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Randomized control trials

Omentectomy in addition to gastric bypass surgery and influence on insulin sensitivity: A randomized double blind controlled trial☆

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S U M M A R Y

Background & aims: Accumulation of visceral adipose tissue is associated with insulin resistance and cardio-vascular disease. The aim of this study was to elucidate whether removal of a large amount of visceral fat by omentectomy in conjunction with Roux en-Y gastric bypass operation (RYGB) results in enhanced improvement of insulin sensitivity compared to gastric bypass surgery alone.
Methods: Eighty-one obese women scheduled for RYGB were included in the study. They were randomized to RYGB or RYGB in conjunction with omentectomy. Insulin sensitivity was measured by hyperinsulinemic euglycemic clamp before operation and sixty-two women were also reexamined 2 years post-operatively. The primary outcome measure was insulin sensitivity and secondary outcome measures included cardio-metabolic risk factors.
Results: Two-year weight loss was profound but unaffected by omentectomy. Before intervention, there were no clinical or metabolic differences between the two groups. The difference in primary outcome measure, insulin sensitivity, was not significant between the non-omentectomy (6.7 ± 1.6 mg/kg body weight/minute) and omentectomy groups (6.6 ± 1.5 mg/kg body weight/minute) after 2 years. Nor did any of the cardio-metabolic risk factors that were secondary outcome measures differ significantly.
Conclusion: Addition of omentectomy to gastric bypass operation does not give an incremental effect on long term insulin sensitivity or cardio-metabolic risk factors. The clinical usefulness of omentectomy in addition to gastric bypass operation is highly questionable.
Clinical Trial Registration number: NCT01785134.

1. Introduction

Obesity is one of the major underlying risk factors for the development of cardio-vascular disease and type 2 diabetes. Not only obesity *per se* but also the distribution of adipose tissue is important for the risk of complications. Visceral obesity increases the risk of insulin resistance and cardio-vascular disease whereas this has not been demonstrated for peripheral body fat accumulation.[1,2] The underlying mechanisms remain elusive. However, since visceral adipose tissue (VAT) is drained by the portal vein it has been suggested that this direct connection to the liver including delivery of non-esterified fatty acids (NEFA) stimulates

Abbreviations: VAT, visceral adipose tissue; NEFA, non-esterified fatty acids; RYGB, Roux en-Y gastric bypass; DEXA, dual-energy X-ray absorptiometry.

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hepatic gluconeogenesis and in turn development of insulin resistance.[3] Moreover, the visceral fat cells are more lipolytically active than subcutaneous adipocytes which selectively enhances NEFA release from the visceral depot as discussed.[4] VAT accumulation may also affect adipokine secretion as has been shown for adiponectin, a circulating cytokine secreted by adipocytes having insulin sensitizing effects.[5,6] Given the role of VAT in metabolic disease, it has been proposed that removal of a substantial amount of the VAT might have beneficial effects including improved insulin sensitivity. In a previous pilot study, 50 patients scheduled for bariatric surgery were randomized to either adjustable gastric banding alone or in combination with removal of the greater omentum.[7] Omentectomy led to improved insulin sensitivity measured by both glucose and insulin tolerance tests and also to a trend towards greater weight loss.

To establish whether reduction of visceral fat mass in combination with bariatric surgery has long-term metabolic effects, we performed a 2-year, double-blinded, controlled trial in a large cohort consisting of obese women randomized to gastric bypass alone or in conjunction with omentectomy. Insulin sensitivity measured by hyperinsulinemic euglycemic clamp was the primary outcome. Enhanced improvements of cardio-vascular risk factors were secondary outcomes.

2. Material and methods

2.1. Ethics statement

The study was approved by the regional Committee on Ethics at Karolinska Institutet in Stockholm, Sweden (http://www.epn.se/en/start/startpage/). Patients were given oral and written information before they gave written consent to participate in the study. The study was conducted according to the principles expressed in the Declaration of Helsinki.

2.2. Subjects

Female obese patients referred and accepted for bariatric surgery (BMI $\geq$ 40 kg/m^2 or BMI $\geq$ 35 kg/m^2 with obesity associated co-morbidities such as type 2 diabetes and/or additional cardiovascular risk factors) were recruited from four different surgical centers (Ersta Hospital, Södertälje Hospital, Karolinska University Hospital Huddinge and Danderyd Hospital) in Stockholm, Sweden. The study was conducted between May 2006 and December 2011. Randomization to gastric bypass surgery alone (non-omentectomy group) or gastric bypass surgery plus omentectomy (omentectomy group) was performed in blocks of 20 patients. After induction of general anesthesia, an opaque envelope with information regarding group allocation was opened. Open Roux en-Y gastric bypass (RYGB) was performed through an upper midline incision. A small gastric pouch (20–30 ml) was created by the use of linear staples. Linear or circular staples were used for the gastroenteroanastomosis, whereas the entero-enteroanastomosis was created by linear staples. The lengths of the alimentary and biliopancreatic limbs were typically 120 and 75 cm, respectively. The mesenteric defects were not closed routinely. In patients randomized to omentectomy, the entire greater omentum was surgically resected. After attachments against the transverse colon were divided, dissection of the omentum along the greater curvature of the stomach and against the duodenum as well as the lower pole of the spleen was performed by the use of ultrasound scissors. Researchers that participated in the collection of data and the recruited patients were blinded to treatment. The surgeons (AT, MW, AT, SB, EN) did not participate in the data handling until after the code was broken. The primary outcome of the study was insulin sensitivity as measured by the clamp technique (see below). Secondary outcomes included anthropometric data and cardiometabolic risk factors. The study is registered at clinicaltrials.gov (NCT01785134) and Karolinska Clinical Trial Registration (http://www.medscinet.net/kctr/Form.aspx?TrialID=61 CT20110061).

One to three weeks before surgery, patients visited the metabolic ward in the morning after an over-night fast. Weight was measured to the nearest 0.5 kg with a digital scale (TANITA model no TBF-305). Waist circumference (measured at the lateral midpoint between the lowest rib and iliac crest with a nonstretchable tape measure) and height (measured by a fixed tape measure at a wall) were measured to the nearest 0.5 cm. Body mass index (BMI) was calculated as weight (kg) divided by square of height (m^2). Blood pressure was measured in the supine position with a cuff of appropriate size after a 15 min rest. Body composition was measured with dual-energy X-ray absorptiometry (DEXA) using a GE-Lunar iDXA (GE Healthcare, Madison, WI, USA) and provided software (enCORE version 14.10.022), as described.[8] A venous blood sample was taken for the measurement of plasma insulin, glucose, total cholesterol, high density cholesterol (HDL), triglycerides, apolipoprotein A1 and apolipoprotein B. Low density cholesterol (LDL) was calculated using the Friedewald formula.[9] Plasma insulin was determined using an ELISA kit (Insulin ELISA, Mercodia Uppsala, Sweden). Homeostasis model for assessment of insulin resistance (HOMA) was calculated as previously described.[10]

Thereafter, all patients underwent a hyperinsulinemic euglycemic clamp procedure (clamp). A catheter was inserted into a forearm vein for infusions and a second catheter into a vein on the dorsal side of the hand. The hand was kept in a heating box (MTA, Karolinska University Hospital, Stockholm, Sweden) with a temperature of 63 °C during the clamp to obtain arterialized venous blood for blood sample collection. An intravenous bolus dose of insulin (1.6 U/m^2 body surface area; Actrapid, Novo Nordisk, Copenhagen, Denmark) was given. This was followed by a continuous infusion for 120 min of insulin (0.12 U/m^2 body surface area/minute) suspended in 82 ml sodium chloride (9 mg/ml) together with 2 ml (200 g/l) human albumin (1.7 mg/min Albunorm, Octapharma, Stockholm, Sweden) and 16 ml potassium cloride (67 μmol/min). Blood glucose was measured in duplicates every fifth minute (Hemocue, Ängelholm, Sweden) and euglycemia (4.5–5.5 mmol/l) was maintained through a variable intravenous infusion of glucose (200 mg/ml). The infusion rate of glucose during the last 60 min of the clamp was used for calculation of whole-body insulin sensitivity (expressed in mg glucose/kg body weight/minute). Ninety-five percent of the blood glucose values during the last 60 min of the clamp were within euglycemic level. The average blood glucose levels during steady state were 5.05 $\pm$ 0.19 mmol/l at baseline and 5.10 $\pm$ 0.18 mmol/l at follow up. The average insulin levels during clamp were 243 $\pm$ 77 mU/l at baseline and 169 $\pm$ 42 mU/l at follow up.

The patients were contacted every sixth month to report their health and weight. Patients were re-examined approximately 24 months after surgery using the same protocol as described at baseline.

2.3. Statistical analyses

Values are mean $\pm$ SD. Groups were compared with unpaired *t*-test in per-protocol analyses. The statistical program Statview 5.0 (SAS Institute Inc., Cary, NC, US) was used for analyses.

The number of patients in the study was based on calculation of the power to detect a statistical difference in insulin-stimulated glucose disposal (M-value) 2 years following gastric by-pass surgery between subjects allocated to omentectomy vs. non-omentectomy. The criterion for significance (alpha) is set to 0.05.