Effects of gastric bypass surgery followed by supervised physical training on inflammation and endothelial function

A randomized controlled trial

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Effects of gastric bypass surgery followed by supervised physical training on inflammation and endothelial function: A randomized controlled trial

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Keywords

C-reactive protein (CRP), exercise, intercellular adhesion molecule 1 (ICAM-1), interleukin 6 (IL-6), tissue-type plasminogen activator antigen (t-PA:Ag), von Willebrand factor (vWF)

Abstract

Background and aims: Obesity and physical inactivity are both associated with low-grade inflammation and endothelial dysfunction. Bariatric surgery improves markers of inflammation and endothelial function, but it is unknown if physical training after bariatric surgery can improve these markers even further. Therefore, we aimed to investigate the effects of Roux-en-Y gastric bypass (RYGB) followed by physical training on markers of low-grade inflammation and endothelial function.

Methods: Sixty patients approved for RYGB underwent examinations pre-surgery, 6, 12, and 24 months post-surgery. Six months post-surgery, they were randomized 1:1 to an intervention group or a control group. The interventions consisted of two weekly sessions of supervised moderate intensity physical training for a period of 26 weeks. Fasting blood samples were analyzed for concentrations of interleukin 6 (IL-6), C-reactive protein (CRP), intercellular adhesion molecule 1 (ICAM-1), tissue-type plasminogen activator antigen (t-PA:Ag) and von Willebrand factor (vWF).

Results: RYGB markedly improved markers of inflammation (IL-6, CRP) \((p<0.001)\) and endothelial function (ICAM-1, t-PA:Ag, vWF) \((p<0.05)\), and the improvements were sustained 24 months post-surgery \((p<0.01)\), except for the effects on vWF. We found no correlations between the changes in weight or BMI and the changes in markers of inflammation and endothelial function, except that the change in vWF was found to be inversely correlated with the changes in weight and BMI. We observed no effects of supervised physical training on markers on inflammation or endothelial function \((p>0.1\ \text{for all})\).

Conclusions: RYGB causes substantial and sustained favorable effects on markers of inflammation and endothelial function. Supervised physical training after RYGB did not cause additional improvements.
Introduction

The prevalence of obesity increases worldwide, and obesity is associated with increased morbidity and mortality \(^{(1, 2)}\). The leading cause of morbidity and mortality related to high BMI is cardiovascular disease (CVD) \(^{(1)}\).

Obesity is a condition with accumulation of excessive body fat in white adipose tissue (WAT). WAT is an active endocrine organ which synthesizes and secretes cytokines, including the pro-inflammatory mediator Interleukin 6 (IL-6) \(^{(3)}\). These cytokines promote an inflammatory state in vascular cells and stimulate the expression of adhesion molecules, e.g. intercellular adhesion molecule 1 (ICAM-1), thereby inducing endothelial dysfunction with increased levels of von Willebrand factor (vWF) and tissue-type plasminogen activator antigen (t-PA:Ag). In the liver, the cytokines stimulate the hepatocytes to produce acute phase proteins, e.g. C-reactive protein (CRP) \(^{(4)}\). The chronic inflammatory state in obesity contributes to the disease processes linked with obesity, such as type 2 diabetes and CVD \(^{(5)}\).

Bariatric surgery has pronounced effects on CVD mortality and morbidity \(^{(6)}\). A possible explanation could be that bariatric surgery reduces concentrations of CRP \(^{(7-19)}\), IL-6 \(^{(7-10)}\), ICAM-1 \(^{(18-20)}\), t-PA:Ag \(^{(21-23)}\), and vWF \(^{(10-12)}\), which markedly improves the low-grade inflammation and endothelial dysfunction in people with obesity. Inflammation and endothelial dysfunction contribute to atherosclerosis, and biomarkers of systemic inflammation and endothelial function have been shown to be predictive for future CVD \(^{(24, 25)}\).

Bariatric surgery candidates are physically inactive compared to normal weight individuals \(^{(26)}\). It has not been fully elucidated if bariatric surgery alone motivates patients to be more physically active \(^{(27, 28)}\), or whether it is also necessary to promote physical activity with exercise interventions. Physical inactivity is independently associated with low-grade inflammation, endothelial dysfunction and increased risk of CVD \(^{(29, 30)}\). It is well-documented that regular exercise reduces the risk of CVD \(^{(31)}\), however, the results regarding effects of moderate intensity exercise on low-grade inflammation and endothelial function are inconsistent \(^{(32-40)}\).
To date, no randomized controlled trials have investigated the effect of physical training after Roux-en-Y gastric bypass (RYGB) on biomarkers of inflammation and endothelial function. Therefore, the aim of this study was to evaluate the effect of a supervised physical training intervention following RYGB on biomarkers of inflammation and endothelial function. Furthermore, this study provides information about the effect of RYGB on the same biomarkers as both pre- and post-surgery measurements before initiation of the physical training were performed.
Materials and methods

Participants and study design

The current paper is part of a study investigating the effects of supervised physical training following RYGB on weight loss, physical activity, health related quality of life, and markers of CVD. Results reported in this paper are based on secondary outcome variables. The study design has been described in detail elsewhere\(^\text{[4]}\). The study was conducted according to the declaration of Helsinki, approved by the local Ethics Committee (Project-ID: S-20120112), and the trial was registered at http:/www.ClinicalTrials.gov (No. NCT01690728).

In brief, we included 60 non-smoking participants, eligible for RYGB according to the national guidelines (BMI > 35 kg/m\(^2\) with obesity related disease or BMI > 50 kg/m\(^2\) with obesity related social or physical complications). All subjects gave oral and written informed consent. The patients underwent laparoscopic RYGB at the Hospital of Southwest Jutland. The surgery was performed by one out of a group of three skilled surgeons, with a 20-30 mL gastric pouch, a 60 cm bilio-pancreatic limb and a Roux limb of 150 cm. Six months after RYGB the participants were randomized 1:1 to either a supervised physical training intervention group (INT, n=32) or a control group (CON, n=28). Randomization was done by one of the two principal investigators (CRS or LHM), by the sealed envelope method and performed in blocks of four, ensuring an equal distribution of type 2 diabetes patients. We excluded patients using vitamin K antagonists or hormones. Physically disabled patients and patients with severe osteoarthritis were also excluded. Due to co-morbidities some of the participants received various types of medicine, e.g. metformin (n=16), liraglutide (n=4), ACE inhibitors (n=21), and statins (n=10). Nineteen patients did not receive any medical treatment.

The intervention consisted of two weekly sessions of 40 minutes of supervised physical training for 26 consecutive weeks at a local fitness center. The participants in INT were provided with free access to the fitness center during the intervention period. The training sessions combined moderate intensity endurance and resistance training and were supervised by physiotherapists. The supervising
physiotherapist ensured weekly progression in resistance and endurance training. Besides the supervised physical training, the participants in INT were encouraged to be physically active with a goal of a total of 210 minutes per week, corresponding to the guidelines from the Danish National Board of Health. CON were given the clinic’s standard information about the importance of being physically active after RYGB. The dietary recommendations were similar in both groups, corresponding to a normal post-bariatric dietary counselling, securing sufficient protein and vitamin intake. The flow of participants in the study is presented in Figure 1. Among participants in INT, 19 were compliant to the intervention (attending > 50% of the supervised physical training sessions) corresponding to 59.4% of all study participants allocated to INT.

The subject characteristics pre- and post-surgery as well pre- and post-intervention are presented in Table 1. These results were published previously (41) and showed that body weight and BMI improved markedly as a result of RYGB, and that supervised physical training resulted in a better weight maintenance 24 months post-surgery in INT compared to CON.

**Blood sampling**

Blood samples were collected between 7.45 and 8.30 in the morning after 10 hours of fasting. Venous blood samples were collected with minimal stasis after 15 minutes rest in a supine position. The first 5 mL collected were discarded. The following 4 mL were collected in clot activator tubes (Becton-Dickinson, Plymouth, UK; BD Ref: 369032) and used for analyses of insulin and CRP in serum. Next, 3 mL were collected in trisodium citrate tubes (0.109 mol/L Na$_3$Citrate, BD Ref: 363048) for analysis of vWF and t-PA:Ag. Finally, 3 mL were collected in EDTA-tubes (K$_2$-EDTA: 5.4 mg, BD Ref: 367525) for IL-6 and ICAM-1, and 3 mL were collected in EDTA-tubes with citric acid and sodium fluoride (Vacuette FC Mix Tube, Greiner Bio-One, Frickenhausen, Germany, Ref: 454513) for plasma glucose measurements. Immediately after sampling, platelet poor plasma was prepared by centrifugation for 20 minutes at 2000 x g (20°C). Plasma and serum were transferred to aliquots, rapidly frozen and stored at -80 °C until testing.
Blood analyses

Plasma glucose (mmol/L) was analyzed immediately with an Architect C16000 (Abbott Diagnostics Division, Copenhagen, Denmark). Plasma and serum samples were thawed in a water bath at 37°C and analyzed in one series for each individual. Insulin (pmol/L) was measured using a commercial electro-chemiluminescence immunoassay (COBAS, Roche Diagnostics, Germany). Concentrations of CRP (mg/L) were determined on a nephelometer (Siemens Healthcare Diagnostics Products GmbH, Marburg, Germany). Commercially available ELISA kits were used for the measurements of plasma levels of ICAM-1 (ng/mL)(Allele-specific Quantikine; R&D Systems, Oxon, UK) and IL-6 (pg/mL) (Quantikine High Sensitivity; R&D Systems). Concentrations of vWF (%) were determined by an in-house ELISA using rabbit anti-human vWF polyclonal IgG as capture and detecting antibodies (DAKO, Glostrup, Denmark, Ref. Nr. A0082). Concentrations of t-PA:Ag (ng/mL) were determined by an in-house ELISA using mouse anti-human t-PA monoclonal IgG as capture (clone 15-4-21) and detection (clone 15-4-6) antibodies.

Plasma samples from two study participants (1 in INT, 1 in CON) were excluded from analysis because they started treatment with vitamin K antagonists during the study.

Statistics

Effects of RYGB were analyzed using the Wilcoxon signed rank test due to non-normally distributed data. The results are presented as median and interquartile range.

Differences between INT and CON at the 6-month examination (baseline for the intervention) were analyzed using Students t-test or Mann-Whitneys test when data were not normally distributed.

Effects of the supervised physical training intervention were assessed by a mixed-effects model for repeated measurements with a between group factor (INT/CON) and a time factor (6, 12 and 24 months). The differences in outcome between groups were assessed by group by time interaction. The model was adjusted for the six months values (baseline for the intervention). The model residuals were tested for
normal distribution, and the assumption of linearity and variance homogeneity was tested before performing analyses. In case of minor deviations from normality, robust estimation methods were performed. Results are presented as median and interquartile range.

Effects of the physical training intervention were analyzed as follows: 1. an intention-to-treat (ITT) approach, and 2. a per protocol (PP) approach where only participants in INT attending at least 50% of the training-sessions and all participants in CON were included. Missing data were handled by multiple imputations (MI), assuming missing values were randomly distributed. The imputations were adjusted for age, sex and weight. The five participants, who became pregnant during the study period and therefore were excluded, did not meet the assumption of missing at random, and MI could not be performed after the exclusion. Complete case analyses (ITT and PP) were also performed to ensure that analyses using the MI approach did not differ substantially from complete case analyses.

To explore the mechanisms behind changes in inflammation profile and endothelial function after RYGB, we performed pre- and post-surgery correlation analyses between biomarkers of inflammation, endothelial function and anthropometry as well as correlations between biomarkers of inflammation, endothelial function and biomarkers of glucose metabolism. Further, we examined correlations between changes from pre-surgery to 6 months post-surgery. Correlation analyses were performed with Pearson’s pairwise correlation test when data were normally distributed and Spearman’s test when data were not normally distributed.

A p-value of less than 0.05 was considered significant, two-sided tests were applied. All analyses were carried out using the Stata statistical software, version 13 (StataCorp, Texas, USA).

Results

Effects of RYGB are presented in Table 2. RYGB caused significant decreases in markers of inflammation (CRP and IL-6) and in markers of endothelial dysfunction (ICAM-1, t-PA:Ag and vWF). To elucidate any confounding effects of medication withdrawal after RYGB, the effects were also evaluated in 19 patients
without oral medication (Table 2). Long term effects of RYGB 24 months post-surgery were evaluated in 19 CON patients completing the study and revealed a significant sustaining effect on CRP, ICAM-1, IL-6 and t-PA:Ag (all \( p < 0.001 \)), but the effect on vWF was no longer significant (Table 2).

There were no differences between INT and CON at baseline for the intervention (results not shown, all \( p > 0.05 \)). Effects of the supervised physical training intervention are presented in Table 3. There were no additional effects of the intervention on markers of inflammation or endothelial function (all \( p > 0.3 \)). Per protocol analyses and complete case analyses were performed and revealed no differences in the results compared to ITT with MI analyses (results not shown). When examined for within group changes significant decreases in t-PA:Ag and CRP from 6-12 months post-surgery were found in both groups. Additionally, we found a significant decrease in CRP from 6-24 months post-surgery in both groups. No within groups changes from 12 to 24 months post-surgery were found.

Correlations are presented in Table 4. At baseline, BMI was positively correlated with CRP and IL-6. These correlations were still present at 6 months post-surgery. We did not find any correlations between the changes in weight or BMI and the changes in IL-6 and CRP (\( r < 0.1, p > 0.3 \)) while the change in vWF was inversely correlated to the changes in weight and BMI. At baseline, fasting glucose and insulin were correlated with t-PA:Ag and vWF. These correlations were still present at 6 months post-surgery. We did not find any correlations between changes in fasting glucose or insulin and the changes in t-PA:Ag, while the change in vWF was correlated with the change in fasting glucose (Table 4).

**Discussion**

The primary aim of the current study was to evaluate the effect of a 6 months supervised physical training intervention following RYGB on markers of low-grade inflammation and endothelial function in a randomized controlled trial. We did not observe an effect of supervised physical training on markers of low-grade inflammation or markers of endothelial function. A second aim was to evaluate the effect of RYGB on the same markers in a longitudinal observational study. Here we found noticeable and sustained effects of
RYGB, resulting in decreased concentrations of markers of low-grade inflammation and endothelial dysfunction, indicating an improved CVD risk profile. Furthermore, we investigated the correlations of the markers of inflammation and endothelial function with BMI, weight and markers of glucose metabolism.

While we found correlations for both pre- and post-surgery values we did not find any correlations between the changes in these variables.

Our results regarding biomarkers of inflammation and endothelial function are in accordance with previous findings, as several studies have reported a reduction in CRP, IL-6, ICAM-1 and vWF six to twelve months after bariatric surgery.

The concentration of CRP is increased in people with obesity and is associated with increased risk of CVD. We found a substantial and sustained reduction in CRP. At baseline, 47 of the 60 participants (78%) had CRP values above 3.0 mg/L. At 6 and 24 months, this number was reduced to 19 of 60 (32%) and 5 of 42 participants (12%), respectively. The clinical relevance of CRP lowering associated with massive weight loss in morbidly obese patients is under investigation. A recent study has shown that a reduction in CRP with anti-inflammatory therapy, without lowering LDL cholesterol, decreased the number of CVD events. Although it is difficult to independently assess the impact of reduced CRP on CVD, it is tempting to speculate that the beneficial effects of RYGB on CVD may partly be explained by a reduction in CRP and thereby an improvement in the state of chronic low-grade inflammation.

The effect of bariatric surgery on concentrations of t-PA:Ag has previously been reported in two case-control studies and one observational study, and our study confirms a significant reduction in t-PA:Ag as a result of RYGB. Tissue-type plasminogen activator is a fibrinolytic protein primarily synthesized and released into the blood by endothelial cells. An increased concentration of t-PA:Ag indicates endothelial dysfunction and predicts higher risk of CVD. The significant and sustained reduction in t-PA:Ag, therefore, might play a role in the reduction of the CVD risk associated with bariatric surgery.

Bariatric surgery increases nitric oxide (NO) availability which is known to improve endothelial function. This could in part explain the significant improvements in vWF, ICAM-1 and t-PA:Ag, which all
represent an improved endothelial function. Another explanation of the improved endothelial function could be the improved glucose metabolism observed as a result of RYGB. Hyperinsulinemia, hyperglycemia and insulin resistance all promote endothelial dysfunction\(^\text{48, 49}\). We and others have previously reported a noticeable reduction in insulin and glucose concentrations and an improvement in insulin sensitivity after RYGB \(^\text{41, 50, 51}\). In the current study, we saw a positive correlation between markers of glucose metabolism and markers of endothelial function represented by t-PA:Ag and vWF. Furthermore, we found that the improvements in vWF were positively associated with the changes in fasting glucose, indicating that the improved glucose profile may facilitate the observed improvements in the endothelial function. The spurious negative correlation between weight loss and change in vWF may be a chance finding and needs to be confirmed in other studies.

Previous studies have reported that the reduction in CRP is driven by weight loss regardless of the type of intervention, e.g. surgery, diet or lifestyle changes \(^\text{14, 52}\), and that the reduction in CRP is associated with the magnitude of weight loss after bariatric surgery \(^\text{12, 16}\). A prospective study with vertical ring gastroplasty found a positive correlation between weight loss and reduction in CRP \(^\text{14}\) whereas studies of RYGB found no association \(^\text{8, 19}\). While we observed a strong effect of bariatric surgery on the measured markers of inflammation and endothelial function, we found no correlations between the changes in BMI or weight and the changes in IL-6, CRP, ICAM-1 or t-PA Ag. This suggests that the changes in biomarkers of inflammation and endothelial function may not relate to the weight loss alone, but may result from other effects of the surgical procedure or the immediate improvement of insulin sensitivity following surgery \(^\text{8, 19}\). White adipose tissue (WAT), especially visceral adipose tissue, is recognized as an endocrine and metabolically active organ. Adipocytes, macrophages, and endothelial cells present in WAT secrete a large number of adipokines, for example IL-6, which contributes to the development of low-grade inflammation \(^\text{53}\). In line with this, we found that the reduction in IL-6 correlated with the reduction in CRP (rho 0.28, \(p<0.05\)). The improved inflammation profile may thus be ascribed to the reduced size and function of WAT seen after bariatric surgery \(^\text{54}\)
Exercise is known to have the potential to reduce low-grade inflammation and improve endothelial function. However, the results are diverging and highly dependent upon the intensity and frequency of the intervention as well as the risk profile of the studied population \cite{32-40}. Although weight loss affects inflammation, it has been demonstrated that the low-grade inflammation can be improved by exercise in the absence of weight loss \cite{38}.

To date no studies have assessed the effect of an exercise intervention following RYGB on biomarkers of inflammation and endothelial function. We found no additional effect of combined moderate intensity endurance and resistance training two times a week on the measured biomarkers, and we suggest that the dramatic effects caused by RYGB makes it difficult to obtain further improvements in the biomarkers of low-grade inflammation and endothelial function. Thus, further research is needed to establish if it is possible to achieve additional effects on biomarkers of inflammation and endothelial function in a post-bariatric population by exercising at a higher intensity and frequency than the intervention in the current study.

Strengths of this study are the randomized controlled design and the long follow up period after termination of the intervention. Additionally, the study provides information about the long term (two years) effects of RYGB itself. The study also has limitations. After bariatric surgery, antidiabetic, lipid lowering and antihypertensive medications were discontinued in a large subgroup of patients, and medication status is a potential confounder. The intervention compliance was lower than expected despite a large effort to keep the participants compliant with the training program. Finally, due to the overwhelming effects of RYGB on biomarkers of inflammation and endothelial function, it is possible that the potential and more modest effects of the supervised physical training intervention are not noticed.

In conclusion, this study demonstrates that RYGB, but not supervised physical training following RYGB, causes marked and sustainable favorable effects on markers of low-grade inflammation or endothelial function and thereby leads to a reduced risk of CVD. Our study indicates that the effects on inflammation and endothelial function are not driven by the weight loss per se and suggests that other
effects of RYGB are involved in reversing the pro-inflammatory state and endothelial dysfunction associated with obesity, a finding which needs to be further investigated.

Conflict of interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

Clinical trial registration number

Registered at ClinicalTrials.gov - no. NCT01690728.

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Author contributions

CRS and LHM carried out the experiments. CRS analyzed data. All authors were involved in detailing the protocol, discussing the results, writing the paper and final approval of the submitted and published versions.

Acknowledgements

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of effort in the supervised physical training intervention, and the technical staff from the Unit of Thrombosis Research, Hospital of Southwest Jutland, for doing a remarkable and time-consuming work with blood sampling and analysis.
Figure 1. Project flowchart

1. Screened at patient school (n=70)
2. Excluded (n=10)
   - Did not meet inclusion criteria (n=3)
   - Declined to participate (n=3)
   - Pregnancy prior to 6 months post-surgery visit (n=2)
   - Received other bariatric surgery (n=1)
   - Complications to RYGB (n=1)
3. Included (n=60)
4. Randomized at 6 months post-surgery examination (n=60)
5. Allocated to intervention (n=32)
   - Completed 12 months follow up (n=27)
   - Missed 12 months follow up (n=5)
     - Pregnancy (n=1)
     - Declined to participate (n=4)
   - Completed 24 months follow-up (n=22)
   - Missed 24 months follow-up (n=5)
     - Pregnancy (n=1)
     - Injury (n=1)
     - Declined to participate (n=3)
6. Allocated to control (n=28)
   - Completed 12 months follow up (n=25)
   - Missed 12 months follow up (n=3)
     - Pregnancy (n=1)
     - Declined to participate (n=2)
   - Completed 24 months follow-up (n=20)
   - Missed 24 months follow-up (n=5)
     - Pregnancy (n=2)
     - Declined to participate (n=3)
### Table 1 Subject characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Effects of RYGB</th>
<th></th>
<th>Effects of intervention</th>
<th></th>
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</thead>
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<tr>
<td></td>
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<td>Control group (n=28)</td>
<td>Intervention group (n=32)</td>
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<tr>
<td></td>
<td>Baseline</td>
<td>6 months post-surgery</td>
<td>6 months post-surgery</td>
<td></td>
</tr>
<tr>
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<td>6 months post-surgery</td>
<td>12 months post-surgery</td>
<td>24 months post-surgery</td>
<td></td>
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<tr>
<td></td>
<td>6 months post-surgery</td>
<td>12 months post-surgery</td>
<td>24 months post-surgery</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6 months post-surgery</td>
<td>12 months post-surgery</td>
<td>24 months post-surgery</td>
<td></td>
</tr>
<tr>
<td>Age (year)</td>
<td>42.3 (9.1)</td>
<td>42.8 (9.4)</td>
<td>43.0 (9.4)</td>
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<tr>
<td>Type 2 diabetes (yes/no)</td>
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<td>7/21</td>
<td>11/21</td>
<td></td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>18/42</td>
<td>7/21</td>
<td>11/21</td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>126.6 (20.9)</td>
<td>99.2 (18.5)***</td>
<td>98.4 (19.3)</td>
<td>99.7 18.0)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>43.0 (6.1)</td>
<td>33.7 (5.8)***</td>
<td>34.1 (5.4)</td>
<td>33.3 (6.2)</td>
</tr>
<tr>
<td>Insulin (pmol/L)</td>
<td>159.5 (106.9)</td>
<td>66.9 (44.9)***</td>
<td>62.7 (43.2)</td>
<td>70.4 (46.6)</td>
</tr>
<tr>
<td>Glucose (mmol/L)</td>
<td>6.2 (1.5)</td>
<td>5.5 (1.0)***</td>
<td>5.7 (1.3)</td>
<td>5.4 (0.6)</td>
</tr>
</tbody>
</table>

*** p<0.001, effect of Roux-en-Y gastric bypass (RYGB).

* p< 0.05, effect of intervention, intention to treat analysis with multiple imputation (MI) for missing values. a number of samples available for MI

Results are presented as mean (SD) unless otherwise mentioned.

Results were previously reported by Mundbjerg et al. 41.
Table 2. Effect of RYGB on markers of inflammation and endothelial function

<table>
<thead>
<tr>
<th>Variable</th>
<th>Entire group</th>
<th></th>
<th>CON-completers only</th>
<th></th>
<th>Patients without oral medication</th>
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<tbody>
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<td>Pre-surgery</td>
<td>6 months post-surgery</td>
<td>Pre-surgery</td>
<td>24 months post-surgery</td>
<td>Pre-surgery</td>
<td>6 months post-surgery</td>
</tr>
<tr>
<td></td>
<td>(N=60)</td>
<td>(N=60)</td>
<td>(n=19)</td>
<td>(n=19)</td>
<td>(n=19)</td>
<td>(n=19)</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>6.11 (3.47-9.71)</td>
<td>1.48 (0.35-3.80)****</td>
<td>6.02 (1.66-18.15)</td>
<td>0.48 (0.31-0.88)***</td>
<td>7.93 (4.09-9.26)</td>
<td>1.48 (0.28-4.05)***</td>
</tr>
<tr>
<td>ICAM-1 (ng/mL)</td>
<td>262 (237-296)</td>
<td>243 (221-259)***</td>
<td>255 (224-294)</td>
<td>227 (202-237)**</td>
<td>251 (230-265)</td>
<td>232 (212-258)</td>
</tr>
<tr>
<td>IL-6 (pg/mL)</td>
<td>3.78 (2.67-5.27)</td>
<td>2.38 (1.89-3.65)****</td>
<td>3.66 (2.16-5.27)</td>
<td>1.94 (1.41-2.85)**</td>
<td>3.61 (2.26-5.51)</td>
<td>2.51 (1.90-3.75)**</td>
</tr>
<tr>
<td>t-PA:Ag (ng/mL)</td>
<td>9.85 (7.50-12.6)</td>
<td>7.55 (5.50-11.2)****</td>
<td>9.45 (7.25-11.60)</td>
<td>6.80 (3.90-8.90)**</td>
<td>8.20 (6.90-11.2)</td>
<td>6.30 (5.60-9.20)*</td>
</tr>
<tr>
<td>vWF (%)</td>
<td>118 (85-154)</td>
<td>107 (82-132)*</td>
<td>97 (81-135)</td>
<td>91 (75-123)</td>
<td>98 (77-155)</td>
<td>93 (82-159)</td>
</tr>
</tbody>
</table>

Data are presented as median (interquartile range).

C-reactive protein (CRP); intracellular adhesion molecule 1 (ICAM-1); interleukin 6 (IL-6); tissue plasminogen activator antigen (t-PA:Ag); von Willebrand factor (vWF); CON (control group).

Differences between pre and post-surgery were analyzed with Wilcoxon signed-rank test.

* $p<0.05$, **$p<0.01$, ***$p<0.001$, ****$p<0.0001$. 
Table 3. Effects of physical training on markers of inflammation and endothelial function

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control group</th>
<th>Intervention group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>6 months</td>
<td>12 months</td>
</tr>
<tr>
<td>n</td>
<td>n=28</td>
<td>n=26</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>1.37 (0.40-4.09)</td>
<td>0.68 (0.30-1.04)§</td>
</tr>
<tr>
<td>ICAM-1 (ng/mL)</td>
<td>243 (214-256)</td>
<td>225 (209-249)</td>
</tr>
<tr>
<td>IL-6 (pg/mL)</td>
<td>2.19 (1.68-3.42)</td>
<td>2.03 (1.57-2.71)</td>
</tr>
<tr>
<td>t-PA:Ag (ng/mL)</td>
<td>7.60 (5.65-9.65)</td>
<td>6.65 (4.50-7.93)§</td>
</tr>
<tr>
<td>vWF (%)</td>
<td>104 (79-121)</td>
<td>92 (77-117)</td>
</tr>
</tbody>
</table>

Data are presented as median (interquartile range).

C-reactive protein (CRP); intracellular adhesion molecule 1 (ICAM-1); interleukin 6 (IL-6); tissue plasminogen activator antigen (t-PA:Ag); von Willebrand factor (vWF).

Differences between groups were calculated with a mixed-effects model with time x group interaction using intention to treat analysis with multiple imputation (MI) for missing values. a number of samples available for MI.

§ Significant change within the group from 6-12 months post-surgery, mixed model for repeated measurement, p<0.05.
Significant change within the group from 6-24 months post-surgery, mixed model for repeated measurement, $p<0.05$.

No significant differences between groups were observed as an effect of the intervention.
Table 4. Correlations pre-surgery and 6 months post-surgery and correlations between changes

<table>
<thead>
<tr>
<th></th>
<th>Pre-surgery</th>
<th>Post-surgery</th>
<th>Post-pre surgery change</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Weight</td>
<td>BMI</td>
<td>Glucose</td>
</tr>
<tr>
<td>IL-6</td>
<td>0.35**</td>
<td>0.39**</td>
<td>0.00</td>
</tr>
<tr>
<td>CRP</td>
<td>0.13</td>
<td>0.31*</td>
<td>-0.13</td>
</tr>
<tr>
<td>ICAM-1</td>
<td>0.02</td>
<td>0.01</td>
<td>0.11</td>
</tr>
<tr>
<td>t-PA:Ag</td>
<td>0.04</td>
<td>0.02</td>
<td>0.35**</td>
</tr>
<tr>
<td>vWF</td>
<td>0.19</td>
<td>0.22</td>
<td>0.28*</td>
</tr>
<tr>
<td>IL-6</td>
<td>0.28*</td>
<td>0.43**</td>
<td>0.15</td>
</tr>
<tr>
<td>CRP</td>
<td>0.20</td>
<td>0.35**</td>
<td>0.14</td>
</tr>
<tr>
<td>ICAM-1</td>
<td>-0.14</td>
<td>-0.14</td>
<td>0.21</td>
</tr>
<tr>
<td>t-PA:Ag</td>
<td>0.33*</td>
<td>0.30*</td>
<td>0.33*</td>
</tr>
<tr>
<td>vWF</td>
<td>0.25</td>
<td>0.22</td>
<td>0.13</td>
</tr>
<tr>
<td>ΔIL-6</td>
<td>-0.02</td>
<td>-0.05</td>
<td>-0.12</td>
</tr>
<tr>
<td>ΔCRP</td>
<td>0.06</td>
<td>0.11</td>
<td>-0.03</td>
</tr>
<tr>
<td>ΔICAM-1</td>
<td>0.03</td>
<td>-0.01</td>
<td>0.18</td>
</tr>
<tr>
<td>Δt-PA:Ag</td>
<td>0.05</td>
<td>0.03</td>
<td>0.22</td>
</tr>
</tbody>
</table>
BMI (body mass index); C-reactive protein (CRP); intracellular adhesion molecule 1 (ICAM-1); interleukin 6 (IL-6); tissue plasminogen activator antigen (t-PA:Ag); von Willebrand factor (vWF).

*p<0.05, **p<0.01.
References


(22) Carmichael AR, Tate G, King RF, Sue-Ling HM, Johnston D. Effects of the Magenstrasse and Mill operation for obesity on plasma plasminogen activator inhibitor type 1, tissue plasminogen activator, fibrinogen and insulin. Pathophysiol Haemost Thromb. 2002;32:40-3.


Highlights

- RYGB causes sustained improvements in inflammation and endothelial function
- No correlations between the change in weight/BMI and the change in inflammation
- Exercise after RYGB did not improve inflammation or endothelial function further