Insulin resistance, inflammation, and the metabolic syndrome following Roux-en-Y Gastric Bypass surgery in severely obese subjects

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Authors:
Obesity Unit 1, Biological Diagnostics 2, Diabetes Unit 3, Laboratory of Experimental Diabetes 4, Institut d’Investigacions Biomediques August Pi i Sunyer (IDIBAPS), Hospital Clinic Universitari, Barcelona, Spain.

Corresponding author:
Dr. Josep Vidal
Obesity Unit
Hospital Clinic Universitari
Villarroel 170
08036 Barcelona
Spain
E-mail: jovidal@clinic.ub.es

Short title: Gastric Bypass and the Metabolic Syndrome
Several studies have demonstrated the benefits of massive weight reduction following Roux-en-Y gastric bypass (RYGBP) on the metabolic syndrome (MS) (1-3). However, the time course of the effects of RYGBP on the MS components and its potential underlying mechanisms has not been reported. In recent years, it has been proposed that low-grade chronic inflammation is a critical factor underlying the MS (4-6). Alternatively, it has been proposed that the MS would be better explained by the combination of factors including but not limited to low-grade systemic inflammation (7). The aim of our study was to evaluate the time course of the MS components, insulin-sensitivity and inflammatory markers following laparoscopic RYGBP in severely obese subjects. To discriminate the effects of modest (10% of initial body weight) versus massive weight loss on the evaluated parameters, we assessed subjects at 6- and 52-weeks after surgery.

**Research Design and Methods**

A total of 36 Caucasian severely obese subjects about to undergo RYGBP surgery (8) were evaluated (Table 1). Twenty normal-weight healthy volunteers matched for gender and age with the obese subjects served as controls (Table 1). The study was approved by the Hospital Ethics Committee. Written informed consent was obtained from all participants. The 36 obese operated subjects were evaluated within 8 weeks before RYGBP and again at 6- and 52-weeks after RYGBP. Control subjects were evaluated on a single occasion.

The diagnosis of the MS was based on the revised ATP III criteria (9). Anthropometrical and blood pressure measurements were performed as previously described (10). Venous blood was collected after an overnight fast. Plasma glucose, total cholesterol, HDL-cholesterol, triglycerides levels, insulin, adiponectin, and insulin sensitivity (HOMA-IR) were assessed as previously described (10). The leukocyte count was measured using an Advia 2400 analyser (Bayer Diagnostics, Tarrytown, NY, USA). High-sensitive CRP (hs-CRP) was determined using an immunonefelometric method (Boehring Nephelometer Analyzer, Dade Boehringer, Marburg). Soluble TNFr1 (p55/p60) and TNFr2 (p75/p80) (HyCult Biotechnology, Uden, Netherlands), and resistin (Linco Research, St Charles, Missouri USA) were measured by an enzyme-linked immunosorbent assay.

All data are expressed as means ± SEM. Statistical analyses were carried out using SPSS 11.5 software (SPSS inc., Chicago, IL, USA). Chi-squared and non-parametric test (Mann-Whitney U, Friedman, or Kruskall-Wallis) were used for comparisons between groups. Correlations were analyzed using Spearman rank correlation analysis or partial correlation analysis. Statistical significance was set at a p <0.05.

**Results**

The time course of the prevalence of the Metabolic Syndrome and its individual components is shown in Table 1.

**Insulin sensitivity and the MS**

Prior to surgery, a significant correlation was found between HOMA-IR and the number of MS components (r=0.570, p<0.005). HOMA-IR significantly correlated with fasting plasma glucose (FPG, r=0.659, p<0.001), and tended to correlate with systolic blood pressure (SBP, p=0.071) and waist circumference (WC, p=0.074) albeit it did not reach statistical significance. HOMA-IR significantly declined following RYGBP (Table 1). At 6 weeks, HOMA-IR significantly correlated with FPG (r=0.589, p<0.005), triglycerides (r=0.367, p<0.05), and HDL-cholesterol.
At 52 weeks, HOMA-IR significantly correlated with the number of MS components \((r=0.366, p<0.05)\), and with FPG \((r=0.394, p<0.05)\). The correlations between HOMA-IR and components of the MS remained significant even after controlling for the different inflammatory parameters.

**Inflammatory Markers and the MS**

Prior to surgery, no significant correlation was found between inflammatory markers and the individual MS components, the number of MS components present in one particular individual, or HOMA-IR. At 6-weeks, changes in some of the inflammatory markers were observed (Table 1). The leukocyte count was the only showing significant correlations with MS components (WC and SBP), but these associations lost significance when HOMA-IR was considered. At 52-weeks, we observed a significant decline in the evaluated pro-inflammatory markers (except for resistin) and an increase in plasma adiponectin relative to baseline. Again, we did not find a significant correlation between the number of MS components and the inflammatory parameters. However, the leukocyte count significantly correlated with systolic and diastolic BP (respectively, \(r=0.384, p<0.05\); and \(r=0.387, p<0.05\)), and triglycerides \((r=0.393, p<0.05)\). Adiponectin significantly correlated with the WC \((r=-0.365, p<0.05)\), DBP \((r=-0.387, p=0.05)\), triglycerides \((r=-0.345, p<0.05)\) and HDL-cholesterol \((r=0.355, p<0.05)\). hs-CRP significantly correlated with FPG \((r=0.34, p<0.05)\). These correlations were barely affected when HOMA-IR was considered. Noteworthy, at 52-weeks after surgery most inflammatory markers remained altered when operated subjects were compared with the normal-weight cohort (Table 1).

**Conclusions**

Marked reductions in the prevalence of the MS have been observed after RYGBP at 1 year or longer follow up (1-3). Noteworthy, our data contributes showing that the improvement in the MS following RYGBP occurs shortly after the surgical procedure at a time when the attained weight loss is still modest. This is consistent with reports showing an early amelioration of altered glucose homeostasis (11), and blood pressure (12) following this type of surgical technique.

It has been proposed that systemic low-grade inflammation is critical for the appearance of the MS, and that an improvement in the inflammatory process is important for the beneficial effects of weight loss (4-6, 13). However, our data would suggest a different scenario at least in severe obesity. Our results are supported by recent findings that increased CRP levels are found in severely obese subjects irrespective of the presence of non-alcoholic steatohepatitis or the MS (14). Likewise, several studies have reported either no change or no association between inflammatory markers and changes in metabolic parameters at short term after RYGBP (15-18). Importantly, our data does not preclude a role of the inflammatory process in the improvement of the MS at longer follow up. At one year after RYGBP, upon massive weight loss, our data and that from others demonstrate that changes in the inflammatory process may help to explain changes in the MS. A significant correlation between CRP plasma concentration (19) or adiponectin (17) and metabolic variables has previously been reported at 6 and 12 months after RYGBP.

The data from the current study suggest that the early changes in the MS following RYGBP are better explained by changes in insulin sensitivity. An early improvement in insulin sensitivity...
following RYGBP has previously been described (11,20). Interestingly, Petersen et al (21) reported mechanistic studies on the changes of glucose homeostasis in type 2 diabetic subjects following a dietary intervention resulting in a weight loss similar to the one presented in our cohort at 6-weeks after surgery. The normalization of glucose homeostasis was associated with a marked improvement in whole-body insulin sensitivity, hepatic triglyceride content and hepatic insulin sensitivity but no changes in circulating levels of inflammatory markers.

We acknowledge our study has several limitations. The small sample size may not allow definite conclusions to be drawn. Second, the inflammatory process involves a complex interplay of inflammatory mediators (5,6) and we only measured a subset of these markers. Thus, further studies with a more comprehensive evaluation are needed to better understand the contribution of the inflammatory process in the changes in obesity-associated metabolic disturbances following RYGBP.

In summary, our data confirms previous reports on the inflammatory state associated with obesity. Moreover, our data supports the view that obesity is an important contributor to the elevation of plasma concentration of inflammatory markers. Finally, we suggest that at short term after RYGBP the changes in the MS components are better accounted for improved insulin sensitivity than decreased low-grade inflammation. Unravelling the mechanisms responsible for the metabolic disturbances associated with obesity may provide new targets to reduce the burden of obesity epidemics.

Acknowledgments
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References


Table 1. Clinical characteristics, insulin sensitivity and inflammatory markers in severely obese subjects at the three study time points and in normal-weight controls.

<table>
<thead>
<tr>
<th></th>
<th>Control subjects (n=20)</th>
<th>Obese subjects Prior to RYGBP (n=36)</th>
<th>6-w after RYGBP (n=36)</th>
<th>52-w after RYGBP (n=36)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>42.8 ± 2.7</td>
<td>43.9 ± 1.8</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>7/13</td>
<td>12/24</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>BMI (Kg/m²)</td>
<td>22.9 ± 0.4</td>
<td>49.0 ± 1.0</td>
<td>43.2 ± 0.9* a</td>
<td>33.0 ± 0.7* a</td>
</tr>
<tr>
<td>Weight loss (%)</td>
<td>---</td>
<td>---</td>
<td>11.6 ± 0.7</td>
<td>32.4 ± 1.1</td>
</tr>
<tr>
<td>MS prevalence</td>
<td>0 %</td>
<td>55 %</td>
<td>36.11%*</td>
<td>11.11 %</td>
</tr>
<tr>
<td>Waist (cm)</td>
<td>80.3 ± 2.5</td>
<td>136.7 ± 2.4 a (100%)</td>
<td>124.6 ± 2.8* a (100 %)</td>
<td>104.1 ± 2.3* a (100%)</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>77.6 ± 1.5</td>
<td>114.0 ± 5.7 a (52%)</td>
<td>94.8 ± 2.3* a (17%)*</td>
<td>86.2 ± 1.5* a (0%)*</td>
</tr>
<tr>
<td>HDL-chol (mg/dL)</td>
<td>52.8 ± 1.8</td>
<td>45.6 ± 1.2 a (31%)</td>
<td>42.0 ± 1.1* a (53%)*</td>
<td>56.0 ± 1.7* a (17%)*</td>
</tr>
<tr>
<td>Tryglicerides (mg/dL)</td>
<td>134.1 ± 2.4</td>
<td>138.1 ± 9.5 (25%)</td>
<td>117.0 ± 4.3* a (11%)*</td>
<td>86.1 ± 5.1* a (6%)*</td>
</tr>
<tr>
<td>SBP /DBP (mmHg)</td>
<td>111.5 ± 1.5 / 70.0 ± 1.6</td>
<td>128.9 ± 2.9 a / 77.9 ± 1.6 a (67%)</td>
<td>122.2 ± 5.6* a / 74.4 ± 1.4* a (50%)*</td>
<td>122.2 ± 2.3* a / 74.7 ± 1.5* a (53%)*</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>2.31 ± 0.26</td>
<td>6.22 ± 0.53 a</td>
<td>3.11 ± 0.25* a</td>
<td>2.11 ± 0.12*</td>
</tr>
<tr>
<td>Adiponectin (mg/L)</td>
<td>20.74 ± 2.27</td>
<td>8.83 ± 0.63 a</td>
<td>11.72 ± 0.90* a</td>
<td>13.16 ± 1.21* a</td>
</tr>
<tr>
<td>Resistin (ng/ml)</td>
<td>11.52 ± 0.71</td>
<td>13.11 ± 0.67</td>
<td>15.06 ± 1.09* a</td>
<td>12.18 ± 0.58</td>
</tr>
<tr>
<td>TNFr1 (ng/ml)</td>
<td>0.44 ± 0.04</td>
<td>1.02 ± 0.72 a</td>
<td>0.96 ± 0.51 a</td>
<td>0.70 ± 0.06* a</td>
</tr>
<tr>
<td>TNFr2 (ng/ml)</td>
<td>0.72 ± 0.06</td>
<td>1.65 ± 0.09 a</td>
<td>1.50 ± 0.07 a</td>
<td>1.17 ± 0.08* a</td>
</tr>
<tr>
<td>PCR (mg/dL)</td>
<td>0.14 ± 0.05</td>
<td>1.08 ± 0.19 a</td>
<td>0.79 ± 0.11 a</td>
<td>0.23 ± 0.05* a</td>
</tr>
<tr>
<td>Leukocytes (x10¹²/L)</td>
<td>5.99 ± 0.36</td>
<td>7.75 ± 0.32 a</td>
<td>6.86 ± 0.26*</td>
<td>6.77 ± 0.26*</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± sem (prevalence of a particular MS component). * p<0.05 relative to baseline examination in severely obese subjects. ** p<0.05 relative to normal-weight controls.