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Original article

Differential response of plasma plasminogen activator inhibitor 1 after weight loss surgery in patients with or without type 2 diabetes

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Abstract

Background: Obesity and type 2 diabetes (T2D) are associated with a suppression of fibrinolysis and an increased risk of intravascular thrombi because of elevated plasma plasminogen activator inhibitor 1 (PAI-1).

Objectives: The aim was to investigate PAI-1 levels in obese patients in the early phase after bariatric surgery, before any weight loss, and in the late phase, to identify the impact of reduced adipose mass versus weight loss independent effects on PAI-1 levels. We also studied the impact of T2D on the rate of PAI-1 reduction.

Settings: Twelve obese patients with and without T2D (n = 6) who were scheduled for surgery at a designated Center of Excellence.

Methods: Plasma PAI-1 antigen was measured by enzyme-linked immunosorbent assay (ELISA) preoperatively and at 4 and 42 days after gastric bypass surgery.

Results: In the early phase, plasma PAI-1 was significantly decreased by 53% ($P = .023$). This difference did not remain significant in the late phase. However, PAI-1 levels in T2D and non-T2D patients were significantly different ($P = .005$). In non-T2D patients, plasma PAI-1 levels decreased significantly in both early and late phases ($P = .038$). Interestingly, in the T2D group, the PAI-1 levels tended to increase in the late phase and differed significantly from the non-T2D group.

Conclusion: We report decreased PAI-1 levels in the immediate postoperative period after gastric bypass, indicating that a mechanism not related to the fat mass regulates the PAI-1 levels. Additionally, there may be a difference in PAI-1 levels between T2D and non-T2D patients 42 days postoperatively. Further studies are required to verify this difference and to elucidate the specific mechanisms responsible for PAI-1 synthesis. (Surg Obes Relat Dis 2016;▮:00–00.)

Keywords: Bariatric surgery; Gastric bypass; Obesity; Type 2 diabetes; PAI-1

Obesity and type 2 diabetes (T2D) are increasing enormously worldwide and are causing economic overload in healthcare systems [1,2]. The major cause of morbidity and mortality is cardiovascular disease and the risk of myocardial infarction is 3- to 5-fold higher in diabetes [3].

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In a cardiovascular event, a thrombus is formed and intravascular fibrinolysis is initiated by an acute release of tissue-type plasminogen activator (tPA) from endothelial cells. tPA activates plasminogen to plasmin, ensuring the degradation of fibrin. Plasminogen activator inhibitor 1 (PAI-1) is the main inhibitor of tPA, and increased plasma levels of PAI-1 lead to a state of hypofibrinolysis in which the removal of thrombus is impaired. Deficiency of PAI-1 leads to accelerated fibrinolysis and bleeding [4,5]. Conversely, an elevated plasma level of PAI-1 is associated with increased risk of vascular events and is a strong independent predictor of myocardial infarction [6,7], as well as a risk factor of venous thromboembolism [8]. There is a strong correlation between body mass index (BMI) and plasma PAI-1 [9], and PAI-1 may be involved in adipose tissue development [10]. Reduction of fat mass, both surgically resected or by diet, has been found to effectively decrease PAI-1 levels [11]. Furthermore, an elevated level of plasma PAI-1 leads to a suppression of fibrinolysis in T2D and is a risk factor for the development of diabetes in healthy individuals independently of common risk factors, including weight and insulin resistance [12,13]. PAI-1, the main inhibitor of the fibrinolytic system, has a complex involvement in the mechanisms behind obesity and T2D. The origin of plasma PAI-1 is disputed. It has been suggested that platelets are the major source in healthy lean individuals; however, there may be a contribution of PAI-1 from adipose tissue in pathologic conditions such as obesity and T2D [14].

At present, the most effective approach to treating grade II and III obesity is bariatric surgery, which leads to marked and long-lasting weight reduction. Glycemic control is improved, with some patients even achieving remission, and overall glycemic control is satisfactory and superior to current pharmacotherapy [15,16]. Recently it was reported that 34.4% of the patients with diabetes had complete remission after bariatric surgery [17]. It has been reported that plasma PAI-1 levels decrease after bariatric surgery in otherwise healthy obese patients, which suggests a long-term beneficial effect on mortality from cardiovascular and thromboembolic disease [18–21]. Conversely, there is an increased risk of deep vein thrombosis or venous thromboembolism within 30 days after bariatric surgery [22].

The aim of the present study was to investigate the rate of the decrease of plasma PAI-1 levels in obese patients after Roux-en-Y gastric bypass (RYGB). The model of gastric bypass was used to get vital clues regarding the importance of reduction of fat mass versus weight loss independent effects on PAI-1 levels. Plasma PAI-1 was measured at early time points, before any clinically relevant weight loss, as well as at later time points, when the effect of weight loss is observed. We also performed a comparative analysis between patients with and without T2D undergoing gastric bypass surgery.

Materials and methods

All human studies were performed according to the principles of the Declaration of Helsinki. The Somerset Research and Ethics committee approved the study (LREC Protocol Number: 05/Q2202/96). Written informed consent was obtained from all participants.

The selection criteria included morbidly obese patients undergoing gastric bypass, and 12 patients were enrolled in the study. Exclusion criteria included pregnancy, substance abuse, and consumption of $>$ 2 alcoholic drinks per day. A 2-week preoperative diet of 1000 kcal was used in all patients before surgery. Six of the enrolled patients had T2D; participants were considered to have T2D if they were on treatment or the diagnosis was made using a fasting glucose or 2-hour postprandial glucose value after an oral glucose tolerance test by their primary care physician. For these T2D patients, glycemic control was optimized with pharmacotherapy and lifestyle changes for 6 months before surgery. None of the patients was on insulin during the study. All surgical procedures were performed in the Department of Bariatric and Metabolic Surgery, Musgrove Park Hospital, Taunton, designated a Center of Excellence by the Surgical Review Corporation.

Patients were studied immediately preoperatively and at 4 and 42 days after surgery. *Early phase* was defined as between preoperatively and day 4, and *late phase* was defined as between day 4 and day 42.

A venous catheter was placed and blood was collected in EDTA and aprotinin 150 minutes after a 400-kcal semi-liquid standard mixed meal high in fat and refined carbohydrates (41% fat, 10.2% protein, 48.8% carbohydrates). The meal was consumed between 8 and 9 AM after a 12-hour fast. Samples were immediately centrifuged and stored at –80°C until analyzed. An automated glucose analyzer (Abbott Laboratories, Chicago, IL) was used, as well as an automated insulin assay (Abbott Laboratories). Plasma PAI-1 antigen was determined by enzyme-linked immunosorbent assay (ELISA; Technoclone GmbH, Vienna, Austria). The recommended postoperative diet, provided by a dietician, was approximately 700–1000 kcal/day for the first week, gradually increased as tolerated during the 6-week period of the study.

Statistical analysis

Results were analyzed using SPSS statistical software (SPSS Inc., Chicago, IL). Data are expressed as mean (standard deviation). The unpaired *t* test was used for parametric demographic data. The paired *t* test was used for homeostatic model assessment of insulin resistance (HOMA-IR), insulin, and plasma glucose responses. To stabilize variances and to get symmetric distributions for the residuals, all statistical analyses of PAI-1 were performed on log transformed data. Analysis of variance on PAI-1 was