91: 3873-7.

[26] Pischon T, Girman CJ, Hotamisligil GS, Rifai N, Hu FB, Rimm EB. Plasma adiponectin levels and risk of myocardial infarction in men. JAMA 2004;291:1730-7.

[27] Hara K, Horikoshi M, Yamauchi T, Yago H, Miyazaki O, Ebinuma H, et al. Measurement of the high–molecular weight form of adiponectin in plasma is useful for the prediction of insulin resistance and metabolic syndrome. Diabetes Care 2006;29:1357-62.