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Gastric bypass specifically impairs liver parameters as compared to sleeve gastrectomy, independently of evolution of metabolic disorders

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Short title: Changes in liver parameters after bariatric surgery

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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

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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⁾.

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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⁾.

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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.

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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.

55 **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 (\pm 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
80 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
arbitrarily defined by a delta > 5 IU/L whereas increased ALT was defined by a delta > 5 IU/L,
85 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 \pm SD or percent
when indicated.

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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
95 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
100 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
105 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.

110 *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,
115 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
120 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
125 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
130 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
135 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 ($19.8 \pm$
 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
140 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),
145 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,
150 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⁾.
155 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
160 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
165 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
170 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
175 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
180 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).
185 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
190 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
synthesized 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
195 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
200 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
205 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.

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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.
215 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). ^{ff}*p* < 0.01, ^{fff}*p* < 0.001 vs baseline, ^{**}*p* < 0.01, ^{***}*p* < 0.001 vs sleeve gastrectomy.

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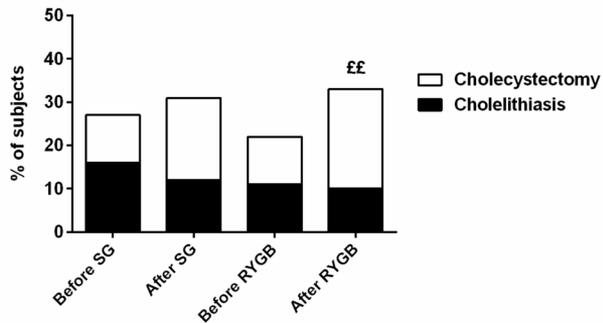
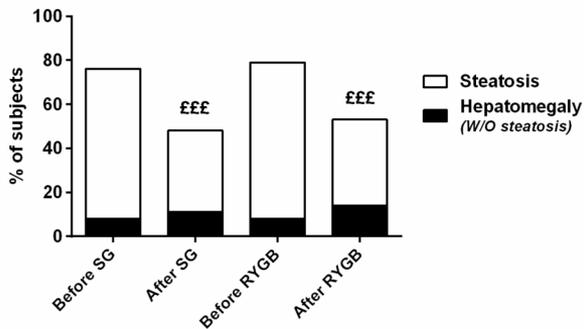
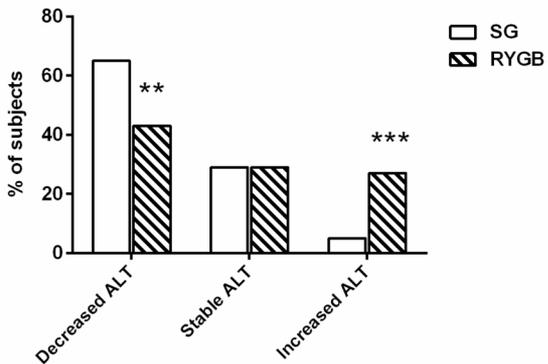
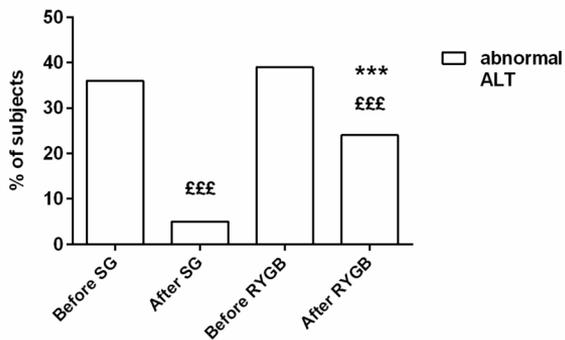
A**B**

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/m ²)	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 ^{£££}
<i>Treatment for (n (%))</i>				
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 ^{fff}	6.1 ± 1.6	4.9 ± 0.8 ^{fff}
Fasting insulin (mIU/l)	20.9 ± 13.4	9.2 ± 8.80 ^{fff}	21.1 ± 13.0	7.2 ± 5 ^{fff***}
HOMA-IR	6.34 ± 5.3	2.12 ± 1.9 ^{fff}	6.0 ± 4.4	1.7 ± 1.4 ^{fff**}
HbA1c (%)	5.9 ± 1.1	5.4 ± 0.7 ^{fff}	6.1 ± 1.0	5.4 ± 0.6 ^{fff}
Triglycerides (mmol/l)	1.4 ± 0.8	0.9 ± 0.5 ^{fff}	1.4 ± 0.8	0.9 ± 0.4 ^{fff}
Total-CT (mmol/l)	5.2 ± 1.0	5.3 ± 1.1	5.2 ± 1.0	4.4 ± 0.8 ^{fff***}
HDL-CT (mmol/l)	1.3 ± 0.3	1.6 ± 0.4 ^{fff}	1.2 ± 0.3	1.5 ± 0.3 ^{fff**}
LDL-CT (mmol/l)	3.2 ± 10.9	3.3 ± 1.0	3.3 ± 1.0	2.5 ± 0.7 ^{fff***}
Uric acid (µmol/l)	307 ± 75	260 ± 67 ^{ff\$}	309 ± 71	241 ± 63 ^{fff**}
ALKP (IU/l)	81.2 ± 23.7	72.9 ± 19.8 ^{fff}	82.5 ± 21.8	88.2 ± 25.2 ^{ff***}
Gamma-GT (IU/l)	42.8 ± 26.5	25.9 ± 14.0 ^{fff}	46.8 ± 42.0	23.7 ± 17.4 ^{fff}
AST (IU/l)	23.2 ± 10.2	17.3 ± 5.9 ^{fff}	24.5 ± 13.1	22.2 ± 8.4 ^{ff***}
ALT (IU/l)	35.8 ± 18.6	22.6 ± 7.7 ^{fff}	37.9 ± 23.2	31.6 ± 18.7 ^{fff***}
Total Bilirubine (IU/l)	8.8 ± 3.1	11.0 ± 5.0 ^{fff}	8.9 ± 3.0	10.4 ± 4.3 ^{fff}
Ferritin (µg/l)	123.1 ± 108.7	117.6 ± 109.4	109.8 ± 108.0	83.4 ± 82.6 ^{fff***}
Serum iron (µmol/l)	13.5 ± 5.2	15.5 ± 5.0 ^{fff}	13.7 ± 4.7	14.8 ± 4.9 ^{ff}
CRP (mg/l)	9.1 ± 6.1	3.9 ± 3.8 ^{fff}	9.5 ± 6.8	2.6 ± 2.5 ^{fff***}
Prothrombin time (%)	104 ± 14	99 ± 13 ^{ff}	105 ± 14	100 ± 13 ^{fff}

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. ^{ff} p < 0.01, ^{fff} 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

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

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.