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ARTICLE

Gastric bypass surgery vs intensive lifestyle and medical intervention for type 2 diabetes: the CROSSROADS randomised controlled trial

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Abstract

Aims/hypothesis Mounting evidence indicates that Roux-en-Y gastric bypass (RYGB) ameliorates type 2 diabetes, but randomised trials comparing surgical vs nonsurgical care are needed. With a parallel-group randomised controlled trial (RCT), we compared RYGB vs an intensive lifestyle and medical intervention (ILMI) for type 2 diabetes, including among patients with a BMI <35 kg/m^2.

Methods By use of a shared decision-making recruitment strategy targeting the entire at-risk population within an integrated community healthcare system, we screened 1,808 adults meeting inclusion criteria (age 25–64, with type 2 diabetes and a BMI 30–45 kg/m^2). Of these, 43 were allocated via concealed, computer-generated random assignment in a 1:1 ratio to RYGB or ILMI. The latter involved ≥45 min of aerobic exercise 5 days per week, a dietitian-directed weight- and glucose-lowering diet, and optimal diabetes medical treatment for 1 year. Although treatment allocation could not be blinded, outcomes were determined by a blinded adjudicator. The primary outcome was diabetes remission at 1 year (HbA_{1c} <6.0% [<42.1 mmol/mol], off all diabetes medicines).

Results Twenty-three volunteers were assigned to RYGB and 20 to ILMI. Of these, 11 withdrew before receiving any intervention. Hence 15 in the RYGB group and 17 in the IMLI group were analysed throughout 1 year. The groups were equivalent regarding all baseline characteristics, except that the RYGB cohort had a longer diabetes duration (11.4 ± 4.8 vs 6.8 ± 5.2 years, $p = 0.009$). Weight loss at 1 year was 25.8 ± 14.5% vs 6.4 ± 5.8% after RYGB vs ILMI, respectively ($p < 0.001$). The ILMI exercise programme yielded a 22 ± 11% increase in $\dot{V}O_{2max}$ ($p<0.0001$), whereas $\dot{V}O_{2max}$ after RYGB was unchanged. Diabetes remission at 1 year was 60.0% with RYGB vs 5.9% with ILMI ($p = 0.002$). The HbA_{1c} decline over 1 year was only modestly more after RYGB than ILMI: from 7.7 ± 1.0% (60.7 mmol/mol) to 6.4 ± 1.6% (46.4 mmol/mol) vs 7.3 ± 0.9% (56.3 mmol/mol) to 6.9 ± 1.3% (51.9 mmol/mol), respectively ($p = 0.04$); however, this drop occurred with significantly fewer or no diabetes medications after RYGB. No life-threatening complications occurred.

Conclusions/interpretation Compared with the most rigorous ILMI yet tested against surgery in a randomised trial, RYGB yielded greater type 2 diabetes remission in mild-to-moderately obese patients recruited from a well-informed, population-based sample.

Trial registration: ClinicalTrials.gov NCT01295229

Keywords Bariatric surgery · Diabetes · Intensive lifestyle · Metabolic surgery · Randomised controlled trial

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Abbreviations

ADA	American Diabetes Association
CROSSROADS	Calorie Reduction Or Surgery: Seeking to Reduce Obesity And Diabetes Study
CVD	Cardiovascular disease

DEXA	Dual-energy x-ray absorptiometry
DPP	Diabetes Prevention Program
FHCRC	Fred Hutchinson Cancer Research Center
GHRI	Group Health Research Institute
ILMI	Intensive lifestyle and medical intervention
RCT	Randomised controlled trial
RYGB	Roux-en-Y gastric bypass
SDM	Shared decision-making
$\dot{V}O_{2max}$	Maximum oxygen consumption

Introduction

Obesity and diabetes are the fastest growing, and among the most important, contributors to disability and death worldwide [1]. Despite an ever-increasing armamentarium of pharmaceutical and behavioural approaches to combat these twin pandemics, major weight loss is uncommonly sustained for prolonged periods using nonsurgical means, and up to 90% of patients with type 2 diabetes fail to achieve treatment goals established to prevent long-term complications [2]. Furthermore, most diabetes medications promote weight gain, potentially compromising metabolic benefits.

Roux-en-Y gastric bypass surgery (RYGB) dramatically improves glycaemic control, leading to type 2 diabetes remission in most cases [3], through mechanisms beyond just reduced food intake and body weight [4]. Large observational studies report that in severely obese individuals, bariatric surgery is associated with long-term reductions in all major cardiovascular disease (CVD) risk factors [5, 6], CVD events such as myocardial infarctions and strokes [7], cancer [8] and all-cause mortality [9, 10], including a 92% decrease in diabetes-related deaths [10]. Results from these observational studies, however, may be biased because the characteristics of populations who undergo surgery can differ from those who do not (i.e. unmeasured confounding) [11–13]. If individuals who choose to undergo surgery are more motivated to improve their health, they may also be more medically compliant and/or lead healthier lifestyles. Such concerns limit the utility of observational data, even from the most exemplary investigations, such as the Swedish Obese Subjects study [5–9].

Establishing the proper place of bariatric surgery in diabetes care requires evidence from randomised controlled trials (RCTs) directly comparing medical and/or behavioural vs surgical approaches, and evaluating the full range of benefits and risks. The latter remain particularly concerning for surgery. Although operative complications have steadily decreased with refinement of minimally invasive laparoscopic techniques [14], long-term risks remain to be determined [15]. Despite the challenges of successfully recruiting and randomly allocating participants into treatment arms as diverse as major surgery vs medical/lifestyle interventions, several RCTs have recently reported that various bariatric operations are more effective than nonsurgical approaches in improving glycaemic control and decreasing other CVD risk factors over 1–3 years [16–22]. However, the lifestyle interventions in most of these were not as rigorous as they might have been [23], and there is still limited evidence in patients with a BMI <35 kg/m^2, the standard minimum threshold for bariatric surgery.

We sought to address these issues in the CROSSROADS trial (Calorie Reduction Or Surgery: Seeking to Reduce Obesity And Diabetes Study). By use of a population-based recruitment strategy to enrol patients with type 2 diabetes and a BMI of 30–45 kg/m^2, we conducted a prospective RCT comparing RYGB to an intensive lifestyle and medical intervention (ILMI), including aggressive, supervised dieting and exercise, modelled after the Diabetes Prevention Program (DPP) [24] and LookAHEAD trials [25]. Our novel recruitment methods used a shared decision-making (SDM) approach to identify, screen, educate and randomise all adults who demonstrated equipoise between surgical and lifestyle treatment of obesity and diabetes in a large, integrated healthcare delivery system [11].

Methods

CROSSROADS is a parallel-group RCT executed by investigators at the University of Washington, Group Health Research Institute (GHRI), and Fred Hutchinson Cancer Research Center (FHCRC) (ClinicalTrials.gov NCT01295229). Institutional review board approval was obtained from all three institutions. The ILMI was provided free of charge. All pre-operative, operative and post-operative care costs for RYGB were paid by Group Health insurance, GHRI, or the Group Health Foundation. Participants were paid US$25 per visit for attending in-person study data collection visits outside of routine care.

Recruitment and randomisation process

By using a population-based SDM approach previously described in greater detail [11], recruitment was conducted between July 2011 and June 2012 at Group Health Cooperative, an integrated healthcare system with >600,000 members. We first searched electronic databases to identify potentially eligible participants. Candidates were then approached by mail and phone, and carefully screened using a multi-phase recruitment process [11]. A study physician obtained in-person, written informed consent, and 1:1 randomisation was conducted via computer-generated random assignment, stratified by BMI ≥35 kg/m^2, with allocation concealed. Although blinding to treatment allocation during the interventions was not possible, final outcomes were determined by a blinded adjudicator

(DRF). Sample size was determined based on prior related studies [16, 17].

Participant eligibility

Candidates were considered eligible if they were 25–64 years old, had a BMI of 30–45 kg/m^2, were currently taking diabetes medications, were covered by insurance that had a bariatric surgery rider (if BMI 35–45 kg/m^2), and were willing to accept randomisation into either intervention group and then follow the full protocol for ≥1 year. Candidates were considered ineligible if they had any of the following: pregnancy, cancer (except nonmelanoma skin cancer), ascites, peritoneal effusion, dementia, bipolar disorder, schizophrenia, cirrhosis, end-stage renal disease, human immunodeficiency virus, inflammatory bowel disease, diagnosed type 1 diabetes, diabetes secondary to a specific disease or glucocorticoid therapy, prior bariatric or major gastrointestinal surgery or organ transplantation. These exclusions were designed to eliminate patients who were at greater-than-average risk for complications, disease-related weight change or nonadherence to treatment and follow-up visits.

The ILMI

The ILMI was a 12-month, in-person and telephone-based programme that included behaviour modification skills counselling, combined with training in diet and exercise change.

Exercise intervention The focus of the exercise intervention was a gradual increase in brisk walking or other activities of similar moderate aerobic intensity over 12 months. Participants were asked to attend ≥3 exercise physiologist-supervised sessions per week at the FHCRC Prevention Center Exercise Testing and Training Center, a dedicated research gym, and they were asked to exercise an additional ≥2 days/week at home for the first 6 months. For the remaining 6 months, participants were asked to exercise ≥1 day/week at the Prevention Center and ≥4 days/week at home. In summary, they were directed to exercise ≥45 min/day, ≥5 days/week, for 1 year.

Dietary intervention The dietary intervention was conducted by a research dietitian trained in behaviour modification. Each participant was required to attend weekly group nutrition sessions for the first 6 months. These sessions were based on DPP [24], with several modifications for our diabetic participants. Although reduced calorie intake and weight loss were strongly encouraged, participants were not given specific weight loss goals. Instead, the dietary intervention emphasised food quality by encouraging consumption of protein, fresh fruits and vegetables, and avoidance of processed foods. The programme advocated a slightly higher percentage of energy from protein and fat, combined with avoidance of high glycaemic index foods. In the second 6-month phase of the study, participants were contacted weekly by the dietitian via telephone or email, and were encouraged to attend monthly in-person group nutrition sessions.

Diabetes-related medical care Medical care, including pharmaceutical diabetes treatment, was provided similarly in both groups by each participant's own primary care physician, based on guidelines of the American Diabetes Association (ADA) and European Association for the Study of Diabetes [26]. Study staff conducted quarterly chart reviews to ensure these guidelines were met. Hypertension and lipid-lowering medications were prescribed according to ADA guidelines using the following treatment goals: blood pressure ≤130/80 mmHg and LDL-cholesterol ≤2.6 mmol/l.

Laparoscopic RYGB

Participants randomised to surgery underwent a laparoscopic proximal RYGB, using an estimated 40 ml gastric pouch, 100–150 cm alimentary limb, a biliopancreatic limb that included 30–50 cm of jejunum beyond the ligament of Treitz, an antecolic/antegastric approach, and combined stapled and sutured technique. Surgical patients also underwent a 4-week pre-operative and 10-month postoperative behavioural treatment regimen. In the pre-operative phase, patients had weekly telephone-based appointments with a health educator and were required to attend 2–3 bariatric support group meetings. Patients continued to have phone appointments with their health educator for 10 months after surgery. The postoperative behavioural treatment programme focused on diet and nutrition counselling, behaviour modification and exercise recommendations.

Outcomes and data collection

The primary outcome was the percentage of participants in each group who achieved diabetes remission at 1 year, defined as an HbA_{1c} of <6.0% (<42.1 mmol/mol), off all diabetes medications. Secondary outcomes included changes in fasting glucose and insulin levels, estimated insulin sensitivity, body weight, waist circumference, body composition, blood pressure, plasma lipids, aerobic fitness, medication usage, quality of life and safety.

Data were collected during in-person study visits at baseline, 6 and 12 months. Additional information was gathered using chart reviews from all clinical visits during the 12-month study. Data collected at in-person visits included height; weight; waist circumference; per cent lean and fat mass determined by dual-energy x-ray absorptiometry (DEXA) and bioelectrical impedance plethysmography (baseline and 12 months only); blood pressure; heart rate; fasting plasma levels of glucose and insulin; levels of HbA_{1c} and cholesterol;

quality of life measured with the EQ-5D questionnaire; and adverse events. The HOMA-IR index (glucose × insulin/22.5) was calculated as a rough estimate of insulin resistance. A physical activity questionnaire was administered at baseline, 6 and 12 months. Cardiorespiratory fitness $\left(\dot{V}O_{2max}\right)$ was assessed using a maximal graded treadmill test according to a modified branching protocol (baseline and 12 months only). This metric is often expressed as oxygen consumption per kg of body weight. However, major weight changes skew data normalised in this manner, leading to erroneous conclusions. Hence we report only absolute $\dot{V}O_{2max}$. Adverse events were captured at each study visit using a standardised questionnaire (available from authors by request) and by automated surveillance of our electronic databases.

Data analysis

The randomised RYGB and ILMI groups were assessed for demographic and baseline health differences using the Mann–Whitney test or Fisher's exact test as applicable. By using an intention-to-treat approach, we tested for differences in health outcomes between baseline and follow-up within each intervention group, and also for differences in the magnitude of change in outcomes between intervention groups. There was no loss to follow-up for our primary outcome at 1 year. Given the sample size, there was not enough statistical power to defend normality assumptions necessary to use parametric analysis methods such as a *t* test; instead, we used the nonparametric Wilcoxon Signed Rank test and Mann–Whitney tests.

Additionally, we performed a series of regression models predicting the change in each health metric using the intervention group and the health metric at baseline as independent variables. Results were from the Mann–Whitney test and regressions were concordant.

Results

Participant characteristics

The results of screening, education and randomisation are summarised in Fig. 1 and have been described elsewhere in detail [11]. We screened 1,808 candidates who, based on administrative and clinical databases, fulfilled essential inclusion and exclusion criteria. Among these, 43 people (2.4%) were ultimately randomised (23 to surgery, 20 to ILMI). Eight individuals in the surgical group and three in the ILMI group withdrew shortly after randomisation, before starting either intervention. These 11 individuals did not complete our baseline study visit; thus, 32 participants are included in our analyses. Of these, five surgery participants and six ILMI participants had baseline BMI <35 kg/m^2. Among participants who initiated their intervention, everyone completed follow-up data collection through 1 year, except for one person in each arm who did not provide fitness and body composition data at the last time point.

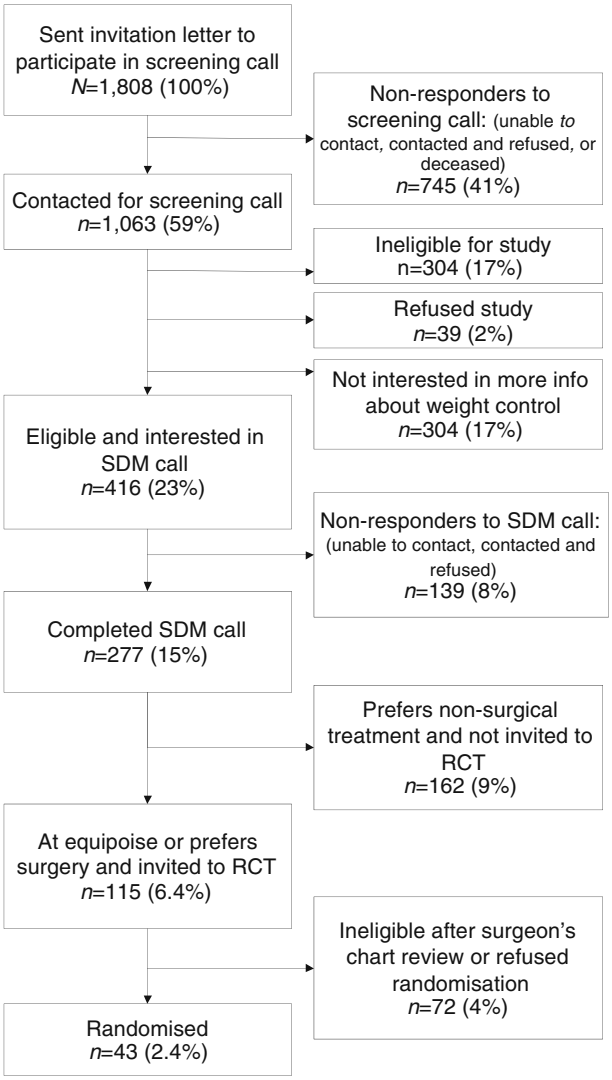

Fig. 1 Participant identification, education and recruitment flow diagram

Participant characteristics are displayed in Table 1. At baseline, the two randomised groups were equivalent regarding measures of demographics, anthropometrics, body composition, fitness, glycaemic control, insulin use, plasma lipids and blood pressure. Mean BMI for the entire cohort was 37.7 kg/m^2 and HbA_{1c} was moderately well controlled at 7.5% (58.5 mmol/mol). Of the 24 variables shown in Table 1, only one differed across groups at baseline. The surgical group had longer duration of known diabetes than the ILMI group (11.4 ± 4.8 vs 6.8 ± 5.2 years, $p = 0.009$).

Diabetes remission and glycaemic control

The primary endpoint of diabetes remission (defined as an HbA_{1c} <6.0% [<42.1 mmol/mol] off all diabetes medications)

Table 1 Baseline characteristics of randomised study participants

Characteristic	Surgical ($n=15$)	ILMI ($n=17$)	p value
Age (year)	52.0 (8.3)	54.6 (6.3)	0.4
Female sex (%)	80.0	58.8	0.3
White ethnicity (%)	80.0	64.7	0.4
Body weight (kg)	108.8 (14.9)	112.8 (16.5)	0.6
Height (cm)	168.4 (7.9)	174.1 (10.3)	0.1
BMI (kg/m^2)	38.3 (3.7)	37.1 (3.5)	0.3
Waist circumference (cm)	121.7 (10.2)	120.8 (10.0)	0.8
Waist-to-hip ratio	1.0 (0.1)	1.0 (0.1)	0.8
Body fat by DEXA (%)	47.6 (5.4)	46.1 (6.4)	0.6
Body fat by BEI (%)	41.4 (6.3)	38.6 (8.2)	0.3
$\dot{V}O_{2max}$ by ETT	19.6 (2.6)	21.1 (3.6)	0.4
HbA_{1c} (%)	7.7 (1.0)	7.3 (0.9)	0.4
HbA_{1c} (mmol/mol)	60.7	56.3	0.4
Fasting plasma glucose (mmol/l)	8.1 (2.6)	8.5 (2.6)	0.7
Fasting plasma insulin (pmol/l)	160 (102)	186 (135)	0.6
Use of insulin (%)	60.0	47.1	0.5
Duration of known diabetes (years)	11.4 (4.8)	6.8 (5.2)	0.009
Dyslipidaemia (%)	86.7	82.4	1.0
Cholesterol (mmol/l)			
Total	4.3 (1.0)	4.4 (0.8)	0.5
LDL	2.4 (0.7)	2.2 (0.6)	0.4
HDL	1.1 (0.3)	1.1 (0.2)	0.6
Triacylglycerols (mmol/l)	1.7 (0.7)	2.3 (1.5)	0.1
Hypertension (%)	80.0	94.1	0.3
Blood pressure (mmHg)			
Systolic	129.3 (20.6)	120.1 (9.6)	0.3
Diastolic	77.0 (10.2)	74.8 (7.5)	0.9

Values are mean (SD)

p value is a Mann–Whitney two-sample statistic or Fisher's exact test

BEI, bioelectrical impedance analysis; ETT, exercise tolerance test

at 1 year was achieved in 60.0% of participants after RYGB vs 5.9% with ILMI ($p=0.002$). The same results occurred using a threshold of HbA_{1c} <6.5% (<47.5 mmol/mol), i.e. 'partial remission' [27]. The odds ratio for diabetes remission at 1 year after RYGB compared with ILMI was 19.8 (95% CI 2.0, 194.6, $p=0.003$). In exploratory analyses, diabetes remission was not predicted by baseline BMI, age or sex, or by the amount of weight lost during 1 year, and there was no correlation between change in body weight and change in HbA_{1c} at 6 or 12 months among those having RYGB; however, the study was not specifically powered to detect this. In further exploratory analyses, there were no apparent differences in the primary outcome among subgroups stratified according to insulin usage or median duration of diabetes at baseline.

The magnitude of HbA_{1c} decline over 1 year was only modestly more after RYGB than ILMI: from 7.7 ± 1.0% (60.7 mmol/mol) to 6.4 ± 1.6% (46.4 mmol/mol) vs 7.3 ± 0.9% (56.3 mmol/mol) to 6.9 ± 1.3% (51.9 mmol/mol), respectively ($p=0.04$), and mean HbA_{1c} values were not statistically different between the groups at baseline, 6 or 12 months (Figs 2 and 3). However, average HbA_{1c} fell progressively over time after RYGB, whereas it reached a nadir at 6 months with ILMI then tended to increase back toward baseline, and the surgical group used fewer diabetes medications at 12 months than the ILMI group (mean 0.5 ± 0.2 vs 1.2 ± 0.2 medicines, respectively, $p=0.009$). Although insulin usage tended to be higher at baseline in RYGB compared with ILMI patients (60% vs 47%), it was less in the surgical group at 12 months (27% vs 41%).

Fasting plasma glucose levels tended to decline in both groups, but these changes were not statistically significant, nor were there differences between interventions (Fig. 3). By contrast, fasting plasma insulin levels decreased significantly with RYGB (from 160 ± 102 to 42 ± 22 pmol/l, $p=0.001$) and also

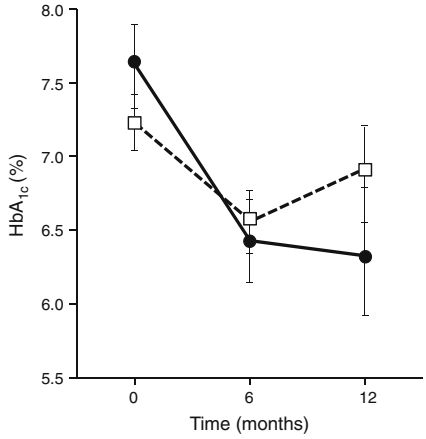

Fig. 2 Change in HbA_{1c} over time by treatment group ($n = 17$ ILMI; $n = 15$ RYGB); dashed line and white squares, ILMI group; solid line and black circles, RYGB group. To convert values for HbA_{1c} in per cent into mmol/mol, subtract 2.15 and multiply by 10.929

with ILMI (from 187 ± 135 to 134 ± 109 pmol/l, $p = 0.002$), although the magnitude of change was much greater after surgery ($p < 0.001$). Similarly, HOMA-IR decreased significantly with both RYGB (from 7.5 ± 3.9 to 1.8 ± 0.9, $p = 0.0001$) and ILMI (from 9.2 ± 6.8 to 6.6 ± 4.1, $p = 0.005$), but the magnitude of decline was much greater after surgery ($p = 0.011$).

Anthropometrics and body composition

Body weight, BMI, waist circumference, waist-to-hip ratio and per cent body fat mass all decreased significantly by 12 months within each group (Fig. 3 and data not shown), but the magnitude of decline for each of these variables was greater with surgery than ILMI. Weight loss at 1 year was 25.8 ± 14.5% vs 6.4 ± 5.8% after RYGB vs ILMI, respectively ($p < 0.001$ for change over time within each group individually and also comparing the magnitude of change between groups).

Despite significant weight loss in the ILMI group, lean body mass remained stable among these individuals (Fig. 3). By contrast, lean body mass decreased by 10% in the surgical group (from 55.0 ± 9.2 to 49.6 ± 8.5 kg; $p = 0.0001$ for change over time in this group, and $p < 0.001$ for difference in magnitude of change between groups).

As a measure of cardiorespiratory fitness, peak oxygen consumption $(\dot{V}O_{2max})$ increased substantially in the ILMI group (from 2369 ± 554 to 2881 ± 740 ml/min, $p < 0.0001$), whereas it was unchanged in the surgical group (from 2137 ± 506 to 2105 ± 524 ml/min, $p = 1.0$; Fig. 3).

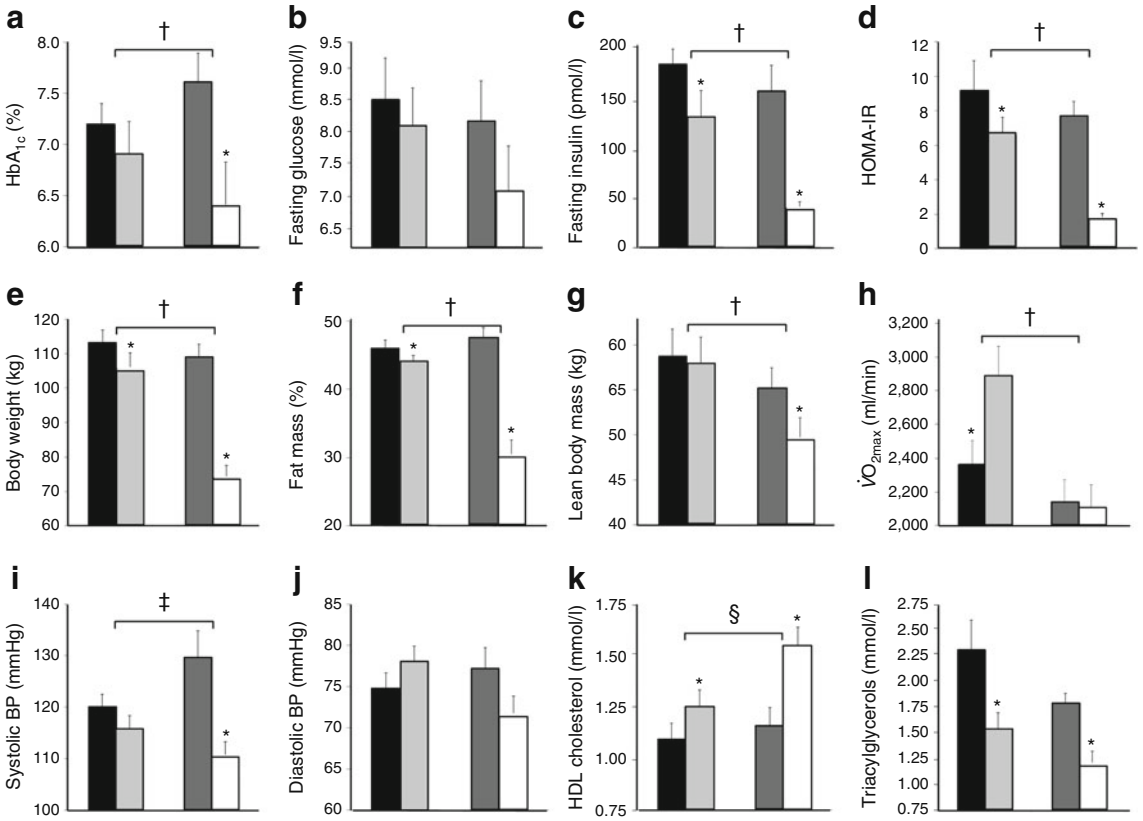

Fig. 3 Changes in secondary outcomes over time by treatment group ($n = 17$ ILMI; $n = 15$ RYGB); black bars, ILMI baseline; light grey bars, ILMI 1 year; dark grey bars, RYGB baseline; white bars, RYGB 1 year. Fat and lean mass determined by DEXA. *$p < 0.05$ for within-group comparison of baseline vs 1 year. †$p < 0.05$ for between-group comparison of change between baseline and 1 year. ‡$p = 0.05$ for between-group comparison of change. §$p = 0.08$ for between-group comparison of change

Other metabolic health outcomes

Systolic blood pressure decreased from baseline to 12 months in the surgical arm (from 129 ± 21 to 110 ± 10 mmHg, $p = 0.003$), but did not change in the ILMI arm (from 120 ± 10 to 116 ± 10, $p = 0.23$; Fig. 3). Diastolic blood pressure was similar at baseline and 12 months in both groups and did not significantly change with either intervention. However, surgical patients used one-third as many hypertension medications at 12 months as ILMI patients (0.6 ± 0.2 vs 1.8 ± 0.4 medications, $p = 0.014$).

Plasma HDL-cholesterol increased significantly (Fig. 3) between baseline and 12 months in each group (from 1.1 ± 0.3 to 1.5 ± 0.3 mmol/l with RYGB, $p = 0.0004$; from 1.1 ± 0.2 to 1.3 ± 0.3 mmol/l with ILMI, $p = 0.02$), and there was a trend for a greater increase with surgery ($p = 0.08$). Triacylglycerol levels decreased significantly in each group (from 1.7 ± 0.7 to 1.1 ± 0.4 mmol/l with RYGB, $p = 0.005$; from 2.3 ± 1.1 to 1.5 ± 0.6 mmol/l with ILMI, $p = 0.002$), with similar magnitude of change in both groups ($p = 0.50$). Neither total nor LDL-cholesterol changed from baseline to 12 months in either group, and there were no differences between groups in these variables at either of these time points or when comparing changes over time between groups. There was no difference between groups in the number of lipid-lowering medications used at 12 months (0.4 ± 0.1 vs 0.5 ± 0.2 medications in surgery vs ILMI, respectively, $p = 0.62$).

Quality of life

As determined by EQ-5D at baseline and 12 months, overall health ratings improved within each group (from 77.5 ± 14.3 to 87.2 ± 8.2 for RYGB, $p = 0.021$; from 62.1 ± 20.7 to 76.5 ± 11.9 for ILMI, $p = 0.035$). The magnitude of this improvement was not different between groups ($p = 0.34$).

Adverse events

During the year of observation, there were no deaths or hospitalisations for serious surgical adverse events (venous thromboembolism, hospitalisation ≥30 days, re-intervention) in either group of enrolled participants. Overall, there were 64 adverse events in the ILMI group and 31 in the RYGB group. Notably, these included more hypoglycaemic events with ILMI than RYGB: 43 vs 16, respectively, including four severe hypoglycaemias in ILMI (i.e. blood glucose <2.2 mmol/l, or <3.3 mmol/l with neuroglycopenic symptoms) vs none after RYGB. The only other severe adverse event was an emergency room visit for acute alcohol intoxication in one RYGB patient. Other reported minor adverse events were very diverse and displayed no obvious differential patterns between groups, except that musculoskeletal complaints were reported in seven cases with ILMI vs two with RYGB.

Discussion

We used a population-based recruitment strategy [11], along with a unique, validated SDM instrument [28] to educate study candidates regarding treatment options, to conduct a prospective RCT of RYGB vs ILMI to treat metabolic disease among patients with type 2 diabetes and a BMI of 30–45 kg/m^2. At 1 year, surgery was superior to ILMI for diabetes remission, glycaemic control, and reductions in body weight, adiposity, systolic blood pressure, estimated insulin resistance, overall health state, and usage of medications for diabetes and hypertension, with a trend for surgical superiority to increase HDL-cholesterol levels. The two interventions were equally effective at decreasing triacylglycerols, and ILMI was superior at increasing physical fitness and maintaining lean body mass despite weight loss. Neither intervention significantly affected diastolic blood pressure, total cholesterol or LDL-cholesterol. The most impressive benefit of surgery compared with ILMI was in ameliorating diabetes, even though by chance the surgical group started with a duration of diabetes nearly twice that of the ILMI group, which biases against such surgical superiority.

Our trial confirms and extends findings from prior RCTs and nonrandomised studies, which together indicate that laparoscopic RYGB is safe, conferring no apparent greater risk among people with a BMI <35 kg/m^2 than among those with a BMI >35 kg/m^2, the currently accepted threshold for bariatric surgery [16–22, 29]. The all-cause 30-day mortality from laparoscopic RYGB is <0.3% [30–32], similar to that for cholecystectomy and hysterectomy. We observed considerable loss of lean body mass after RYGB, whereas it was preserved despite significant weight loss in the ILMI group following a strenuous exercise programme. The long-term consequences of RYGB-induced reductions in lean mass are unclear but warrant examination. Importantly, ILMI also involved risks, and compared with RYGB, we observed more total and serious hypoglycaemic events in this group (which ended up using significantly more glucose-lowering medications), as well as more musculoskeletal complaints.

Several features distinguish this study from prior related RCTs [16–22]. For example, typical previous recruitment strategies are likely to have enrolled highly motivated participants who may actively seek participation in studies, theoretically limiting the generalisability of the findings [11]. By contrast, our population-based, SDM approach to identify, educate and enrol participants from a broad at-risk population was designed to yield a more representative and generalisable study sample. Despite our extensive efforts, we found that randomised participants still differed significantly from the overall population of potentially eligible adults in terms of their sex, disease severity and hypoglycaemic medication

use [11]. Thus, we failed to demonstrate that our SDM recruitment approach would yield a more representative and generalisable study sample than in prior RCTs.

Whereas the lifestyle interventions in prior studies may not have been considered the most rigorous [23], we used a highly intensive nonsurgical intervention, including an aggressive, supervised dieting and aerobic exercise regimen, modelled after the DPP [24] and LookAHEAD trials [25], along with state-of-the-art pharmaceutical care. Our findings indicate that even completion of what we view as the most intensive lifestyle–medical approach that could reasonably be considered in practice cannot improve diabetes and other CVD risk factors as well as RYGB. We also examined diabetic patients with better initial glycaemic control, with an average baseline HbA_{1c} of 7.5 ± 0.9% (58.5 mmol/mol), than have been studied in prior relevant RCTs, where average baseline HbA_{1c} levels ranged from 7.9% (62.8 mmol/mol) to 9.6% (81.4 mmol/mol), and all but one prior RCT started with an average HbA_{1c} >8.5% (69.4 mmol/mol) [16–22]. Although the lower baseline glycaemia in our study cohort made it more difficult a priori to demonstrate further glycaemic improvements and differences between groups, we nevertheless found that surgery outperformed ILMI on all diabetes-related variables, as have prior studies of patients with poorer initial glycaemic control. Finally, there is still limited evidence from RCTs examining surgical approaches to type 2 diabetes treatment in patients with a BMI <35 kg/m^2, the standard threshold for bariatric surgery, and our study adds Level-1 data to that evidence base.

Despite differences among trials, our study and related RCTs consistently demonstrate various bariatric/metabolic operations as superior to a variety of lifestyle/medical interventions to treat diabetes and obesity, including among patients with a BMI <35 kg/m^2, for at least 1–3 years [16–22].

Our findings highlight how the results in trials of this nature vary greatly depending upon the method of reporting diabetes outcomes. Focusing on diabetes remission, we found a more than tenfold increase in the RYGB compared with the ILMI group (60.0% vs 5.9%, respectively, $p = 0.002$), with a ~20-fold higher adjusted odds ratio of achieving that endpoint using surgery. These findings were identical whether we concentrated on 'complete' or 'partial' remission (i.e. HbA_{1c} <6.0% [42.1 mmol/mol] or <6.5% [47.5 mmol/mol], respectively, off diabetes medications [27]), although results from other studies vary widely depending on differences in these thresholds [33]. In contrast to the large superiority of RYGB over ILMI indicated by diabetes remission, examining glycaemic control, which was relatively good at baseline in both groups, yields a very different impression. Mean HbA_{1c} and fasting glucose values were statistically equivalent between groups throughout the study. These highly different impressions are rendered because although glycaemic control was similar between groups, ILMI patients achieved this using more diabetes medications than did RYGB patients, and absence of such agents is required to define remission.

Important limitations of this trial include the modest duration of observation (although longer follow-up is underway), its single-centre and necessarily unblinded nature (except for randomisation and adjudication of outcomes) and relatively small sample sizes. This study is insufficient to assess more clinically relevant 'hard' outcomes such as microvascular and macrovascular disease, as are all published RCTs comparing surgical vs nonsurgical treatment of obesity and/or diabetes [16–22]. However, we did observe greater improvements with surgery compared with ILMI in body composition and important CVD risk factors, including glycaemic control, systolic blood pressure and HDL-cholesterol. Another limitation is that although we sought to improve generalisability through our SDM recruitment strategy, some characteristics of our randomised cohort differed significantly from those who declined participation in the trial, thereby limiting our study's generalisability (11).

Despite these limitations, our trial and other relevant RCTs [16–22] demonstrate that commonly used bariatric/metabolic operations (RYGB, sleeve gastrectomy, and gastric banding) are all more effective than a variety of medical and/or lifestyle interventions to promote weight loss, diabetes remission, glycaemic control, and improvements in other CVD risk factors, with acceptable complications, for at least 1–3 years. These results apply to patients with a BMI <35 kg/m^2, and our study and others show that neither baseline BMI nor the amount of weight lost dependably predicts diabetes remission after RYGB, which appears to ameliorate diabetes through mechanisms beyond just weight reduction [4]. These findings call into serious question the longstanding practice of using strict BMI cutoffs as the primary criteria for surgical selection among patients with type 2 diabetes [34].

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