

# Decreased serum CA19-9 is associated with improvement of insulin resistance and metabolic control in patients with obesity and type 2 diabetes after Roux-en-Y gastric bypass

Yinfang Tu<sup>1</sup>, Haoyong Yu<sup>1</sup>, Pin Zhang<sup>2</sup>, Jianzhong Di<sup>2</sup>, Xiaodong Han<sup>2</sup>, Songhua Wu<sup>1</sup>, Yuqian Bao<sup>1</sup>, Weiping Jia<sup>1\*</sup>

<sup>1</sup>Department of Endocrinology and Metabolism, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Shanghai Clinical Center for Diabetes, Shanghai Diabetes Institute, Shanghai Key Laboratory of Diabetes Mellitus, Shanghai Key Clinical Center for Metabolic Disease, and <sup>2</sup>Department of General Surgery, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Shanghai, China

## Keywords

Carbohydrate antigen 19-9, Insulin resistance, Obesity

## \*Correspondence

Weiping Jia  
Tel.: +86-021-2405-8570  
Fax: +86-021-6451-9943  
E-mail address: wpjia@sjtu.edu.cn

*J Diabetes Invest* 2014; 5: 694–700

doi: 10.1111/jdi.12200

## ABSTRACT

**Aims/Introduction:** Patients with type 2 diabetes are known to show elevated serum levels of carbohydrate antigen 19-9 (CA19-9). The aim of the present study was to investigate the possible relationships of CA19-9 with metabolic control, insulin resistance (IR), and pancreatic  $\beta$ -cell function in patients with obesity and type 2 diabetes who underwent Roux-En-Y gastric bypass (RYGB).

**Materials and Methods:** The present study included 81 healthy volunteers, and 33 patients diagnosed with obesity and type 2 diabetes who underwent RYGB. Anthropometry, serum levels of CA19-9, glucose and lipid metabolic profiles, and serum insulin levels were determined at baseline and at 12 weeks after RYGB.

**Results:** Changes in CA19-9 were significantly and positively correlated with changes in fasting plasma glucose ( $r = 0.552$ ,  $P = 0.001$ ), 2-h post-challenge plasma glucose levels ( $r = 0.623$ ,  $P = 0.000$ ), glycated hemoglobin levels ( $r = 0.819$ ,  $P = 0.000$ ), glycated albumin levels ( $r = 0.711$ ,  $P = 0.000$ ), total cholesterol ( $r = 0.449$ ,  $P = 0.009$ ) and the Homeostasis Model of Assessment-IR index ( $r = 0.407$ ,  $P = 0.019$ ). Furthermore, a multiple stepwise regression analysis showed that the changes in serum levels of CA19-9 were independently and significantly associated with changes in glycated hemoglobin ( $\beta = 0.598$ ,  $P = 0.000$ ), fasting plasma glucose ( $\beta = 0.309$ ,  $P = 0.000$ ) and Homeostasis Model of Assessment-IR ( $\beta = 0.235$ ,  $P = 0.010$ ) after adjusting for confounding factors.

**Conclusions:** CA19-9 could be an effective indicator of IR, and glycemic and lipid metabolism in patients with obesity and type 2 diabetes after rapid metabolic control by RYGB. Additionally, CA19-9 might be a marker with which to evaluate the short-term effects of glycolipid toxicity on IR in these patients.

## INTRODUCTION

In 1976, Koprowski *et al.*<sup>1</sup> determined that carbohydrate antigen 19-9 (CA19-9) is a tumor-associated antigen. CA19-9 was originally defined by a monoclonal antibody produced by a hybridoma prepared from murine spleen cells immunized with

a human colorectal cancer cell line. In humans, CA19-9 is expressed by the exocrine pancreas *in vivo*, and is elevated in the blood of many patients with pancreatic cancers, cancers of the upper gastrointestinal tract, ovarian cancer, hepatocellular cancer and colorectal cancer<sup>2</sup>. Furthermore, this antigen has a high value during the diagnosis of pancreatic cancer, because it has a sensitivity of 70–90% and a specificity of 68–91%<sup>3</sup>.

CA19-9 levels are higher in patients with diabetes than in non-diabetic controls, as well as in patients with poor glycemic

Yinfang Tu and Hao-yong Yu are contributed equally to this work.  
Received 4 September 2013; revised 2 December 2013; accepted 24 December 2013

control, relative to those with good glycemic control<sup>4-9</sup>. Additionally, CA19-9 has been found to be elevated in diabetic patients during acute metabolic situations (ketoacidosis and hyperglycemic coma), which are strongly correlated with blood glucose concentration, and it has been suggested that glucose toxicity could play a role in the high serum levels of CA19-9 in these patients<sup>7</sup>.

However, follow-up studies have been unable to determine whether serum levels of CA19-9 are rapidly and significantly altered in conjunction with the rapid return of good glycemic control. Roux-en-Y gastric bypass (RYGB) is prescribed to treat obesity and type 2 diabetes, and is appropriate for Chinese type 2 diabetes patients with a body mass index (BMI) of 25–35 kg/m<sup>2</sup><sup>10</sup>. Type 2 diabetes is reversed in up to 90% of patients after RYGB, which typically leads to restoration of normal blood glucose without medication, sometimes within days<sup>11,12</sup>. In the present study, serum levels of CA19-9 were evaluated in patients with type 2 diabetes before and after RYGB. Additionally, the possible relationships of the serum level of CA19-9 with metabolic control, insulin resistance (IR) and pancreatic  $\beta$ -cell function were investigated in these subjects.

## MATERIALS AND METHODS

### Participants

The present 12-week follow-up study included 81 healthy volunteers (50 males, 31 females; age  $45.7 \pm 10.0$  years) who were examined in our outpatient clinic, and a total of 33 subjects with obesity and type 2 diabetes (16 males, 17 females; age  $47.3 \pm 12.7$  years) who were examined and treated with RYGB in our inpatient department. The diagnostic criteria for obesity were based on The Asia-Pacific Perspective (2000) from the International Obesity Taskforce, and were determined using a BMI of  $25 \text{ kg/m}^2$ <sup>13</sup>. A diagnosis of type 2 diabetes was based on the 1999 World Health Organization criteria<sup>14</sup>. Patients with malignant disease, a history of chemotherapy or radiotherapy and/or acute or chronic pancreatitis were excluded from this study. Patients with diabetes who were suffering from any coexisting diseases that are associated with high serum levels of CA19-9 were also excluded. CA19-9 was measured in all participants, and those with high levels were further evaluated using abdominal ultrasonography and computed tomography (CT) imaging. Upper gastrointestinal endoscopy and colonoscopy were carried out when required.

All participants provided written informed consent, and the study was approved by the ethics committee of Shanghai Jiao Tong University Affiliated Sixth People's Hospital and complied with the Declaration of Helsinki.

### Measurements

All 33 patients who underwent RYGB showed a reversal of symptoms and exhibited normal blood glucose without medication.

Blood samples were collected after an overnight fast before breakfast (0 min) and 120 min after breakfast to record glucose and insulin measurements. Plasma glucose concentrations were measured using the glucose oxidase method. Glycated hemoglobin A1c (HbA1c) values were determined using high-performance liquid chromatography (Bio-Rad Laboratories; Hercules, CA, USA). Glycated albumin (GA) was measured using the enzymatic method (LUCICA GA-L; Asahi KASEI, Tokyo, Japan). Serum lipid profiles, which included total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-c) and low-density lipoprotein cholesterol (LDL-c), were measured by enzymatic procedures using an autoanalyzer (Hitachi 7600-020; Hitachi, Tokyo, Japan). CA19-9 was assayed using a chemiluminescence method (Siemens Immulite 2000, Siemens Healthcare Diagnostics, Tarrytown, NY, USA) and an Access GI Monitor kit (Immulite 2000; Beckman Coulter, Brea, CA, USA). The normal range for serum CA19-9 levels was 0–35 U/mL in the present study; and measurements above this level were considered abnormal.

A complete physical examination, which included height, weight, systolic blood pressure (SBP) and diastolic blood pressure (DBP), was carried out on each participants at baseline and 12 weeks after RYGB. BMI was calculated as weight in kilograms divided by squared height in meters (kg/m<sup>2</sup>).

### Calculations

Evaluations of IR and basal insulin secretion were estimated using the Homeostasis Model of Assessment (HOMA) index, which is based on fasting glucose and insulin measurements as follows:  $\text{HOMA-IR} = [\text{fasting insulin (mU/l)} \times \text{FPG (mmol/l)}] / 22.5$  and  $\text{HOMA of beta cell function (HOMA-B\%)} = [20 \times \text{fasting insulin} / (\text{FPG} - 3.5)]^{15}$ .

### Statistical Analysis

All statistical analyses were carried out using SPSS version 20.0 (SPSS, Chicago, IL, USA). Data were expressed as means  $\pm$  standard deviation for normal distributions or as medians (interquartile range) for skewed variables. Data that were not normally distributed as determined by the Kolmogorov–Smirnov test were logarithmically transformed before analysis. The clinical characteristics of controls and patients with obesity and type 2 diabetes were compared at baseline using an independent-samples *t*-test. To analyze the effects of RYGB over the examination period, paired-sample *t*-tests were used to compare baseline data and data obtained after 12 weeks. Pearson's correlation was used to evaluate the relationships between serum levels of CA19-9 and the various clinical parameters, and a multiple stepwise regression analysis was carried out to identify the independent parameters correlated with CA19-9 at baseline and changes in CA19-9 at 12 weeks. Variables that were significantly correlated with serum levels of CA19-9 (after correlation analysis) were selected for the stepwise regression. All reported *P*-values are two-tailed, and  $P < 0.05$  was considered to show statistical significance.

## RESULTS

### Clinical Characteristics of the Control Group, Patients with Obesity and Type 2 Diabetes at Baseline, and Patients at 12 Weeks after RYGB

The general characteristics and clinical parameters among non-diabetic controls, patients with obesity and type 2 diabetes at baseline, and patients 12 weeks after RYGB are shown in Table 1. Participants with obesity and type 2 diabetes showed significantly higher levels of TG, FPG, 2hPG, HbA1c, fasting insulin (FINS) and the HOMA-IR index, and lower levels of HDL-c compared with the control group (all  $P < 0.05$ ). Compared with baseline, weight, BMI, DBP, SBP, TC, TG, LDL-c, FPG, 2hPG, HbA1c, GA, FINS and the HOMA-IR index were all significantly decreased at end of the study (all  $P < 0.05$ ).

In patients with obesity and type 2 diabetes, serum levels of CA19-9 were significantly lower at 12 weeks after RYGB than at baseline, but still higher than the control group (Figure 1a). The percentages of positive serum levels of CA19-9 (more than 35 U/L) in the control group, patients with obesity and type 2 diabetes at baseline, and patients at 12 weeks after RYGB were 0% (0/81), 12.1% (4/33) and 3.0% (1/33), respectively. Only five patients with obesity and type 2 diabetes showed a minimal but insignificant increase of CA19-9 ( $<4$  U/L) from baseline to 12 weeks after RYGB. In contrast, 25 of 33 patients (75.8%)

showed good glycemic control (HbA1c  $< 7.0\%$ ) after RYGB, whereas just 12.1% (4/33) did at baseline. There was a decrease of 23.3% in serum levels of CA19-9, and a 15.9% decrease in HbA1c levels at 12 weeks after RYGB. Increases in IR (Figure 1b) were similar to the increase in levels of CA19-9 and HbA1c. Using a cut-off value of 2.8 in the HOMA-IR index<sup>16</sup>, IR was 81.8% (27/33) at baseline and just 30.3% (10/33) at 12 weeks after RYGB.

### Correlation Analysis and Multiple Linear Regression Analysis of Parameters Related to Serum Levels of CA19-9 at Baseline

A correlation analysis showed that serum levels of CA19-9 at baseline were positively correlated with TC, HDL-c, 2hPG, HbA1c and GA (Table 2; all  $P < 0.05$ ). A multiple stepwise regression analysis showed that HbA1c ( $\beta = 0.476$ ,  $P = 0.002$ ) and HDL-c ( $\beta = 0.346$ ,  $P = 0.021$ ) were independently related to CA19-9 at baseline (Table 3).

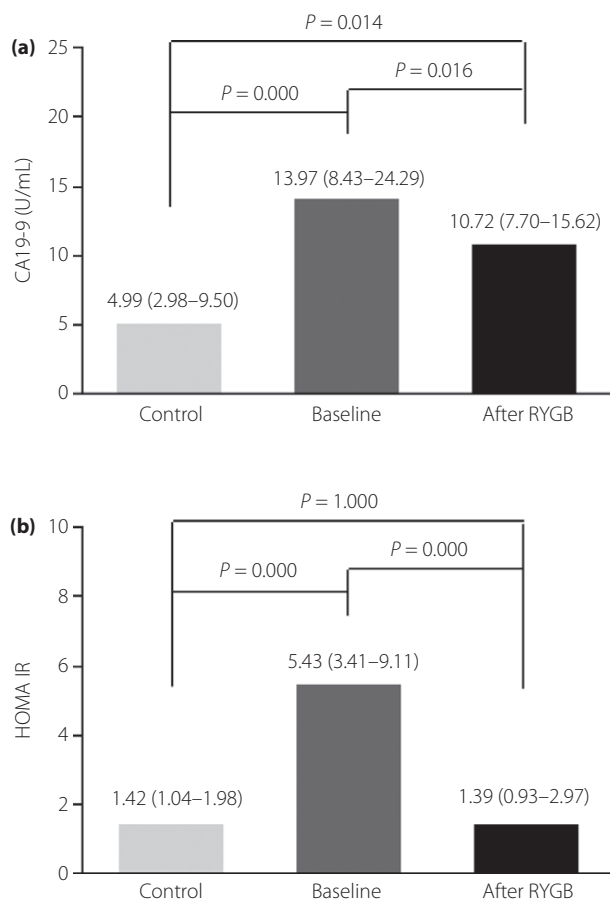
### Relationship between Changes in Serum Levels of CA19-9 vs Changes in Anthropometric and Biochemical Parameters

At 12 weeks after RYGB, changes in serum levels of CA19-9 were positively correlated with changes in TC, FPG, 2hPG, HbA1c and GA (all  $P < 0.01$ ), as well as the HOMA-IR index ( $P < 0.05$ ; Table 4; Figure 2a,b). A multiple stepwise regression

**Table 1** | Clinical characteristics of the control group, patients with obesity and type 2 diabetes at baseline, and patients at 12 weeks after Roux-En-Y gastric bypass

Variables	Control	Obesity and type 2 diabetes at baseline	12 weeks after RYGB
<i>n</i>	81	33	33
Sex (male/female)	50/31	16/17	16/17
Age (years)	45.7 $\pm$ 10.0	46.4 $\pm$ 12.9	—
Duration (years)	—	7.2 $\pm$ 5.3	—
Weight (kg)	63.1 $\pm$ 8.4	87.1 $\pm$ 12.2**	72.1 $\pm$ 9.8##
BMI (kg/m <sup>2</sup> )	22.8 $\pm$ 2.8	31.3 $\pm$ 3.6**	25.9 $\pm$ 2.9##
SBP (mmHg)	125 (120–130)	130 (120–140)**	120 (117–130)##
DBP (mmHg)	75 (70–78)	84 (80–90)**	80 (74–80)##
TC (mmol/L)	4.72 $\pm$ 0.83	5.01 $\pm$ 1.21	4.04 $\pm$ 0.76##
TG (mmol/L)	1.10 (0.78–1.90)	1.83 (1.36–3.05)**	1.15 (0.87–1.44)#
HDL-c (mmol/L)	1.24 (1.07–1.49)	0.94 (0.85–1.07)**	0.94 (0.85–1.16)
LDL-c (mmol/L)	3.13 $\pm$ 0.82	2.90 $\pm$ 0.92	2.39 $\pm$ 0.60##
FPG (mmol/L)	5.03 (4.84–5.26)	7.79 (6.61–10.61)**	5.84 (4.52–6.94)##
2hPG (mmol/L)	6.13 (5.49–7.03)	13.32 (11.20–18.02)**	6.93 (5.96–9.45)##
HbA1c (%)	5.5 (5.3–5.8)	8.2 (7.0–9.9)**	6.9 (6.0–9.5)##
GA (%)	—	19.5 (17.0–23.3)	15.2 (13.5–18.0)##
FINS (mU/L)	6.24 (4.89–8.83)	13.11 (8.79–19.84)**	6.19 (3.69–9.87)##
HOMA-IR	1.42 (1.04–1.98)	5.43 (3.41–9.11)**	1.39 (0.93–2.97)##
HOMA-B%	79.71 (65.79–121.03)	58.10 (37.51–115.09)	66.59 (28.42–98.39)

Data are mean  $\pm$  standard deviation or median (interquartile range). 2hPG, 2-h postchallenge plasma glucose; BMI, body mass index; DBP, diastolic blood pressure; FINS, fasting insulin; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; HDL-c, high density lipoprotein cholesterol; HOMA-B %, homeostasis model assessment index of  $\beta$ -cell function; HOMA-IR, homeostasis model assessment index of insulin resistance; LDL-c, low density lipoprotein cholesterol; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride. \* $P < 0.05$ , \*\* $P < 0.01$  vs control group. ## $P < 0.05$ , ### $P < 0.01$  vs patients with obesity and type 2 diabetes at baseline.



**Figure 1** | Comparison of serum levels of carbohydrate antigen 19-9 (CA19-9) and the Homeostasis Model of Assessment of insulin resistance (HOMA-IR) index among the control group, patients with type 2 diabetes at baseline, and patients at 12 weeks after Roux-En-Y gastric bypass (RYGB). (a) Comparison of CA19-9 among the three groups. The  $P$ -value for the three-group comparison was  $<0.001$ . (b) Comparison of HOMA-IR among the three groups. The  $P$ -value for the three-group comparison was  $<0.001$ .

analysis showed that the changes in HbA1c ( $\beta = 0.598$ ,  $P = 0.000$ ), FPG ( $\beta = 0.309$ ,  $P = 0.000$ ), and the HOMA-IR index ( $\beta = 0.235$ ,  $P = 0.010$ ) were independently and positively related to changes in CA19-9 after adjusting for confounding factors (Table 5).

## DISCUSSION

CA19-9 is typically used as a screening tool with which to diagnose pancreatic cancer, and as a marker of pancreatic tissue damage caused by diabetes. In a limited number of cross-sectional studies, patients with type 2 diabetes showed significantly higher serum levels of CA19-9 than non-diabetic control groups<sup>4–9</sup>. The present study confirmed these results in patients with obesity and type 2 diabetes, in addition to showing that HbA1c was independently related to CA19-9 at baseline. On the contrary, another early study did not show any value more

**Table 2** | Anthropometric and biochemical parameters showing significant correlations with serum levels of carbohydrate antigen 19-9 at baseline

	CA19-9	
	Univariate†	
	$r$	$P$
BMI	0.145	0.422
TC	0.465**	0.006
TG	0.034	0.852
HDL-c	0.456**	0.008
LDL-c	0.314	0.075
FPG	0.257	0.149
2hPG	0.518**	0.002
HbA1c	0.555**	0.001
GA	0.500**	0.003
HOMA-IR	0.307	0.083
HOMA-B%	-0.124	0.419

\* $P < 0.05$ , \*\* $P < 0.01$ , †Pearson's correlation analyses were carried out. 2hPG, 2-h postchallenge plasma glucose; BMI, body mass index; FPG, fasting plasma glucose; GA, glycated albumin; HbA1c, glycated hemoglobin; HDL-c, high density lipoprotein cholesterol; HOMA-B%, homeostasis model assessment index of  $\beta$ -cell function; HOMA-IR, homeostasis model assessment index of insulin resistance; LDL-c, low density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride.

**Table 3** | Multiple stepwise regression analysis showing variables independently associated with serum levels of carbohydrate antigen 19-9 at baseline

Independent variable	$\beta$	SEM	Standardized $\beta$	$t$	$P$
enter the model					
HbA1c	2.259	0.677	0.476	3.336	0.002
HDL-c	19.264	7.931	0.346	2.429	0.021

A multiple stepwise regression analysis was carried out. Age, sex, total cholesterol, high-density lipoprotein cholesterol (HDL-c), 2-h postchallenge plasma glucose, glycated albumin and glycated hemoglobin (HbA1c) at baseline were included in the original model. SEM, standard error of the mean.

than 40 U/mL among a population of 18 patients with diabetes<sup>17</sup>. Banfi *et al.*<sup>18</sup> observed that a correlation between CA19-9 and glycated hemoglobin was non-existent.

Furthermore, BMI, TC, TG, LDL-c, FPG, 2hPG, HbA1c, GA, and the HOMA-IR index changed rapidly, progressively and significantly 12 weeks after RYGB in a cohort of patients diagnosed with obesity and type 2 diabetes. In accordance with this finding, the clinical and laboratory manifestations of type 2 diabetes are resolved or improved in the greater majority of patients after bariatric surgery<sup>19,20</sup>. Serum levels of CA19-9 decreased markedly and significantly 12 weeks after RYGB, similar to the patients treated with sulfonylureas or insulin<sup>21</sup>.

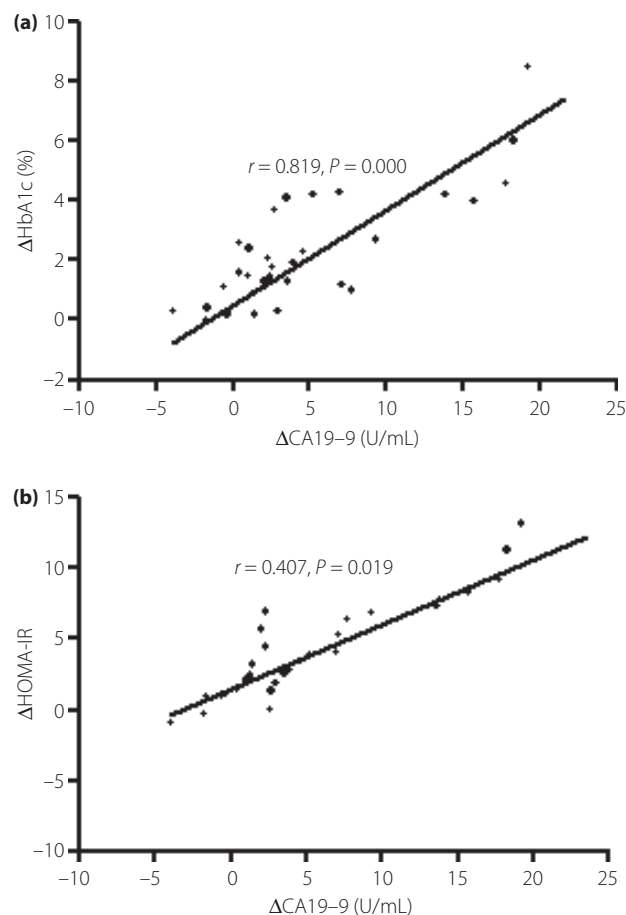
**Table 4** | Changes in anthropometric and biochemical parameters showing significant correlations with changes in serum levels of carbohydrate antigen 19-9 at 12 weeks after Roux-En-Y gastric bypass treatment

	$\Delta$ CA19-9	
	Univariate†	
	<i>r</i>	<i>P</i>
$\Delta$ BMI	−0.276	0.121
$\Delta$ TC	0.449**	0.009
$\Delta$ TG	0.038	0.834
$\Delta$ HDL-c	0.049	0.787
$\Delta$ LDL-c	0.264	0.138
$\Delta$ FPG	0.552**	0.001
$\Delta$ 2hPG	0.623**	0.000
$\Delta$ HbA1c	0.819**	0.000
$\Delta$ GA	0.711**	0.000
$\Delta$ HOMA-IR	0.407*	0.019
$\Delta$ HOMA-B%	−0.113	0.533

\* $P < 0.05$ , \*\* $P < 0.01$ . †Pearson's correlation analyses were carried out. 2hPG, 2-h postchallenge plasma glucose; BMI, body mass index; CA19-9, carbohydrate antigen 19-9; FPG, fasting plasma glucose; GA, glycated albumin; HbA1c, glycated hemoglobin; HDL-c, high density lipoprotein cholesterol; HOMA-B%, homeostasis model assessment index of  $\beta$ -cell function; HOMA-IR, homeostasis model assessment index of insulin resistance; LDL-c, low density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride.

Changes in HbA1c and FPG were independently and positively related to the changes in CA19-9. HbA1c is a marker of chronic glucose toxicity, which might result from exposure to chronic oxidative stress due to poor long-term glycemic control<sup>22–24</sup>. The present study provides clinical evidence that improved glucose control after RYGB is an important regulator of serum levels of CA19-9 in patients with obesity and type 2 diabetes. Consistent with the current findings, Murai *et al.*<sup>21</sup> reported that the serum levels of CA19-9 in six diabetic patients with markedly elevated CA19-9 levels decreased in conjunction with HbA1c after treatment with sulfonylureas or insulin. Additionally, Benhamou *et al.*<sup>7</sup> showed that in patients having the worst metabolic control (ketoacidosis and hyperglycemic coma), CA 19-9 levels decreased after successful metabolic control. However, some controversy exists regarding this point, because Banfi *et al.*<sup>18</sup> did not find a correlation between CA19-9 and glycemia or glycated hemoglobin, and no differences between insulin-dependent and non-insulin-dependent patients were observed. A subgroup analysis of two diabetic patients by Ventrucchi *et al.*<sup>2</sup> showed that serum levels of CA19-9 were persistently elevated throughout the follow-up period (5 years). It is likely that diabetic patients with especially poor glucose control are more prone to persistent high serum levels of CA19-9.

Diabetes and obesity are often accompanied by abnormal blood lipid and lipoprotein profiles. In obesity and type 2



**Figure 2** | Correlations between the changes in serum levels of carbohydrate antigen 19-9 (CA19-9), and changes in glycated hemoglobin (HbA1c) and Homeostasis Model of Assessment of Insulin Resistance (HOMA-IR). (a) Correlations of the changes in serum levels of CA19-9 and the changes in levels of HbA1c. (b) Correlations of changes in serum levels of CA19-9 and the changes in the HOMA-IR index. RYGB, Roux-En-Y gastric bypass.

diabetes patients in the current study, a relationship between the change in serum levels of CA19-9 and the change in TC was observed, although the change in TC was not independently related to CA19-9. Hao *et al.*<sup>25</sup> suggested that excess cellular cholesterol plays a direct role in islet pancreatic  $\beta$ -cell dysfunction, and might be a key factor underlying the progression of type 2 diabetes. Using several animal models, they showed that elevated serum cholesterol leads to increased cholesterol in pancreatic islets.

The novel finding of the present study was the independent and positive relationship between the change in serum levels of CA19-9 and the HOMA-IR index after RYGB. To our knowledge, no correlation between CA19-9 and this index has been previously reported, although  $\beta$ -cell function seldom changes after RYGB. The precise mechanism responsible for the CA19-9-associated decrease in the HOMA-IR index is



**Table 5** | Multiple stepwise regression analysis showing variables independently associated with changes in serum levels of carbohydrate antigen 19-9

Independent Variable enter the Model	$\beta$	SEM	Standardized $\beta$	$t$	$P$
$\Delta$ HbA1c	1.906	0.273	0.598	6.976	0.000
$\Delta$ FPG	0.529	0.134	0.309	3.948	0.000
$\Delta$ HOMA-IR	0.238	0.086	0.235	2.753	0.010

A multiple stepwise regression analysis was carried out. Age, sex, and changes in total cholesterol, fasting plasma glucose (FPG), 2-h postchallenge plasma glucose, glycated hemoglobin (HbA1c), glycated albumin and homeostasis model assessment index of insulin resistance (HOMA-IR) were included in the original model. SEM, standard error of the mean.

unclear. Glucose toxicity is an acquired factor that induces IR, and good glycemic control is negatively correlated with IR<sup>24,26</sup>. Therefore, the change in serum levels of CA19-9 might parallel the changes in HbA1c and IR. Furthermore, according to a new understanding of the concepts underlying the pathogenesis of diabetes, type 2 diabetes might be considered the last step of chronic pancreatitis, and the elevation of CA 19-9 could be due to chronic pancreatitis and not to pancreatic cancer<sup>21</sup>. The histology of pancreatic islets from patients with type 2 diabetes was known to be associated with an inflammatory process, which also involved the exocrine pancreas<sup>27–29</sup>. There appears to be an intimate relationship between metabolic diseases and immune dysfunction; the glycemic and lipid toxicities in obesity might lead to the initiation of a chronic inflammatory state, which leads to IR<sup>30</sup>. Thus, CA19-9, a marker of chronic pancreatitis, might be an indicator of inflammation in adipose tissue that was activated by the immune system of obese individuals with type 2 diabetes, and could correlate with IR. The present findings support the idea that increased serum levels of CA19-9 might be a biomarker of IR and glycemic metabolism in patients with obesity and type 2 diabetes after the rapid metabolic control by RYGB. The decreased serum levels of CA19-9 in patients with obesity and type 2 diabetes after RYGB suggest that further investigation of pancreatitis, glycemic and lipid control, and IR is warranted. These results could indicate the requirement for evaluation of IR in patients with high CA 19-9 levels.

One limitation of the present study was the small sample size with a short follow-up period. Additionally, CA 19-9 is not expressed in genotype negative subjects with Lewis blood group. It has been reported that those with the Lewis blood group phenotype of Lea (23%) had higher serum levels of CA19-9 than those of Leb (67%) and Le(-) (10%)<sup>31,32</sup>; but Lewis blood was not tested in the present study.

In summary, the present study is the first prospective investigation to show that the HOMA-IR index is a contributing factor in the changes of serum levels of CA19-9 after the rapid metabolic control by RYGB. Therefore, serum levels of CA19-9

might be an effective indicator of IR, and glycemic and lipid metabolism in patients with obesity and type 2 diabetes after RYGB, as well as a method of evaluating the short-term effects of glycolipid toxicity on IR in these patients.

## ACKNOWLEDGMENTS

This work was funded by the Science Foundation of Shanghai Jiao Tong University Affiliated Sixth People's Hospital (no. 1435), the Chinese National 973 Program (2013CB530606), Major Program of Shanghai Municipality for Basic Research (08dj1400601), Shanghai Key Laboratory of Diabetes Mellitus (08DZ2230200) and Key Discipline of Public Health of Shanghai (Epidemiology) (12GWZX0104). The authors declare no conflict of interest.

## REFERENCES

- Koprowski H, Steplewski Z, Mitchell K, *et al.* Colorectal carcinoma antigens detected by hybridoma antibodies. *Somatic Cell Genet* 1979; 5: 957–971.
- Ventrucci M, Pozzato P, Cipolla A, *et al.* Persistent elevation of serum CA 19-9 with no evidence of malignant disease. *Dig Liver Dis* 2009; 41: 357–363.
- Goonetilleke KS, Siriwardena AK. Systematic review of carbohydrate antigen (CA 19-9) as a biochemical marker in the diagnosis of pancreatic cancer. *Eur J Surg Oncol* 2007; 33: 266–270.
- Nakamura N, Aoji O, Yoshikawa T, *et al.* Elevated serum CA19-9 levels in poorly controlled diabetic patients. *Jpn J Med* 1986; 25: 278–280.
- Gul K, Nas S, Ozdemir D, *et al.* CA 19-9 level in patients with type 2 diabetes mellitus and its relation to the metabolic control and microvascular complications. *Am J Med Sci* 2011; 341: 28–32.
- Uygur-Bayramicli O, Dabak R, Orbay E, *et al.* Type 2 diabetes mellitus and CA 19-9 levels. *World J Gastroenterol* 2007; 13: 5357–5359.
- Benhamou PY, Vuillez JP, Halimi S, *et al.* Influence of metabolic disturbances of diabetes mellitus on serum CA 19-9 tumor marker. *Diabete Metab* 1991; 17: 39–43.
- Petit JM, Vaillant G, Olsson NO, *et al.* Elevated serum CA19-9 levels in poorly controlled diabetic patients. Relationship with Lewis blood group. *Gastroenterol Clin Biol* 1994; 18: 17–20.
- Huang Y, Xu Y, Bi Y, *et al.* Relationship between CA 19-9 levels and glucose regulation in a middle-aged and elderly Chinese population. *J Diabetes* 2012; 4: 147–152.
- Huang CK, Shabbir A, Lo CH, *et al.* Laparoscopic Roux-en-Y gastric bypass for the treatment of type II diabetes mellitus in Chinese patients with body mass index of 25–35. *Obes Surg* 2011; 25: 1344–1349.
- Adams TD, Gress RE, Smith SC, *et al.* Long-term mortality after gastric bypass surgery. *N Engl J Med* 2007; 357: 753–761.
- Pories WJ, Swanson MS, MacDonald KG, *et al.* Who would have thought it? An operation proves to be the most

- effective therapy for adult-onset diabetes mellitus *Ann Surg* 1995; 222: 339–350 discussion 350–352.
13. Steering Committee. The Asia-Pacific perspective: Redefining obesity and its treatment. International Diabetes Institute, Melbourne, 2000.
  14. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabet Med* 1998; 15: 539–553.
  15. Matthews DR, Hosker JP, Rudenski AS, *et al.* Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 1985; 28: 412–419.
  16. Tam CS, Xie W, Johnson WD, *et al.* Defining insulin resistance from hyperinsulinemic-euglycemic clamps. *Diabetes Care* 2012; 35: 1605–1610.
  17. Ritts RE, Del Villano BC, Go VL, *et al.* Initial clinical evaluation of an immunoradiometric assay for CA 19-9 using the NCI serum bank. *Int J Cancer* 1984; 33: 339–345.
  18. Banfi G, Ardemagni A, Bravi S, *et al.* Are diabetic metabolic compensation and CA19.9 really correlated?. *Int J Biol* 1996; 11: 207–210.
  19. Raghoebar R. Bariatric surgery-mediated weight loss and its metabolic consequences for type-2 diabetes. *World J Diabetes* 2013; 15: 47–50.
  20. Buchwald H, Estok R, Fahrbach K, *et al.* Weight and type 2 diabetes after bariatric surgery: systematic review and meta-analysis. *Am J Med* 2009; 122: 248–256.
  21. Murai J, Soga S, Saito H, *et al.* Study on the mechanism causing elevation of serum CA19-9 levels in diabetic patients. *Endocr J* 2013; 60: 885–891.
  22. Robertson RP, Harmon J, Tran PO, *et al.* Beta-cell glucose toxicity, lipotoxicity, and chronic oxidative stress in type 2 diabetes. *Diabetes* 2004; 53(Suppl 1): S119–S124.
  23. Karunakaran U, Park KG. A systematic review of oxidative stress and safety of antioxidants in diabetes: focus on islets and their defense. *Diabetes Metab J* 2013; 37: 106–112.
  24. Evans JL, Goldfine ID, Maddux BA, *et al.* Are oxidative stress-activated signaling pathways mediators of insulin resistance and beta-cell dysfunction? *Diabetes* 2003; 52: 1–8.
  25. Hao M, Head WS, Gunawardana SC, *et al.* Direct effect of cholesterol on insulin secretion: a novel mechanism for pancreatic  $\beta$ -cell dysfunction. *Diabetes* 2007; 56: 2328–2338.
  26. Zierath JR, Krook A, Wallberg-Henriksson H. Insulin action and insulin resistance in human skeletal muscle. *Diabetologia* 2000; 43: 821–835.
  27. Donath MY, Schumann DM, Faulenbach M, *et al.* Islet inflammation in type 2 diabetes: from metabolic stress to therapy. *Diabetes Care* 2008; 31: S161–S164.
  28. Hayden MR, Patel K, Habibi J, *et al.* Attenuation of endocrine-exocrine pancreatic communication in type 2 diabetes: pancreatic extracellular matrix ultrastructural abnormalities. *J Cardiometab Syndr* 2008; 3: 234–243.
  29. Hardt PD, Krauss A, Bretz L, *et al.* Pancreatic exocrine function in patients with type 1 and type 2 diabetes mellitus. *Acta Diabetol* 2000; 37: 105–110.
  30. Patel PS, Buras ED, Balasubramanyam A. The role of the immune system in obesity and insulin resistance. *J Obes* 2013; 2013: 616193. doi:10.1155/2013/616193. Epub 2013 Mar 21.
  31. Aoki Y, Yanagisawa Y, Ohfusa H, *et al.* Elevation of serum CA 19-9 in parallel with HbA1c in a diabetic female with the Lewis (a+b-) blood group. *Diabetes Res Clin Pract* 1991; 13: 77–81.
  32. Shimojo N, Naka K, Nakajima C, *et al.* The effect of non-insulin-dependent diabetes on serum concentrations of tumor-associated carbohydrate antigens of CA19-9, CA-50, and sialyl SSEA-1 in association with the Lewis blood phenotype. *Clin Chim Acta* 1990; 190: 283–289.