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Abstract

Background: Numerous studies have shown that Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy (SG) differently affect metabolic disorders associated with obesity. While bariatric surgery has been shown to improve non-alcoholic fatty liver disease, very few studies have compared liver parameters after both procedures.

Objectives: To compare the evolution of liver parameters after SG and RYGB and their relationships with improvement of metabolic disorders.

Methods: Metabolic parameters and abdominal ultra-sonography (US) were recorded before and 1 year after bariatric surgery, in all patients who underwent SG or RYGB between 2004 and 2016 in our institution.

Setting: University Hospital, Colombes, France.

Results: 533 subjects (15% men, 43±11 yr) were analyzed, including 326 RYGB and 207 SG. Before surgery, body mass index (44.7±5.7 vs. 44.4±7.4 kg/m²) and metabolic parameters were not significantly different. One year after surgery, RYGB induced greater weight loss (31.9±7.7 vs 28.6±8.3 %, p<0.001). Metabolic parameters improved in both groups, but fasting insulin, LDL-cholesterol, C-reactive protein and ferritin were lower after RYGB (p<0.001). In contrast, transaminases were higher after RYGB as compared to SG (31.6±18.7 vs. 22.6±7.7 IU/l for alanine aminotransferase (ALT), p<0.001). The persistence of ALT > 34 IU/l (27% vs. 7% of subjects, p<0.001) was independent of the persistence of US steatosis (39% vs. 37% of subjects) one year after RYGB and SG, respectively.

Conclusion: Despite a greater improvement of metabolic disorders, RYGB has less beneficial effects on liver parameters as compared to SG. Further studies are required to define the mechanisms explaining these differences between both procedures.

Key words: obesity, bariatric surgery liver, NAFLD

Introduction

Bariatric surgery is currently the more efficient technique to treat severe obesity. The two surgical procedures most commonly performed in the world are sleeve gastrectomy (SG) and Roux-en-Y gastric bypass (RYGB), because they induce remission or amelioration of obesity-related comorbidities in a majority of cases with an acceptable rate of complications. Notably, numerous studies have shown that these procedures improve non-alcoholic fatty liver diseases (NAFLD) whose prevalence is particularly high in obese patients and thus in candidates for bariatric surgery, reaching 86% on per-operative liver biopsies [(1).]

It is generally admitted that RYGB is more efficient than SG on improving metabolic disorders associated with obesity, because of specific mechanisms beside weight loss related to proximal gut exclusion [(2)]. This was notably shown for glucose disturbances, but a specific effect of RYGB on cholesterol level or hypertension was also found in several studies [(3)]. Thus, a better effect on NAFLD is expected after RYGB than after SG. However, some cases of severe liver alterations have been reported after RYGB associated with malnutrition [(4)].

Very few studies have compared the effects of RYGB and SG on liver parameters (using blood tests, imaging or liver biopsies), some showing a better improvement after SG [(5-7)], one showing a better improvement after RYGB [(8)], while others [(9-11)] being not conclusive on the superiority of one of these procedures on NAFLD evolution after surgery. Moreover, all were short term studies from 6 to 18 months after surgery. Finally, it was not tested whether the evolution of liver tests after both procedures was only related to the evolution of metabolic parameters or whether other mechanisms of liver alterations could be implicated, including alterations of nutritional parameters.

The aim of our study was thus to compare the evolution of liver parameters after SG and RYGB and their relationships with improvement of metabolic disorders.

Subjects and methods

Patients and surgical procedures

This study is a retrospective analysis of our prospective database of patients who underwent bariatric surgery since 2004. All subjects who underwent either SG or RYGB between 2004 and 2016 with available metabolic explorations both before and 1 year (± 3 months) after surgery were included. The data available more than 3 years after surgery were also recorded in a subgroup of patients. The exclusion criteria for this study were pregnancy at the time of the visits, alcohol abuse or know liver disease of origin other than NAFLD. Bariatric surgery was performed in accordance with the recommendations of international committees and consensus conferences [(12)]. All procedures were performed laparoscopically, as previously described [(13)] with a 150 cm alimentary limb and a 60 cm biliopancreatic limb for RYGB. Intraoperative liver biopsies were systematically planned from 2013 and scored according to the classification of Bedossa [(14)]. Pre- and postoperative multidisciplinary management in our institution were previously described elsewhere [(15)]. All investigations were performed with a medical care goal. Informed consent was obtained in all patients before surgery and the data collection was approved by our institution and the local ethic committee.

Clinical and biological assessments

All patients underwent a routine examination, an abdominal ultra-sonography (US) and systematic fasting biological analyses in a day-hospitalization, before and one year after surgery and then every 3 years in average after surgery. Clinical, biological parameters and US liver abnormalities were prospectively assessed as previously described [(16)].

Statistical analysis

Statistical analyses were performed with SigmaStat 3.5 software. Quantitative parameters were compared in univariate analysis using unpaired Student's t-test or non-parametric tests when the distribution was not normal. Qualitative parameters were compared using the Pearson's Chi square test or the fisher exact test, when appropriate. Patients with missing data were excluded only from the analyses of the missing parameter. Correlations between the deltas of pre- and postoperative parameters (value after surgery minus value before surgery) were analyzed by Spearman correlation. Decreased alanine aminotransferase (ALT) was arbitrary defined by a delta > 5IU/L whereas increased ALT was defined by a delta > 5IU/L, in order to exclude unspecific changes, taking into account the intra-assay and inter-assay variations that are respectively below 2 and 5 IU/L based on the indications of the manufacturer (Dimension® Siemens Healthineers). ALT was considered abnormal if > 34 IU/L for women and >45 IU/L for men [(6)]. Results are expressed as mean ± SD or percent when indicated.

Results

Clinical characteristics

Among the 554 subjects evaluated before and one year after surgery, 21 were excluded because of pregnancy at the moment of explorations. None had known liver disease other than NAFLD and none had alcohol abuse. Only 6 subjects reported to drink alcohol on a regular but mild basis before surgery and only 9 after (2 after SG and 7 after RYGB) and their transaminases were not higher in average than in the whole cohort. Thus, 533 subjects were analyzed, including 326 RYGB and 207 SG. Abdominal US was missing in 79 subjects before surgery (15%) and 49 subjects after surgery (8%). Intraoperative liver biopsies were available in 150 RYGB and 80 SG and the percentage of subjects with histologic NASH did not differ between groups (27 vs 24%, respectively).

The characteristics of the subjects are indicated in Table 1. Baseline characteristics were similar in RYGB and SG groups. One year after surgery, percent weight loss was significantly higher after RYGB than after SG,with a trend towards lower absolute postoperative weight that did not reach significance. The decreases in caloric and protein intakes were similar, but the subjects ate less lipids after RYGB than after SG. The number of subjects with treatment for obstructive sleep apnea syndrome or diabetes decreased in the same proportion after both procedures. In contrast, the decrease in the number of subjects treated for hypertension or lipids disorders was only significant after RYGB.

Evolution of biological and US parameters

Metabolic parameters were similar before surgery and improved in both groups after surgery (Table 2). However, the decrease in fasting insulin and cholesterol was greater after RYGB than after SG, as for the inflammation marker C-reactive protein. Despite improvement of metabolic parameters, liver tests including alkaline phosphatases and transaminases, decreased less after RYGB than after SG. In contrast, Gamma-GT and ferritin, whose increase is usually associated with metabolic liver disease, were similar or even lower after RYGB (Table 2). In the same line, the number of subjects with persistent US steatosis did not differ (Figure 1A). The liver test alterations after RYGB were not explained by gallbladder disease, the number of subjects with cholelithiasis or who underwent cholecystectomy being similar after both procedures (figure 1A). It cannot be excluded that the lower ferritin level after RYGB was explained by iron malabsorption. However, serum iron concentration increased in the same manner in both groups (Table 1). Again, higher alkaline phosphatases levels after RYGB could be explained by a difference in bone resorption, but parathyroid hormone did not differ one year after both procedures (43.5 ± 21.0 vs. 42.2 ± 25.6 pg/ml after RYGB and SG respectively).

Long-term data

At 3 years or more after surgery (Supplemental table 1), the subjects that underwent SG were significantly heavier than those who underwent RYGB and all metabolic parameters were better improved after RYGB, except for transaminases and alkaline phosphatases that were still higher after RYGB. Again, ferritin and gamma GT were lower and the number of patients with US liver abnormalities was not significantly different after RYGB and SG (Supplemental table 1).

Characteristics of the subjects according to the evolution of transaminases after RYGB

The percentage of subjects with abnormal ALT was significantly higher one year after RYGB than after SG (Figure 1B). Furthermore, not far from a third of subjects increased their ALT one year after RYGB as compared to less than 5 % after SG (Figure 1B). However, even after exclusion of subjects with increased ALT, transaminases were still higher after RYGB (19.8 ± 5.3 vs 17.1 ± 5.6 IU/l for AST and 26.2 ± 8.3 vs 22.1 ± 7.5 IU/l for ALT, $p < 0.001$). The subjects with increased ALT after RYGB were older but did not differ from those with decreased ALT in term of preoperative BMI, weight loss, and caloric intake. However, they had better liver tests before surgery, less US steatosis, less histologic abnormalities on liver biopsies and less metabolic disorders (Supplemental Table 2). In the whole cohort of RYGB, the decrease in ALT after surgery was positively correlated to weight loss and to improvement of other markers of liver metabolic disease and of insulin resistance (Table 3), whereas in those with increase in ALT, the delta of ALT was inversely correlated to the delta of fasting insulin, total cholesterol, transferrin and albumin.

Discussion

The impact of bariatric surgery on NAFLD has been extensively studied, and in our study, NAFLD assessed by blood liver tests and liver US improved after both procedures in parallel with the improvement of metabolic disorders, as expected [17, 18]. Beside weight loss and decrease in insulin resistance, some mechanisms for NAFLD improvement have been proposed, including modifications in incretins release, adipokines secretion, bile acid metabolism and microbiota, notably for surgical procedures with intestinal derivation [17]. Thus, it can be expected that RYGB should be more efficient on NAFLD remission than restrictive procedures. In this line, a study with liver biopsies performed in a large cohort of 1236 obese patients, has shown that NAFLD improves better 5 years after RYGB than after gastric banding [1]. Unfortunately, no study with such a level of proof is available for comparison with SG. The 2 studies that have compared the improvement of NAFLD assessed by liver biopsies after RYGB and SG, were inconclusive on the superiority of one of these procedures, but they included no more than 30 subjects and the follow-up duration was 6 months [9, 10]. One study [8] reported a better improvement of liver stiffness assessed by elastography one year after RYGB but another study using MRI [11] did not find any difference between RYGB and SG, 6 months after surgery. These results are in accordance with our study showing that remission of US steatosis did not differ between both procedures.

However, two previous studies based on blood liver enzymes, one in a small cohort of 34 diabetic subjects [5] and one in a large registry cohort [6], showed a better improvement of liver enzymes, including transaminases and alkaline phosphatases but not gamma-GT, one year after SG as compared to RYGB, as in our study. These results are unlikely to be explained by a more severe NAFLD before surgery in candidates for RYGB, because the 2 groups were comparable for metabolic disorders, BMI, liver blood tests, US steatosis and histologic finding at baseline in our study. Furthermore, the difference in liver enzymes persists at 3 years or more, despite weight regain and more marked metabolic alterations after SG. Finally, in the RYGB group, some subjects increased their ALT, as reported by Spivak et al [6] and this increase was not explained by greater insulin-resistance and was unrelated to other markers of NAFLD, including US steatosis, gamma-GT and ferritin. Altogether, these results do not support the hypothesis previously suggested [5] that RYGB induces a poorer improvement of NAFLD than SG, but instead argue for mechanisms independent of NAFLD underlying the increase in transaminases after RYGB. This effect was unmasked in subjects with baseline normal transaminases but was also present in subjects with NAFLD since after exclusion of subjects with increased ALT, transaminases were still less decreased after RYGB than after SG.

Malnutrition could be an underlying mechanism. Indeed, some cases of liver failure have been described in a context of malnutrition after RYGB but these extreme cases are rare [4, 19]. However, more subtle malnutrition could be involved and, in this line, it was shown that omega-loop gastric bypass, with a longer bypassed biliopancreatic limb and therefore greater malabsorption, induces a larger increase in liver enzymes than RYGB [6, 20] Unfortunately, the authors did not study the link between transaminases and markers of malnutrition. In our study, we observed that the increase in ALT after RYGB was inversely correlated to cholesterol, albumin and transferrin, could argue for this hypothesis. However, no correlations were found with minerals and vitamins usually assessed after surgery [13] (data not shown).

On the other hand, the lower concentrations of cholesterol, albumin and transferrin, all synthetized by the liver, could also reflect alterations of liver functions independently of nutritional status in subjects with the higher transaminases after RYGB. In this line, a previous study has shown that patients with non-alcoholic steatohepatitis undergoing RYGB are more susceptible than those undergoing SG to early transient deterioration of liver functions with increase in International Normalized Ratio (INR) and decrease in albumin concentration [7]. Thus, we cannot exclude that other mechanisms could influence liver functions after RYGB, for example related to changes in bile acids metabolism or perturbations in gut permeability and gut-liver axis induced by gut derivation.

The main limitations of our study are: 1) the non-randomized design that could induce bias, but the baseline characteristics of candidates for RYGB and SG were very similar and the collection of liver parameters was performed by medical staff unaware of the study; 2) the retrospective nature of the analysis of our prospective database; 3) the absence of histological data for some subjects before surgery which did not allow us to match the patients based on histologic degree of liver involvement at baseline, but ALT levels were significantly lower after SG than after RYGB both in subjects with or without NASH (data not shown) and above all 4) the lack of liver biopsies after surgery, the morphological characteristics being evaluated only by ultrasound after surgery.

Conclusion

RYGB has less beneficial effects on liver enzymes as compared to SG, independently of improvement of metabolic disorders and of NAFLD, both in the short and long terms. These alterations could be linked to subtle malnutrition but other mechanisms need to be explored. Randomization trials should be conducted to confirm the differential effects of SG and RYGB on liver parameters and should be continued in the long-term to determine the consequences of increased liver enzymes after RYGB. If these results are confirmed by other studies, this could have an impact on the choice of surgical procedure, suggesting that SG is the preferred operation in subjects at risk of developing liver failure.

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Figure 1. Evolution of liver parameters 1 year after sleeve gastrectomy (SG) and Roux-en-Y gastric bypass (RYGB). A. ***Liver US parameters:*** percent of subjects with liver (left) or gallbladder (right) abnormalities. **B.** ***Alanine aminotransferase (ALT) concentrations:*** percent of subjects (left) with abnormal ALT (> 34 IU/L for women and > 45 for men). Percent of subjects (right) with decreased ALT (postoperative minus preoperative value < -5 IU/L), stable ALT or increased ALT (postoperative minus preoperative value > 5 IU/L). $^{££}$ *p < 0.01,* $^{£££}$ *p < 0.001 vs baseline, **p < 0.01, ***p < 0.001 vs sleeve gastrectomy*.

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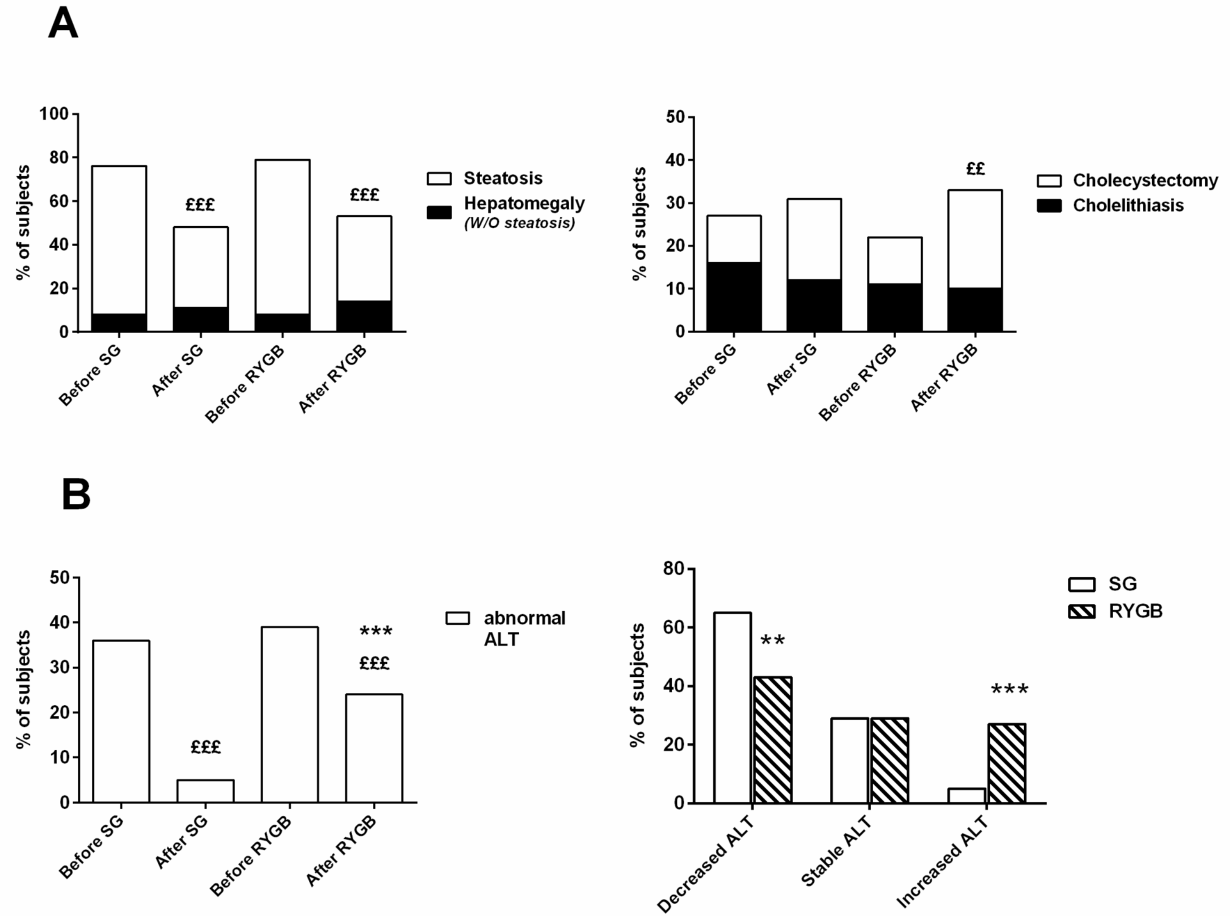
A
100
80
60
40
20
0
% of subjects
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£££
Before SG
After SG
Before RYGB
After RYGB
Steatosis
Hepatomegaly
(W/O steatosis)
50
40
30
20
10
0
% of subjects
££
Before SG
After SG
Before RYGB
After RYGB
Cholecystectomy
Cholelithiasis
B
50
40
30
20
10
0
% of subjects
£££
***
£££
Before SG
After SG
Before RYGB
After RYGB
abnormal
ALT
80
60
40
20
0
% of subjects
**
***
Decreased ALT
Stable ALT
Increased ALT
SG
RYGB

Table 1. Clinical characteristics of the subjects before and one year after surgery

	Sleeve Gastrectomy		Roux-en-Y Gastric Bypass	
	Before	After	Before	After
N	207	207	326	326
Male gender (n (%))	31 (15)	-	50 (15)	-
Age (years)	43 ± 11	-	43 ± 11	-
Time from surgery (months)	-	12 ± 1	-	12 ± 1
Weight (kg)	120.3 ± 22.7	87.7 ± 20.5 £££	122.9 ± 21.1	84.7 ± 16.7 **£££**
BMI (kg/m²)	44.4 ± 7.4	32.2 ± 6.8 £££	44.7 ± 5.7	31.2 ± 9.0 £££
Weight loss (%)	-	28.6 ± 8.3	-	**31.9 ± 7.7 *** **
EWL (%)	-	72.7 ±29.8	-	79.3 ± 44.9
EBMIL (%)	-	68.6 ± 25.6	-	71.2 ± 50.4
Systolic BP (mmHg)	132.6 ± 13.9	122.2 ± 12.1 £££	132.9 ± 14.0	120.6 ± 12.7 £££
Diastolic BP (mmHg)	71.5 ± 10.5	67.6 ± 9.6 £££	72.0 ± 10.6	66.2 ± 10.0 £££
Treatment for (n (%))				
Sleep apnea	45 (22)	17 (8) £££	80 (25)	20 (6) £££
Diabetes	37 (18)	16 (8) ££	61 (19)	17 (5) £££
Hypertension	32(32)	29 (29)	72 (32)	51 (23) £
Lipid disorders	15 (15)	10 (10)	33 (15)	9 (4) £££
Food intake (Kcal/24h)	1696 ± 399	1163 ± 351 £££	1770 ± 444	1223 ± 402 £££
Carbohydrates (%)	46 ± 7	46 ± 8	45 ± 6	47 ± 7.3 ££
Lipids (%)	34 ± 6	36 ± 7 £	35 ± 6	**34 ± 6 £***
Proteins (%)	20 ± 4	18 ± 4 £££	20 ± 4	19 ± 4

*£ p < 0.05, ££ p < 0.01, £££ p < 0.001 vs baseline, *p < 0.05, ***p < 0.001 vs after sleeve gastrectomy*

BP: blood pressure, EWL: excess weight loss, EBMIL : excess BMI lost

Table 2. Biological parameters of the subjects before and one year after surgery

	Sleeve Gastrectomy		Roux-en-Y Gastric Bypass	
	Before	After	Before	After
N	207	207	326	326
FBG (mmol/l)	6.1 ± 2.0	5.0 ± 0.8 $^{£££}$	6.1 ± 1.6	4.9 ± 0.8 $^{£££}$
Fasting insulin (mIU/l)	20.9 ± 13.4	9.2 ± 8.80$^{£££}$	21.1 ± 13.0	**7.2 ± 5** $^{£££}$***
HOMA-IR	6.34 ± 5.3	2.12 ± 1.9 $^{£££}$	6.0 ± 4.4	**1.7 ± 1.4** $^{£££}$**
HbA1c (%)	5.9 ± 1.1	5.4 ± 0.7 $^{£££}$	6.1 ± 1.0	5.4 ± 0.6 $^{£££}$
Triglycerides (mmol/l)	1.4 ± 0.8	0.9 ± 0.5 $^{£££}$	1.4 ± 0.8	0.9 ± 0.4 $^{£££}$
Total-CT (mmol/l)	5.2 ± 1.0	5.3 ± 1.1	5.2 ± 1.0	**4.4 ± 0.8** $^{£££}$***
HDL-CT (mmol/l)	1.3 ± 0.3	1.6 ± 0.4 $^{£££}$	1.2 ± 0.3	**1.5 ± 0.3** $^{£££}$**
LDL-CT (mmol/l)	3.2 ± 10.9	3.3 ± 1.0	3.3 ± 1.0	**2.5 ± 0.7** $^{£££}$***
Uric acid (µmol/l)	307 ± 75	260 ± 67 $^{££\$}$	309 ± 71	**241 ± 63** $^{£££}$**
ALKP (IU/l)	81.2 ± 23.7	72.9 ± 19.8 $^{£££}$	82.5 ± 21.8	**88.2 ± 25.2** $^{££}$***
Gamma-GT (IU/l)	42.8 ± 26.5	25.9 ± 14.0 $^{£££}$	46.8 ± 42.0	23.7 ± 17.4 $^{£££}$
AST (IU/l)	23.2 ± 10.2	17.3 ± 5.9 $^{£££}$	24.5 ± 13.1	**22.2 ± 8.4** $^{££}$***
ALT (IU/l)	35.8 ± 18.6	22.6 ± 7.7 $^{£££}$	37.9 ± 23.2	**31.6 ± 18.7** $^{£££}$***
Total Bilirubine (IU/l)	8.8 ± 3.1	11.0 ± 5.0 $^{£££}$	8.9 ± 3.0	10.4 ± 4.3 $^{£££}$
Ferritin (µg/l)	123.1 ± 108.7	117.6 ± 109.4	109.8 ± 108.0	**83.4 ± 82.6** $^{£££}$***
Serum iron (µmol/l)	13.5 ± 5.2	15.5 ± 5.0 $^{£££}$	13.7 ± 4.7	14.8 ± 4.9 $^{££}$
CRP (mg/l)	9.1 ± 6.1	3.9 ± 3.8 $^{£££}$	9.5 ± 6.8	**2.6 ± 2.5** $^{£££}$ ***
Prothrombin time (%)	104 ± 14	99 ± 13 $^{££}$	105 ± 14	100 ± 13 $^{£££}$

FBG = fasting blood glucose, HOMA-IR = homeostasis model assessment index of insulin resistance, HbA1c = glycated hemoglobin, CT = cholesterol, ALKP = alkaline phosphatase, GT = glutamyl transferase, AST = aspartate aminotransferase, AST = alanine aminotransferase. CRP = C-reactive protein. $^{££}p < 0.01$, $^{£££}p < 0.001$ *vs baseline,* $^{**}p < 0.01$, $^{***}p < 0.001$ *vs after sleeve gastrectomy.*

Table 3. Relationships between delta of alanine aminotransferase and delta of other parameters after Roux-en-Y gastric bypass

	Whole Cohort (N = 326)		Subjects with decreased ALT (N = 141)		Subjects with increased ALT (N = 90)	
Spearman correlations	R	*p*	R	*p*	R	p
% Weight loss	0.115	*0.0394*	-	-	-	-
Ferritin	0.167	*0.0026*	0.196	*0.0202*	-	-
Gamma-GT	0.480	<*0.0001*	0.427	<*0.0001*	-	-
ALKP	0.167	*0.0136*			-	-
HOMA-IR	0.197	*0.0005*	-	-	-	-
Fasting insulin	0.180	*0.0013*	-	-	-0.210	*0.0491*
Total-Cholesterol	-	-	-	-	-0.220	*0.0383*
Albumin	-	-	-	-	-0.218	*0.0415*
Transferrin	-	-	-	-	-0.270	*0.0148*

Delta are defined by the postoperative value minus the preoperative value. Decreased and increased alanine aminotransferase (ALT) were defined by a delta < -5 IU/L and > 5 IU/L respectively.