## ARTICLE

# Laparoscopic adjustable gastric banding and progression from impaired fasting glucose to diabetes

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### Abstract

*Aims/hypothesis* Obesity and dysglycaemia are major risk factors for type 2 diabetes. We determined if obese people undergoing laparoscopic adjustable gastric banding (LAGB) had a reduced risk of progressing from impaired fasting glucose (IFG) to diabetes.

*Methods* This was a retrospective cohort study of obese people with IFG who underwent LAGB. Weight and diabetes outcomes after a minimum follow-up period of 4 years (mean  $\pm$  SD 6.1 $\pm$ 1.7 years) were compared with those of Australian adults with IFG from a population-based study (AusDiab).

*Results* We identified 281 LAGB patients with baseline IFG. Their mean  $\pm$  SD age and BMI were 46 $\pm$ 9 years and 46 $\pm$ 9 kg/m<sup>2</sup>, respectively. The diabetes incidence for patients in the lowest, middle and highest weight loss tertile were 19.1, 3.4 and 1.8 cases/1,000 person-years, respectively. The AusDiab cohort had a lower BMI (28 $\pm$ 5 kg/m<sup>2</sup>) and a diabetes incidence of 12.5 cases/1,000 person-years. This increased

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to 20.5 cases/1,000 person-years when analysis was restricted to the 322 obese AusDiab participants, which was higher than the overall rate of 8.2 cases/1,000 person-years seen in the LAGB group (p=0.02). Multivariable analysis of the combined LAGB and AusDiab data suggested that LAGB was associated with ~75% lower risk of diabetes (OR 0.24 [95% CI 0.10, 0.57], p=0.004).

*Conclusions/interpretation* In obese people with IFG, weight loss after LAGB is associated with a substantially reduced risk of progressing to diabetes over  $\geq$ 4 years. Bariatric surgery may be an effective diabetes prevention strategy in this population.

**Keywords** Bariatric surgery · Diabetes prevention · Impaired fasting glucose · Obesity

## Abbreviations

FPG	Fasting plasma glucose
IFG	Impaired fasting glucose
IGT	Impaired glucose tolerance
LAGB	Laparoscopic adjustable gastric banding
SOS	Swedish Obese Subjects

# Introduction

Effective strategies to prevent type 2 diabetes are fundamental to addressing the huge health and economic burden of this disease [1]. People with impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT) are at high risk of developing type 2 diabetes [2], and obesity increases the risk of progressing from IGT to diabetes [3, 4].

In moderately overweight populations with IGT, intensive lifestyle intervention [5–8] or drug therapy with metformin [5, 6], acarbose [9] or pioglitazone [10] reduces the risk of progression to type 2 diabetes by 30–70%. There is less

evidence to guide diabetes prevention strategies for people with severe obesity (BMI >35 kg/m<sup>2</sup>). Torgerson et al [11] showed that orlistat reduced the risk of diabetes by 37% over 4 years in a predominantly normoglycaemic population of severely obese people. In addition, a trial designed to determine the effects of phentermine/topiramate combination on body weight in a population with a mean BMI of 36 kg/m<sup>2</sup> reported that 2 years of drug therapy achieved ~10% weight loss and reduced the risk of diabetes by ~65% [12].

Bariatric surgery is an effective and durable weight loss treatment [13] that has been proven in three randomised controlled trials to induce remission of type 2 diabetes more commonly than a conventional medical treatment programme [14–16]. This raises the possibility of using bariatric surgery to prevent diabetes in high-risk severely obese populations. This proposition was strengthened by a recent report by the Swedish Obese Subjects (SOS) investigators [17]. Using a case–control study of non-diabetic people with a BMI >34 kg/m<sup>2</sup> (mean  $\pm$  SD 42 $\pm$ 5 kg/m<sup>2</sup>), the investigators showed that people undergoing gastroplasty, gastric band or gastric bypass surgery achieved an average weight loss of 20 kg after 15 years and ~80% reduction in diabetes incidence, compared with a lifestyle intervention delivered to an equally obese control group.

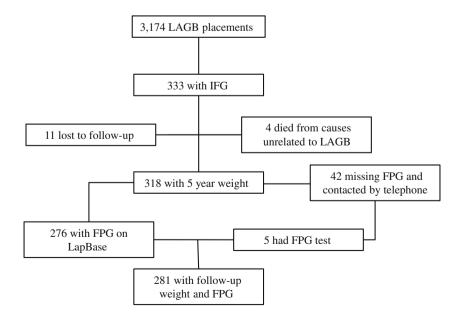
To clarify the potential benefit of substantial weight loss in preventing type 2 diabetes, we determined the relationship between weight loss after laparoscopic adjustable gastric banding (LAGB) and the rate of progression from IFG to type 2 diabetes. We also compared the overall LAGB patient outcomes with those of a contemporaneous communitydwelling cohort of predominantly non-obese people with IFG who participated in the AusDiab Study [18].

## Methods

*Study design and participants* We performed a longitudinal cohort study of all patients treated for obesity by authors P. O'Brien and S. Skinner at the Centre for Bariatric Surgery in Melbourne between October 1995 and August 2007. Postoperative management mandated regular medical review to assess weight loss and to adjust the band. The median (interquartile range) number of clinic attendances in follow-up years 1, 2, 3, 4 and 5 was 8 (6–10), 6 (2–9), 3 (1–7), 2 (0–6) and 2 (0–4), respectively.

Data sources and measurement All patients had fasting plasma glucose (FPG), lipid profile and HbA<sub>1c</sub> measured up to 3 months before LAGB. Follow-up FPG levels were ordered as required by the family physician or bariatric physician. These assays were performed by clinical laboratories in Melbourne, and results were included if generated at least 4 years after surgery. Nearly all follow-up FPG levels were obtained from an electronic clinical record (LapBase; LapBase Pty Ltd, Melbourne, VIC, Australia), with five FPG values obtained after patients were telephoned and asked to have the test (see Fig. 1). Of the 281 follow-up FPG values, 56 were obtained between 4 and 5 years of follow-up, and the rest after 5 years. If multiple FPG results were available, we used the first one obtained after 5 years of follow-up. Follow-up weight data were collated from LapBase. For correlations between weight loss and glycaemic status, weight records within 3 months of the follow-up FPG were used.

The AusDiab dataset comprised clinical and biochemical data obtained in 1999/2000 and again in 2004/2005 from over 11,000 community-dwelling Australians aged over 25 years [18]. The AusDiab subgroup used in this study comprised



#### Fig. 1 Study flow diagram

people with complete data who had IFG but not diabetes at baseline. To match for age, AusDiab participants over 55 years old were excluded.

The study was approved by the Monash University Human Research and Ethics Committee and was registered with the Australian and New Zealand Clinical Trials Registry (ACTR N12613000548730).

Definitions IFG was defined as FPG of 5.6–6.9 mmol/l (100– 125 mg/dl) in the context of no history of diabetes or of glucose-lowering drug use [19]. Diabetes was defined as a patient report of being diagnosed by another practitioner during the 5 year follow-up period or FPG of  $\geq$ 7.0 mmol/l based on the single value described above.

Statistical analysis Percentage weight loss measures from each patient were linearly interpolated at specific time points (0, 3, 6, 12, 18, 24, 30, 36, 42, 48, 54 and 60 months) using the approxfun function in R (www.r-project.org). For time points outside the measured range for a given patient, the final observed value was carried forward. Average weight loss over 5 years was calculated for each patient and used to compare the weight loss curves of different groups. Multivariable logistic regression with generalised linear models was performed separately for each cohort, and on the combined dataset using R. The significance of each variable was assessed by analysis of deviance using a  $\chi^2$  test. Other data were analysed using GraphPad Prism (v5.0a) software. Continuous variables were assessed using the *t* test. Comparison of rates of diabetes used Fisher's exact test and  $\chi^2$  test for trend, and assumed that the duration of follow-up was the same in each group. A *p* value of <0.05 was considered significant.

## Results

Figure 1 provides a flow chart for the participant selection. Of a total of 3,174 patients who underwent LAGB between October 1995 and August 2007, 333 (248 women and 85 men) had IFG (5.6–6.9 mmol/l) and no history of diabetes or of glucose-lowering drug use. Of these 333 people, 281 (84%; 210 women and 71 men) had follow-up weight and FPG data. Their baseline characteristics are given in Table 1.

After 5 years, the LAGB cohort lost an average of 25 kg, representing 19% weight loss and a mean BMI reduction from 46 to 37 kg/m<sup>2</sup>. Figure 2a shows the weight loss curves of the 14 and 169 patients who respectively did and did not develop diabetes after a minimum follow-up period of 4 years (mean  $\pm$  SD 6.1 $\pm$ 1.7 years). These weight trajectories were significantly different (*p* =0.003), whereas there were no significant differences between the weight trajectories of women compared with men, or of the 281 people with follow-up FPG compared with the 37 people with weight outcome data but no follow-up FPG. During the first 5 years of patient follow-up, revision surgery to resite the band was performed in 25% of women and 12% of men (*p* <0.02), and LAGB explant was performed

 Table 1
 Baseline characteristics of the LAGB and AusDiab cohorts and their subgroups

Characteristic/variable	LAGB	AusDiab					
	All (19±13% WL)	Tertile 1 (6±9% WL)	Tertile 2 (19±3% WL)	Tertile 3 (32±8% WL)	All	Non-obese	Obese
n	281	94	94	93	1,043	721	322
Percentage female	75	80	69	75	35**	45	$30^{\dagger\dagger}$
Age (years)	46±9	45±9	$47 \pm 10$	45±10	46±7	46±7	46±7
Weight (kg)	127±27	$120 \pm 22$	126±27	$134 \pm 31^{\dagger\dagger}$	84±16**	77±11	$100{\pm}15^{\dagger\dagger\dagger}$
Height (cm)	$167 \pm 9$	$166 \pm 8$	168±9	$167 \pm 9$	172±9**	$173 \pm 9$	$171 \pm 10$
BMI (kg/m <sup>2</sup> )	46±9	44±7	45±8	$48{\pm}10^{\dagger\dagger}$	28±5**	26±3	$34{\pm}4^{\dagger\dagger\dagger}$
Fasting blood indices							
Glucose (mmol/l)	$5.9 \pm 0.3$	$5.9 {\pm} 0.3$	$5.9 {\pm} 0.3$	$6.0 {\pm} 0.3$	5.9±0.3	5.9±0.3	$6.0 {\pm} 0.3$
HbA <sub>1c</sub> (%)	$5.7 {\pm} 0.4$	5.7±0.4	$5.7 {\pm} 0.4$	$5.7 {\pm} 0.5$	5.2±0.3**	5.2±0.3	$5.3 {\pm} 0.3$
HbA1c (mmol/mol)	39±4	39±4	39±4	39±5	33±3**	33±3	34±3
Total cholesterol (mmol/l)	$5.5 \pm 1.0$	$5.5 \pm 1.0$	$5.6 \pm 1.1$	$5.6 \pm 1.0$	5.7±1.0	5.7±1.0	5.8±1.0
Triacylglycerol (mmol/l)	$2.0 \pm 1.2$	$2.0 \pm 1.0$	$2.0{\pm}1.5$	$2.0 {\pm} 0.9$	1.7±1.2	1.6±1.0	$2.0{\pm}1.5^{\dagger\dagger}$
HDL-cholesterol (mmol/l)	$1.3 \pm 0.3$	1.3±0.3	1.3±0.3	1.3±0.3	$1.3 \pm 0.3$	$1.3 \pm 0.3$	$1.2{\pm}0.3^{\dagger}$

Continuous data are mean  $\pm$  SD

\* and <sup>†</sup> denote significant between- and within-group differences, respectively, with one, two and three symbols representing p < 0.05, p < 0.01 and p < 0.001, respectively. Within-group differences of LAGB patients were determined by  $\chi^2$  test for trend or ANOVA followed by post test for linear trend WL, weight loss

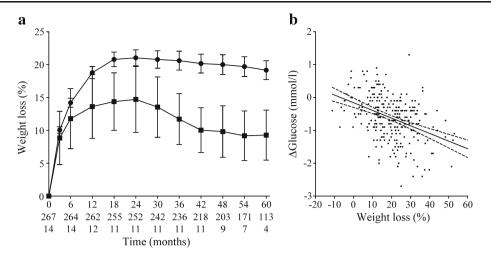


Fig. 2 Weight loss and its effect on FPG. (a) Weight trajectories of LAGB patients who did (n=14; squares) and who did not (n=267; circles) develop diabetes after a minimum of 4 years follow-up. Data are mean percentage weight loss and 95% CI. Numbers of patients with weight data at each time point are indicated below the

x axis. (b) Correlation between weight loss and  $\Delta$ FPG. Data from patients in the LAGB group who did not develop diabetes (*n*=267; one outlier with -62% weight loss omitted), with line of best fit (*m*=-0.023±0.003) and 95% CIs depicted in solid and dashed lines, respectively

in 14 patients (5%), of whom one proceeded to biliopancreatic diversion after 39 months of follow-up.

We divided the LAGB group into weight loss tertiles to determine the relationship between weight loss and risk of diabetes. In the 281 LAGB patients, weight loss correlated with baseline body weight, but not with any other baseline patient characteristic (Table 1). Fourteen patients developed diabetes during the study period, corresponding to an incidence rate of 8.2 cases/1,000 person-years. There were 12 cases of diabetes in women and two in men, corresponding to incidence rates of 9.2 and 4.9 cases/1,000 person-years, respectively, a difference that was not statistically significant. Table 2 shows the relationship between weight loss tertile and progression to diabetes. There was one case of diabetes in a patient in the highest tertile of weight loss: a 67-year-old woman who developed diabetes after gallstone pancreatitis complicated by recurring pancreatic pseudocysts and portal vein thrombosis. Diabetes incidence progressively reduced with weight loss, with 19.1, 3.4 and 1.8 cases/1,000 personyears in tertiles 1, 2 and 3, respectively (p < 0.001 for trend).

Regression analysis of weight change vs  $\Delta$ FPG reflected these findings, with 10% weight loss corresponding to a 0.23 mmol/l reduction in FPG after  $\geq$ 4 years (p <0.001; Fig. 2b).

We then compared these results with those of 1,043 community-dwelling Australians (362 women and 681 men) recruited into the AusDiab cohort study in 1999/2000 [20] who had IFG and were followed for 5 years (Table 1). In these people, the mean  $\pm$  SD age of 46 $\pm$ 7 years was comparable with that of the LAGB group, while BMI  $(28\pm5 \text{ kg/m}^2)$ and the proportion of women (35%) were significantly lower (p < 0.001 for each comparison). After 5 years, 65 AusDiab participants developed diabetes, yielding a diabetes incidence of 12.5 cases/1,000 person-years, a rate that was not significantly different from the rate seen in LAGB patients. However, AusDiab diabetes incidence increased significantly (p < 0.001) to 20.5 cases/1.000 person-years when analysis was restricted to obese participants (n=322; mean BMI  $34\pm4$  kg/m<sup>2</sup>). This rate was greater than the overall LAGB rate of 8.2 cases/1,000 person-years (p < 0.02).

Table 2 Five-year incidence of diabetes among women and men undergoing LAGB, according to weight loss

	Women			Men			Entire LAGB group					
	n	%WL	Cases	Incidence	n	%WL	Cases	Incidence	n	%WL	Cases	Incidence
Entire group	210	18±13	12	9.2	71	20±11	2	4.9	281	19±13	14	8.2
Tertile 1	70	5±10	9	20.6	24	10±5	2	14.4	94	6±9	11	19.1
Tertile 2	70	18±3	2	4.5	24	20±3	0	0	94	19±3	2	3.4
Tertile 3	70	32±7	1	2.4	23	32±9	0	0	93	32±8	1	1.8

%WL, percentage weight loss as mean ± SD

Incidence is cases/1,000 person-years

To adjust rates of progression to diabetes for possible relevant variables, we performed multivariable analyses. The input variables were baseline age, baseline BMI, baseline FPG, sex, percentage weight change, duration of follow-up and, for LAGB patients, revision surgery and/or band explant during the follow-up period. The outcome variable, progression to diabetes, was independently associated with poor weight loss and baseline FPG in the LAGB cohort, and with baseline FPG, baseline BMI and female sex in the AusDiab group (Table 3). To determine whether LAGB was independently associated with progression to diabetes, we combined data from both groups, replacing percentage weight change with the presence or absence of LAGB surgery. In this group of 1,324 individuals, LAGB was associated with a reduced risk of diabetes of more than 75% (OR 0.239 [95% CI 0.095, 0.571], p=0.004), with female sex and baseline FPG also significantly associated with progression to diabetes (Table 3).

## Discussion

We report long-term weight and diabetes outcomes for obese people with IFG who underwent LAGB surgery. Surgery induced a substantial and sustained mean weight loss of 19% of body weight, with one-fifth of patients requiring revision surgery to resite the band. These outcomes are similar to those observed in the general population of obese people who have this operation [13]. The rate of progression from IFG to diabetes reduced significantly across the tertiles of weight loss. Taken together with the findings of the multivariable analysis, we conclude that weight loss in obesity complicated by IFG prevents progression to diabetes. This accords with the

 Table 3 Multivariable analysis to determine correlates of progression from IFG to diabetes

Cohort	OR (95% CI)	p value					
LAGB cohort ( $n = 281$ )							
Weight loss (per 10% body mass)	0.57 (0.35, 0.86)	0.017					
Baseline glucose (per 0.1 mmol/l)	1.21 (1.04, 1.41)	0.013					
AusDiab ( $n = 1043$ )							
Baseline glucose (per 0.1 mmol/l)	1.39 (1.28, 1.51)	< 0.001					
Baseline BMI (per kg/m <sup>2</sup> )	1.05 (1.00, 1.11)	0.006					
Female sex	2.56 (1.44, 4.55)	0.001					
Both groups combined ( $n=1324$ )							
Baseline glucose (per 0.1 mmol/l)	1.33 (1.24, 1.42)	< 0.001					
Female sex	2.60 (1.55, 4.39)	0.001					
LAGB	0.24 (0.10, 0.57)	0.004					

Input variables were baseline age, BMI and fasting glucose, sex, percentage weight loss and duration of follow-up. Revision surgery and/or band explant were included in the LAGB incidence cohort analysis. In the combined analysis, these surgical outcomes were omitted and percentage weight loss replaced with presence or absence of LAGB surgery recent SOS findings [17], trials of weight loss drugs [11, 12] and other reports of remission of diabetes after medical [21] or surgically induced weight loss [14–16].

There are several reasons why the differences in diabetes incidence observed in the LAGB and AusDiab cohorts were underestimated. First, although surgical patients were followed-up on average 1 more year than AusDiab participants, we had to assume these variables were equal in order to perform statistical comparisons. Second, the risk of diabetes in severely obese people (BMI > 35 kg/m<sup>2</sup>) is roughly double that of less obese people [22-24], making it likely that the diabetes incidence of the obese AusDiab cohort (mean BMI  $34.3 \text{ kg/m}^2$ ) underestimated the baseline diabetes risk in our LAGB population. This accords with a much greater (over threefold) diabetes incidence of 91 cases/1,000 person-years observed in morbidly obese people (n=290, BMI 41±4 kg/m<sup>2</sup>) in the SOS control group who had IFG [17]. On the other hand, using the same definition of diabetes, the 301 members of the SOS surgical group with baseline IFG achieved similar weight loss and a slightly increased rate of diabetes (15/1,000 person-years after 15 years) compared with our LAGB patients (8/1,000 personyears after 6 years). Finally, the relatively small numbers of men undergoing LAGB surgery and of obese AusDiab participants reduced our ability to detect differences between these groups and their relevant comparators.

LAGB is a common outpatient procedure [25], and yet has comparable durability and a superior record of safety and patient acceptability compared with the two major alternatives of sleeve gastrectomy and gastric bypass surgery [13, 26]. These features are important considerations for the design of prevention strategies for type 2 diabetes in obesity.

In conclusion, we show that the rate of progression from IFG to diabetes is substantially reduced in obese people who undergo LAGB surgery. Given the uncertain efficacy of lifestyle intervention in severely obese people at risk of diabetes, these findings strengthen the case for a randomised trial to determine whether LAGB surgery is a safe and cost-effective approach to preventing type 2 diabetes in this population.

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**Contribution statement** All authors contributed to conception and design, acquisition of data, analysis and interpretation of data. JMW and PEO drafted the manuscript and revised it with all other authors, who also approved the final version. JMW takes full responsibility for the work as a whole, including the study design, access to data, and the decision to submit and publish the manuscript.

**Duality of interest** All authors declare that there is no duality of interest associated with this manuscript.

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