Effect of Massive Weight Loss induced by Bariatric Surgery on Serum Levels of Interleukin-18 and Monocyte-Chemoattractant-Protein-1 in Morbid Obesity

Gerit-Holger Schernthaner, MD1; Hans-Peter Kopp, MD2; Stefan Kriwanek, MD3; Katarzyna Krzyzanowska, MD2; Miriam Satler, MSC1; Renate Koppensteiner, MD1; Guntram Schernthaner, MD2

1Department of Internal Medicine II, Division of Angiology, Medical University of Vienna, Vienna; 2Department of Internal Medicine I, Rudolfstiftung Hospital, Vienna; 3Department of Surgery, Rudolfstiftung Hospital, Vienna, Austria

Background: Morbid obesity is associated with insulin resistance (IR), chronic inflammation and premature atherosclerosis. Since vascular inflammation may contribute to the increased risk of cardiovascular morbidity and mortality of these patients, we studied circulating Interleukin-18 (L-18) and monocyte-chemoattractant-protein-1 (MCP-1) levels in 37 patients with morbid obesity before and after significant weight loss induced by bariatric surgery and their preoperative and postoperative associations with C-reactive protein (CRP) and IR-associated factors.

Methods: High sensitivity assays were used to measure concentrations of fasting CRP, IL-18 and MCP-1. Differences between patients before and after bariatric surgery were analyzed by Student’s paired t-test. To investigate the associations of the observed reductions of values, delta of parameters were calculated and preoperative, postoperative and delta data were tested by univariate and multivariate linear regression.

Results: After a mean follow-up period of 26.5 months and a massive weight loss of 35 kg induced by bariatric surgery, circulating IL-18 levels decreased by 37% (P<0.001) and circulating MCP-1 levels by 47% (P<0.001). Multiple linear regression of delta values of IL-18 showed that only 2-hour glucose (P=0.008) remained independently and significantly associated with IL-18, whereas multiple linear regression analysis of delta values of MCP-1 revealed that only delta of HOMA-IR (P<0.001) remained independently and significantly associated with MCP-1, respectively.

Conclusions: Because both biomarkers have been shown to play an important role in the development and progression of atherosclerosis, the observations presented in this study could be of clinical relevance for morbidly obese patients undergoing bariatric surgery.

Key words: Interleukin-18, monocyte-chemoattractant-protein-1, morbid obesity, insulin resistance, chronic inflammation

Introduction

Morbid obesity is associated with an increased risk of coronary heart disease, stroke, hypertension, type 2 diabetes, dyslipidemia, and all-cause mortality. The risk is proportional to body mass index and duration of obesity and increases with visceral obesity.1,2 The increased morbidity is assumed to be mediated mainly by insulin resistance (IR), diabetes, hypertension, lipid disturbances and coagulation abnormalities.3,4 More recently, it has been suggested that vascular inflammation and endothelial dysfunction may contribute to the increased risk of cardiovascular morbidity and mortality of these patients.5,9 Morbidly obese subjects and their marked weight loss after bariatric surgery emerge as a valuable
model for studying the impact of changes in body weight and the associated cardiovascular risk factors. Studies investigating the impact of weight loss on cardiovascular end-points as well as various surrogate markers of cardiovascular disease are of particular interest. Recent studies have shown that circulating interleukin-18 (IL-18) levels were strongly predictive of future cardiovascular mortality in patients with coronary artery disease and that elevated baseline levels of monocyte-chemoattractant-protein-1 (MCP-1) were associated with an increased risk for death or myocardial infarction in acute coronary syndrome. Because patients with morbid obesity are at high risk for cardiovascular mortality, it was of interest to study the biomarkers IL-18 and MCP-1 in patients with morbid obesity before and after significant weight loss induced by bariatric surgery.

**Patients and Methods**

**Patients**

The study was approved by the institutional ethics committee and complies with the Declaration of Helsinki including current revisions and the Good Clinical Practice guidelines. The procedures followed were in accordance with institutional guidelines. All subjects gave written informed consent before the study. Peripheral blood samples were collected from 37 patients (29 women, 8 men; mean age 40±8 years; mean HbA1c 5.6±0.7%) with morbid obesity before and after open bariatric surgery with vertical banded gastroplasty as described previously in detail. Evaluation at follow-up was performed 26.6±11.5 months after surgery. At that time, all patients were weight stable and not on hypocaloric nutrition. None of the subjects had a history of cerebro- or cardiovascular disease except for arterial hypertension. Patients with hepatic or renal failure, Cushing’s syndrome, thyroid dysfunction, other major endocrine disorders, or infectious diseases were excluded. Subjects with overt eating disorders, heavy alcohol consumption, and major psychiatric disease were omitted. None of the patients had lipid-lowering drug therapy before or after surgery. A standard oral glucose tolerance test with 75 g glucose was performed, and glucose tolerance status was defined according to the Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. IR was estimated from fasting glucose and insulin concentrations with the homeostatic model assessment (HOMA), as described previously.

**Determination of Biomarkers of Inflammation**

A fasting 20-mL sample of venous blood was taken for estimation of biochemical and inflammatory factors. Serum samples for measurement of high sensitive C-reactive protein (CRP), IL-18, and MCP-1 concentrations were stored at -80°C. High sensitivity assays were used to measure concentrations of CRP, IL-18 and MCP-1: CRP was measured with a nephelometric assay in serum (Dade Behring, Marburg, Germany). Serum MCP-1 and IL-18 were determined by the use of an ELISA (Bender MedSystems, Vienna, Austria). Intrassay and interassay variability coefficients were as follows, respectively: for CRP, 4.7% and 8.3%; for IL-18 6.5% and 8.1%; for MCP-1 6.2% and 7.7%. Baseline and postoperative samples of all patients were assayed in the same batch to minimize interassay variability.

Blood glucose, cholesterol, HDL cholesterol, and triglycerides were measured by enzymatic *in vitro* tests (Roche Diagnostics Corp); the intraassay and interassay coefficient of variation were 1.1% and 2.9%, 0.8% and 1.7%, 1.3% and 2.6%, 1.5% and 1.8%, respectively. Glycosylated hemoglobin was measured by high-performance liquid chromatography (Diamat, BioRad). For quantification of insulin concentrations, an ELISA system was used (Enzymuntest Insulin, ES 600, Boehringer Mannheim), for which the intraassay and interassay coefficients of variation were 3.5% and 5.6% respectively.

**Statistics**

Data are presented as mean±SD. In case of non-normal distribution, a logarithmic transformation was used to render the distribution normal for parametric tests. Differences between patients before and after bariatric surgery were analyzed by Student’s paired *t*-test. In order to investigate the associations of the observed reductions of the values, delta (change) of parameters were calculated. Preoperative, postoperative and delta data were tested for association within