

# Improvements in insulin sensitivity and $\beta$ -cell function (HOMA) with weight loss in the severely obese

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## Abstract

**Aims** To examine the effect of weight loss on insulin sensitivity and  $\beta$ -cell function in severely obese subjects of varying glycaemic control.

**Patients and methods** Subjects were 254 (F:M 209:45) patients having adjustable gastric banding for severe obesity, with paired biochemical data from before operation and at 1-year follow up. The homeostatic model assessment method was used to calculate insulin sensitivity (HOMA%S) and  $\beta$ -cell function (HOMA%B). Subjects were grouped by diabetic status and by pre-weight loss HbA<sub>1c</sub>.

**Results** Initial mean (SD) weight and body mass index were 128 (26) kg and 46.2 (7.7) kg/m<sup>2</sup>, respectively, and at 1-year were 101 (22) kg and 36.4 (6.7) kg/m<sup>2</sup>. The percentage of excess weight lost (%EWL) was 44.3 (14)%. HOMA%S improved from 37.5 (16)% presurgery to 62 (25)% ( $P < 0.001$ ). %EWL was the only predictor of HOMA%S improvement ( $r = 0.28$ ,  $P < 0.001$ ). Subjects with normal fasting glucose, impaired fasting glucose and Type 2 diabetes had a fall, no change and increase in HOMA%B, respectively. The improvement in HOMA%B in subjects with diabetes ( $n = 39$ ) was inversely related to the time with diabetes ( $r = -0.36$ ,  $P = 0.02$ ). In non-diabetic subjects the HOMA%S–HOMA%B relationship was favourably altered with weight loss, so that for any given HOMA%S there was an increase in HOMA%B ( $f = 11.8$ ,  $P = 0.001$ ). This improvement in HOMA%B was positively related to %EWL ( $r = 0.25$ ,  $P = 0.019$ ).

**Discussion** There are beneficial changes in both insulin sensitivity and  $\beta$ -cell function with weight loss. Modern laparoscopic obesity surgery may have an important early role in the management of Type 2 diabetes in obese subjects.

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**Keywords** diabetes, LAGB, surgery, co-morbidity, metabolism

## Introduction

Insulin sensitivity falls with increasing obesity, especially central obesity, and there is associated impairment of glucose tolerance, dyslipidaemia and systemic hypertension. These features constitute the metabolic syndrome, and each is known to be associated with increased cardiovascular risk [1].

Two fundamental features in the pathogenesis of Type 2 diabetes are insulin resistance with both central and peripheral components, and pancreatic  $\beta$ -cell dysfunction which involves a failure to compensate for insulin resistance by secreting adequate insulin [2–4]. Weight reduction increases insulin sensitivity and improves diseases associated with the metabolic syndrome [5–7]. The effect of weight loss on pancreatic  $\beta$ -cell function is less clear, with reports of variable improvement [8–10].

Pancreatic  $\beta$ -cell function is influenced throughout life by a number of factors, some of which are potentially reversible. Abnormal  $\beta$ -cell function often has a genetic basis [11] and precedes the development of diabetes [12].  $\beta$ -cell function

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deteriorates with age [13], but more rapidly in those with impaired glucose tolerance [14] and diabetes, especially if poorly controlled. In addition, increasing obesity and insulin resistance increase the rate of  $\beta$ -cell deterioration in those with Type 2 diabetes [15]. Thus, deterioration of  $\beta$ -cell function is integrally involved in a positive feedback loop with obesity, insulin sensitivity and hyperglycaemia. Without intervention Type 2 diabetes is an inexorably progressive disease.

The beneficial effect of weight reduction on control of Type 2 diabetes has been known for some time [16]. Weight reduction is associated with a reduced risk of developing Type 2 diabetes, improved glycaemic control and, with considerable weight loss, remission of Type 2 diabetes [5,17–19]. Patients with Type 2 diabetes can also achieve significant benefit from modest weight loss [20,21].

Weight reduction has been difficult to achieve and maintain with non-surgical methods of weight loss. In the severely obese (body mass index (BMI) > 35 kg/m<sup>2</sup>) surgical methods of weight loss have a dramatic effect on preventing and treating Type 2 diabetes [5,17,18,22,23] and significant reduction in mortality has been demonstrated [24].

We have been using the laparoscopic adjustable gastric band (LAGB) as the primary surgical modality of treatment for severe obesity since 1994. The LAGB is a minimally invasive, surgical approach which has been shown to be safe and effective [25] and therefore has the potential to be broadly acceptable. It consists of a band of silicone elastomer with an inflatable inner shell and a buckle closure connected by tubing to an access port placed outside the abdominal cavity. The inner diameter of the band can be readily adjusted by the addition or removal of saline through the access port. The band is placed laparoscopically around the upper stomach approximately 1 cm below the esophago–gastric junction.

We have previously reported the broad health, co-morbidity and quality of life outcomes of severely obese Type 2 diabetic subjects after LAGB surgery [17]. The aim of this study was to assess insulin sensitivity and pancreatic  $\beta$ -cell function, using the homeostatic model assessment method [26], in severely obese patients before and 1 year following LAGB gastric restrictive surgery. Specifically we wished to: (i) identify and examine factors that predict preoperative insulin sensitivity and  $\beta$ -cell function and any changes in these with weight loss in severely obese subjects grouped (a) conventionally into normal, impaired and diabetic fasting plasma glucose and (b) in a novel way into quartiles based on preweight loss HbA<sub>1c</sub>; (ii) examine any change in the relationship between insulin sensitivity and  $\beta$ -cell function with weight loss in non-diabetic subjects.

## Patients and methods

Subjects for this study were selected from a group of patients to have LAGB surgery for severe obesity. Patients had a BMI > 35 kg/m<sup>2</sup> and had been extensively evaluated preoperatively. Informed written consent was obtained from all patients prior

to surgery. Biochemical tests are performed preoperatively and were repeated at yearly intervals following surgery as part of routine metabolic and nutritional follow up after LAGB surgery. This study was been carried out in accordance with the Helsinki convention.

## Study design

Data from 254 patients were selected for analysis in this study. Selection criteria required complete preoperative data that included height, weight, fasting plasma glucose, fasting plasma insulin, C-peptide and glycosylated haemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>) and complete paired data collected at 12 months ( $\pm 1$  month) after LAGB surgery. Patients with incomplete data or those reviewed outside the window period were excluded. All patients who fulfilled the criteria were included. Less than 2% of all operated patients were lost to follow up. Two sets of data were examined: the preoperative data and data at 1 year. The best measure of overall recent glycaemic control was considered to be HbA<sub>1c</sub> concentration. The two sets of data were examined in several ways: (i) subjects were grouped conventionally into normal, impaired fasting glucose or Type 2 diabetes; (ii) in a novel way into quartiles based on their pre-weight loss HbA<sub>1c</sub> level. This was chosen to allow analysis of the whole spectrum of preoperative HbA<sub>1c</sub> levels in this obese population; and (iii) with pre-weight loss HbA<sub>1c</sub> as a continuous variable.

A validated method of estimating insulin resistance and pancreatic  $\beta$ -cell function using the fasting plasma glucose and C-peptide measures was used to calculate percentage insulin sensitivity (HOMA%S) and the percentage of pancreatic  $\beta$ -cell function (HOMA%B). This homeostasis model assessment (HOMA) was originally developed by Matthews and has later been modified [26,27]. This method has been validated in subjects with Type 2 diabetes and obesity [28,29]. Diagnosis of Type 2 diabetes was based on the American Diabetes Association criteria [30].

Insulin levels were measured using an immunoenzymometric assay (MEIA; Abbott Diagnostics, North Chicago, IL, USA) with inter- and intra-assay coefficients of variation < 3%. C-peptide was measured using a double antibody competitive radioimmunoassay with inter- and intra-assay coefficients of variation < 7%. HbA<sub>1c</sub> levels were measured using an ion exchange high-pressure liquid chromatography method (Variant II HbA<sub>1c</sub> program; BioRad Labs, Hercules, CA, USA). Inter- and intra-assay coefficients of variation were < 2%. The non-diabetic reference range for HbA<sub>1c</sub> is 3.9–6.1% (mean 4.8%). Standard laboratory methods were used to measure fasting plasma glucose. The assays were performed in a Royal Australasian College of Pathologists accredited laboratory participating in the relevant external quality assurance programmes.

Weight loss is expressed as percentage of excess weight lost at 1 year (%EWL), a standard method for reporting results of weight loss surgery. Pre-operative excess weight is calculated as weight (kg) at the time of surgery less ideal weight (kg) as measured by the Metropolitan Life tables [31]. %EWL is calculated as weight change at 12 months, divided by excess weight preoperatively, multiplied by 100.

Our group has previously reported details of the LAGB surgery, complications and sustained weight loss achieved [32].

We have recently reported a broad range of outcomes for 50 consecutive diabetic subjects at 1 year following LAGB surgery [17].

### Statistical analysis

Two samples of quantitative variables were tested by paired or independent two-tailed Student's *t*-test with mean (SD) or by Wilcoxon sign test or Mann–Whitney *U*-test with median (interquartile range) as appropriate. More than two groups were examined with ANOVA using the Tukey method of *post hoc* analysis or Kruskal–Wallis as appropriate. Some quantitative laboratory variables, e.g. fasting plasma insulin, required log transformation prior to parametric analysis.  $\chi^2$  method with Fisher's exact test was used to test the significance of differences between proportions and categorical variables. Variables were assessed for correlation using parametric or non-parametric bivariate analysis as appropriate. Linear regression analysis was used to assess the effects of multiple factors on a normally distributed variable. A *P*-value of < 0.05 was considered statistically significant. No correction was used for assessing for correlation with multiple variables. All analysis was performed using SPSS for Windows version 10 [33].

### Results

There were 254 patients (of 259) with paired results preoperatively and at 1 year after surgery. There were 209 women and 45 men with a mean age (SD) of 42.3 (9.3) years. Five patients

could not be contacted and therefore 1-year data were unavailable. The study population weighed 128 (26) kg (mean (SD)) prior to surgery and weighed 101 (22) kg at 1 year following surgery. The mean percentage of excess weight lost (%EWL) at 1 year was 44.3 (14)%. Major improvements in all mean indices of glucose metabolism occur with weight loss. Geometric mean (interquartile range) concentrations of fasting plasma glucose, insulin and C-peptide were 5.7 (1.3) mmol/l, 15.8 (13.3) mU/l and 1.23 (0.46)  $\mu$ mol/ml, respectively, before surgery, and 5.0 (0.60) mmol/l, 9.6 (7.7) mU/l and 1.00 (0.44)  $\mu$ mol/l at 1 year after surgery (*P* < 0.001 for all).

### Normal, impaired fasting glucose, Type 2 diabetes

Initial analysis involved dividing the group into those with normal fasting glucose (*n* = 182), impaired fasting glucose (*n* = 33) and Type 2 diabetes (*n* = 39). Table 1 shows measures of HbA<sub>1c</sub>, HOMA%S and %B preoperatively, at 1 year and the change in these measures at 1 year.

There was a major increase in insulin sensitivity (HOMA%S) for the whole group, with weight loss, measured as %EWL, the only factor that predicted improvement in insulin sensitivity (*r* = 0.28, *P* < 0.001). The lower weight loss in those with Type 2 diabetes explained the lower rise in insulin sensitivity.

The mean changes in  $\beta$ -cell function (HOMA%B) were quite different for each of the three groups. There was a fall in those with normal fasting glucose, no significant change in those

**Table 1** Analysis of subject grouped by normal fasting glucose, impaired fasting glucose and those with Type 2 diabetes preoperatively: HbA<sub>1c</sub>, HOMA%S and HOMA%B (mean (SD)), pre-weight loss and 1 year following LAGB placement

	Normal, <i>n</i> = 182	Impaired fasting glucose, <i>n</i> = 33	Type 2 diabetes, <i>n</i> = 39	<i>P</i> -value* Difference between groups
Age (years)	41.1 (9.2)	44.5 (9.5)	46.5 (9.4)	0.002
BMI (kg/m <sup>2</sup> )	45.3 (7.2) <sup>a</sup>	48.3 (9.0)	48.6 (7.8) <sup>b</sup>	0.013
Percent male <sup>c</sup>	13%	24%	36%	0.002
%EWL	45.4 (15) <sup>a</sup>	44.3 (14)	38.4 (13) <sup>b</sup>	0.042
HbA <sub>1c</sub> (%)	5.40 (0.37)	6.16 (0.39)	8.04 (1.8)	
1-year HbA <sub>1c</sub> (%)	5.14 (0.39)	5.22 (0.41)	6.11 (1.4)	
Percent change in HbA <sub>1c</sub> <sup>d</sup>	−4.5 (7.5)	−14.8 (10)	−21.7 (19)	< 0.001
<i>P</i> -value of change within group†	< 0.001	< 0.001	< 0.001	
Pre-HOMA%S	41.7 (15) <sup>a</sup>	27.7 (11) <sup>b</sup>	26.9 (13) <sup>b</sup>	< 0.001
1-year HOMA%S	65.5 (24) <sup>b</sup>	60.1 (30) <sup>b</sup>	46.8 (21) <sup>a</sup>	< 0.001
Change HOMA%S	+23.8 (22)	+32.9 (30) <sup>a</sup>	+19.9 (18) <sup>b</sup>	0.031
<i>P</i> -value of change within group†	< 0.001	< 0.001	< 0.001	
Pre-HOMA%B	179 (57) <sup>b</sup>	160 (44) <sup>b</sup>	94 (52) <sup>a</sup>	< 0.001
1-year HOMA%B	150 (53)	148 (43)	134 (61)	0.138
Change HOMA%B	−29.8 (58) <sup>b</sup>	−11.1 (53) <sup>b</sup>	+40.1 (57) <sup>a</sup>	< 0.001
<i>P</i> -value of change within group†	< 0.001	0.14	< 0.001	

\*Differences between groups analysed using ANOVA with the Tukey method of *post hoc* analysis.

†Change within a group at 1 year was assessed using paired two-sided Student's *t*-test.

Group mean values marked (a) were significantly different from those marked (b).

<sup>c</sup> $\chi^2$ .

<sup>a</sup>Percent change in HbA<sub>1c</sub> for all three groups was significantly different from one another.

HOMA%B, Homeostatic model assessment method for calculating  $\beta$ -cell function; LAGB, laparoscopic adjustable gastric band; BMI, body mass index; %EWL, percentage of excess weight lost; HOMA%S, homeostatic model assessment method for calculating insulin sensitivity.

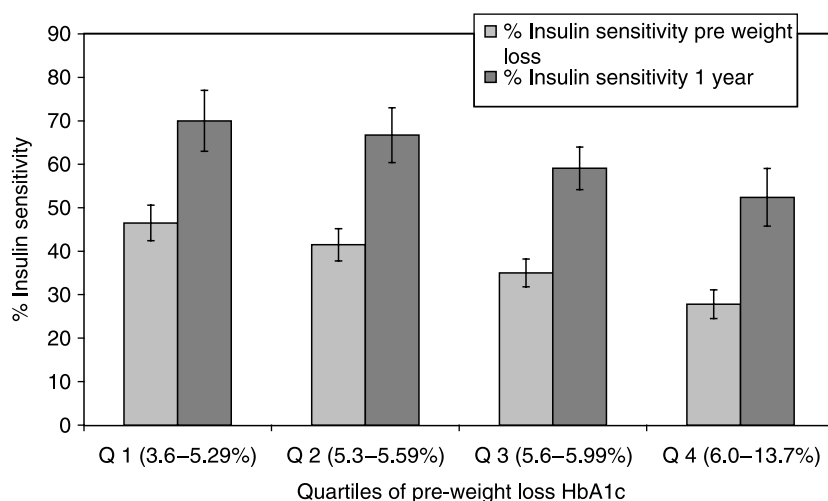
**Table 2** Characteristics of four groups based on the quartiles for presenting glycosylated HbA<sub>1c</sub>, and significant differences between groups

	Total, n = 254	Quartile 1, n = 62	Quartile 2, n = 59	Quartile 3, n = 73	Quartile 4, n = 60	P-value*
HbA <sub>1c</sub> range (%)	3.6–13.7	3.6–5.29	5.3–5.59	5.6–5.99	6.0–13.7	
Age (years)	42.3	40.3 <sup>a</sup>	41.8	41.7	45.6 <sup>b</sup>	0.02
Percent male	18	7	16	16	33	< 0.001†
Weight (kg)	128	121 <sup>a</sup>	125	131	135 <sup>b</sup>	0.006
BMI	46.2	44.1 <sup>a</sup>	44.6 <sup>a</sup>	47.4	48.5 <sup>b</sup>	0.003
%EWL1	44%	46%	43%	45%	42%	0.5

The percentage of excess weight loss for groups at 1 year is included.

\*There is a significant difference between groups marked (a) and (b) (ANOVA two-sided, *post hoc* analysis Tukey method).

† $\chi^2$  method.



**Figure 1** Insulin sensitivity (HOMA%S) for 254 patients before (light grey) and 1 year after (dark grey) LAGB weight loss surgery. Quartiles based on preoperative HbA<sub>1c</sub> levels. (Group mean levels  $\pm$  95% confidence interval of mean.)

with impaired fasting glucose, and an increase in those with Type 2 diabetes. At 1 year there was no significant difference in HOMA%B between the three groups (Table 1).

The rise in  $\beta$ -cell function amongst diabetic subjects was negatively related to the time that the patient had had a diagnosis of diabetes ( $r = -0.36$ ,  $P = 0.02$ ). Those with known diabetes < 3 years ( $n = 20$ , median 1 year) had a mean rise in HOMA%B of 62.7 (56)% and for those  $\geq 3$  years ( $n = 19$ , median 5 years) a mean rise of 13.4 (59)% ( $P = 0.02$ ). This remained significant after controlling for the patients' age, presenting BMI and %EWL ( $P = 0.03$ ).

#### Quartiles of HbA<sub>1c</sub>

The patients were divided into four groups based on their presenting HbA<sub>1c</sub> level. Cut-offs for quartiles of HbA<sub>1c</sub> were 25th percentile 5.3%, 50th percentile 5.6%, and 75th percentile 6.0%. Of the 39 subjects with Type 2 diabetes, 36 were in quartile 4 with the others in quartile 3. Of the 33 with impaired fasting glucose, 21 were in quartile 4 and the remaining 12 were in quartile 3. Thus 57 of the 60 subjects in quartile 4 had impaired fasting glucose or Type 2 diabetes.

The characteristics of the four groups based on their presenting HbA<sub>1c</sub> are shown in Table 2. Greater age, weight and BMI, and

male sex are associated with higher HbA<sub>1c</sub> levels. There was no significant difference in %EWL between the four groups ( $P = 0.5$ ).

#### Insulin sensitivity

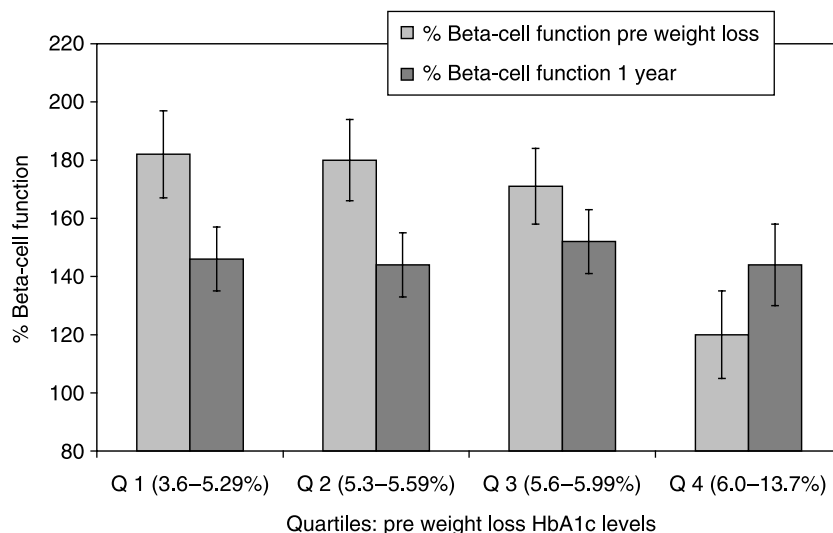
Clinical features that were independent preoperative predictors of low insulin sensitivity were higher BMI ( $r = -0.35$ ,  $P < 0.001$ ) and male sex ( $r = -0.23$ ,  $P < 0.001$ ) with a combined effect of  $r^2 = 0.17$ . There was a progressive fall in preoperative HOMA%S from quartiles 1–4 of HbA<sub>1c</sub> level (Fig. 1). Log<sub>e</sub>-transformed HbA<sub>1c</sub> correlates with preoperative HOMA%S ( $r = -0.36$ ,  $P < 0.001$ ).

Improvement in insulin sensitivity affected all four groups equally based on preoperative HbA<sub>1c</sub> concentration (Figs 1 and 3). This was confirmed using HbA<sub>1c</sub> concentration as a continuous variable. The extent of improved insulin sensitivity can be seen in Fig. 1. Subjects in the least insulin-sensitive group had insulin sensitivity levels at 1 year comparable to the most sensitive quartile preoperatively.

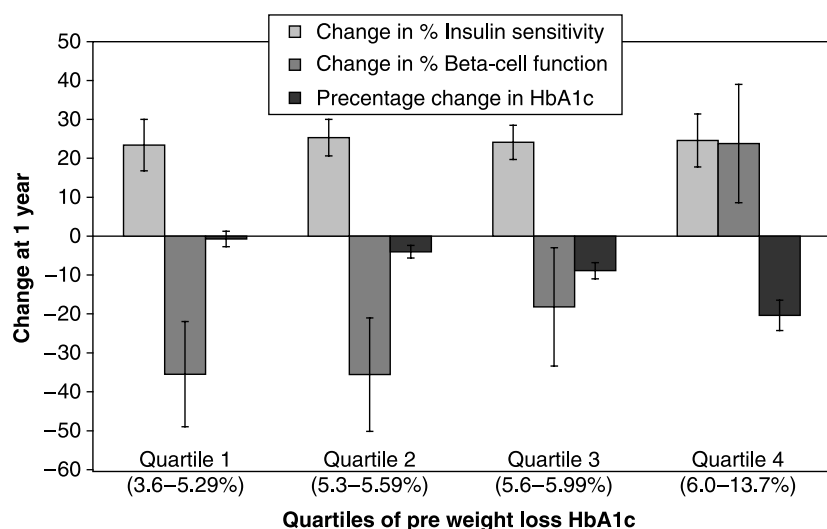
#### Pancreatic $\beta$ -cell function

Age was the only clinical feature that predicted lower pre-weight loss  $\beta$ -cell function ( $r = -0.23$ ,  $P < 0.001$ ) other than a

**Figure 2**  $\beta$ -cell function (HOMA%B) for 254 patients before (light grey) and 1 year after (dark grey) LAGB weight loss surgery. Quartiles based on preoperative HbA<sub>1c</sub> levels. (Group mean levels  $\pm$  95% confidence interval of mean.)



**Figure 3** Mean change ( $\pm$ 95% CI) of percent  $\beta$ -cell function (dark grey), percent insulin sensitivity (light grey) (HOMA) and percentage change in HbA<sub>1c</sub> (black) with weight loss following LAGB surgery ( $n = 254$ ). Quartiles based on preoperative HbA<sub>1c</sub> levels.



diagnosis of diabetes. Despite a progressive fall in pre-weight loss HOMA%S over the four quartiles, there was no compensatory increase in  $\beta$ -cell function (Fig. 2), but indeed a decrease as log<sub>e</sub> HbA<sub>1c</sub> increased ( $r = -0.52$ ,  $P < 0.001$ ). This remained when subjects with diabetes were excluded from the analysis ( $r = -0.20$ ,  $P = 0.003$ ). This indicates an increasingly inadequate  $\beta$ -cell response for subjects with increasing HbA<sub>1c</sub> concentrations.

There was a small but significant fall in  $\beta$ -cell function for the whole group at 1 year following surgery. Change in  $\beta$ -cell function was positively correlated with preoperative fasting plasma glucose ( $r = 0.45$ ,  $P < 0.001$ ), HbA<sub>1c</sub> ( $r = 0.39$ ,  $P < 0.001$ ) and a diagnosis of diabetes ( $r^2$  Cox and Snell = 0.14,  $P < 0.001$ ). Fasting glucose and a diagnosis of diabetes had independent effects on variance with a combined  $r^2 = 0.26$ .

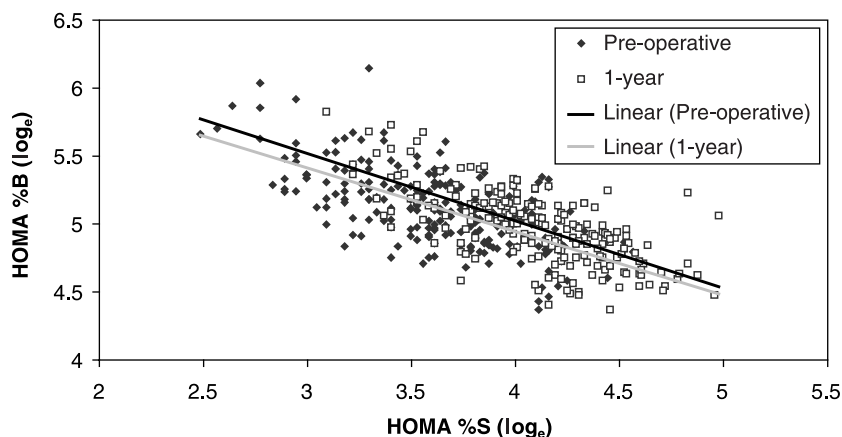
In contrast to the effects of weight loss on insulin sensitivity, there were differential effects on  $\beta$ -cell function for quartiles based on pre-weight loss HbA<sub>1c</sub> level. Mean  $\beta$ -cell function fell significantly for quartiles 1–3 and rose significantly for

quartile 4 (HbA<sub>1c</sub> > 6%) (Fig. 2). The fall in  $\beta$ -cell secretory function in quartiles 1–3 suggests reduced  $\beta$ -cell demand, whilst the rise in quartile 4 suggests reversal of  $\beta$ -cell dysfunction. Preoperative  $\beta$ -cell function in quartile 4 was significantly lower than the three other quartiles (analysis of variance (ANOVA),  $P < 0.001$ ). However, at 1 year there was no difference in  $\beta$ -cell function between any of the quartiles (ANOVA,  $P = 0.71$ ).

The change in HOMA%B and S%, and percentage change in HbA<sub>1c</sub> for quartiles of preoperative HbA<sub>1c</sub> are shown in Fig. 3. The fall in HbA<sub>1c</sub> for those in quartile 4 was associated with significant improvement in insulin sensitivity and  $\beta$ -cell function.

**The relationship between HOMA%B and HOMA%S in non-diabetic patients**

The nature of the fall in  $\beta$ -cell secretion in non-diabetic subjects is potentially important. As expected, there was an inverse relationship between HOMA%B and HOMA%S (both preoperative and at 1 year) for the non-diabetic patients



**Figure 4** The relationship between ( $\log_e$  transformed HOMA %S and %B) insulin sensitivity and  $\beta$ -cell function in those without diabetes ( $n = 216$ ) preoperatively (solid diamonds) and at 1 year after (open square) LAGB surgery. The preoperative (grey) and 1 year (black) linear trend lines are shown. Linear trend lines are significantly different ( $P = 0.001$ , univariate ANOVA).

(Fig. 4). This reflects the physiological compensation of  $\beta$ -cell insulin secretion with increasing insulin resistance. The improvement in insulin sensitivity and reduced  $\beta$ -cell secretion with weight loss can be visualized with the right shift of the 1-year scatter plot points (Fig. 4, open squares).

After controlling for the differences in insulin sensitivity,  $\beta$ -cell function increased at 1 year after surgery for non-diabetic patients ( $F = 11.8$ ,  $P = 0.001$ , univariate ANOVA). This effect can be seen in Fig. 4 as a significant difference between preoperative and 1-year trend lines. Furthermore, %EWL was found to be an independent predictor of improved  $\beta$ -cell function ( $r = 0.25$ ,  $P = 0.019$ ) after controlling for the change in HOMA %S ( $r = -0.43$ ,  $P < 0.001$ ) with a combined  $r^2 = 0.23$ . Hence, the HOMA %S–HOMA %B relationship itself is favourably altered in non-diabetic subjects with weight loss, so that for any given insulin sensitivity there is an increase in  $\beta$ -cell secretion. The extent of the improved relationship is related to the %EWL.

## Discussion

This study shows that improvement in insulin sensitivity with weight loss is related to the degree of weight loss and is not influenced by preoperative fasting glucose or HbA<sub>1c</sub> concentration. While modest weight loss for those with Type 2 diabetes is of benefit [20,21], greater benefit through improved insulin sensitivity is likely to be achieved with more substantial weight loss. Change in  $\beta$ -cell function with weight loss was shown to vary differentially by fasting glucose status and through the quartiles of HbA<sub>1c</sub>. Those with normal fasting glucose, impaired fasting glucose and Type 2 diabetes had a fall, no change and increase in  $\beta$ -cell secretion, respectively. The fall in HbA<sub>1c</sub> concentration with weight loss in those with Type 2 diabetes is a result of a favourable change in the two fundamental features of Type 2 diabetes [2]: improvement in insulin sensitivity, and improved  $\beta$ -cell function, as measured indirectly by the homeostasis method [27].

Improved  $\beta$ -cell secretion in subjects with diabetes indicates that, to some extent,  $\beta$ -cell dysfunction is reversible with

weight loss. Furthermore, it strongly supports the hypothesis that obesity, or the metabolic environment associated with it, is causative of  $\beta$ -cell degeneration. Lipotoxicity or glucose toxicity may be important [34,35]. Raised levels of free fatty acids, cytosolic triglycerides or hyperglycaemia associated with obesity and insulin resistance may affect  $\beta$ -cell function in those predisposed to diabetes [35–37] and provide a possible explanation for the reversibility with weight loss and improved insulin sensitivity. This study also highlights the clinical significance of  $\beta$ -cell improvement associated with substantial weight loss, as subjects with Type 2 diabetes developed similar  $\beta$ -cell secretory function to other subjects by 1 year after surgery.

As a response to reduced insulin sensitivity,  $\beta$ -cell secretion should theoretically increase. The absence of a difference in  $\beta$ -cell secretion between HbA<sub>1c</sub> quartiles 1 and 2 preoperatively, and the comparatively reduced  $\beta$ -cell secretion in quartiles 3 and 4 (the subjects with greater insulin resistance) suggest that  $\beta$ -cell function is progressively impaired with rising HbA<sub>1c</sub> concentration. There does not appear to be a threshold effect, suggesting that in these severely obese subjects  $\beta$ -cells are operating close to their functional limit.

In non-diabetic subjects we find a considerable fall in  $\beta$ -cell secretion with improved insulin sensitivity in association with weight loss. This is an expected physiological response to improved insulin sensitivity and lower plasma glucose concentrations, indicating lower  $\beta$ -cell demand. In addition, we demonstrate two potentially important features of  $\beta$ -cell function in these non-diabetic subjects. First, there is improved  $\beta$ -cell secretion for any given level of insulin sensitivity after weight loss, and second, this improvement is positively related to the percentage of excess weight lost.

The favourable improvement in insulin sensitivity and changes in  $\beta$ -cell function with weight loss should reduce  $\beta$ -cell stress [38] and are likely to lead to the development of  $\beta$ -cell functional reserve. The changes demonstrated may help explain the marked reduction in the development of diabetes in overweight adults who achieve and maintain weight loss [17,39].

Previous studies have shown improvement in  $\beta$ -cell function with weight loss in subjects with Type 2 diabetes [9,40–42]. However, the level of improvement varies and some abnormalities of meal-stimulated insulin oscillatory activity remain [8,10]. Improvement in  $\beta$ -cell function is probably influenced by factors other than weight loss. Our study shows that those with known diabetes for < 3 years have greater improvement in  $\beta$ -cell function with weight loss than do those with a longer diagnosis, after controlling for age and percentage of excess weight lost. We have previously shown that a shorter time with a diagnosis of diabetes is an important positive predictor of remission of Type 2 diabetes with weight loss [17]. This is presumably related to an irreversible fall in  $\beta$ -cell function with time in subjects with diabetes [43].  $\beta$ -cells in cell culture behave similarly, with those exposed to short periods of hyperglycaemia more likely to recover secretory function than those exposed to prolonged periods [35].

Early and intensive treatment of Type 2 diabetes reduces morbidity, mortality and poor quality of life [44–46]. It also reduces the rate of deterioration of pancreatic  $\beta$ -cell function [47]. Substantial weight loss through obesity surgery has a powerful effect on the prevention and management of Type 2 diabetes [24]. We demonstrate the beneficial changes in both insulin sensitivity and  $\beta$ -cell function with weight loss. These changes appear to be maximal in recently diagnosed Type 2 diabetic subjects. The benefit through improved  $\beta$ -cell function in those with Type 2 diabetes is limited by the time with the condition [17]. Early detection of Type 2 diabetes in our community is commendable, but implies optimal management of those detected. As obesity surgery is currently the only method of achieving and sustaining substantial weight loss, its potential should be explored as part of an early intervention programme in the severely obese subject with impaired fasting glucose or Type 2 diabetes.

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