Decrease of dipeptidyl peptidase 4 activity is associated with weight loss after bariatric surgery

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Abstract

**Purpose** Dipeptidyl peptidase 4 (DPP4) is expressed and secreted by adipocytes. DPP4 induces insulin resistance independently of its effect on glucagon-like peptide 1, thus it is conceivable that DPP4 directly contributes to metabolic dysfunction in patients with morbid obesity. The aim of this study was to investigate the impact of weight loss induced by bariatric surgery on DPP4 activity, and whether these changes are associated with improvements in markers of metabolic dysfunction and fatty liver disease.

**Materials and Methods** We included 68 non-diabetic patients who underwent bariatric surgery. Serum DPP4 activity was measured using a fluorogenic substrate before and after surgery.

**Results** Results: After a median follow-up period of 12 (IQR 11-17) months, median serum DPP4 activity decreased from 230 (IQR: 194-273) to 193 (164-252) pmol/min (p=0.012). The decrease in DPP4 activity was significantly correlated with decreases in BMI, improved cholesterol levels, reduced hepatic injury markers as well as improved post-prandial insulin sensitivity. After multivariable adjustment, ΔDPP4 activity remained significantly associated with Δcholesterol (beta=0.341, p=0.025), ΔLDL cholesterol (beta=0.350, p=0.019), Δgamma-glutamyltransferase (beta=0.323, p=0.040) and ΔMatsuda index (beta=-0.386, p=0.045).

**Conclusion** We demonstrated that weight loss induced by bariatric surgery results in decreased circulating DPP4 activity beyond the initial phase of weight loss. The associations between decreased DPP4 activity and improved cholesterol levels as well as hepatic injury markers point towards pleiotropic effects of DPP4 beyond glucose metabolism which warrant further investigation.

**Keywords** dipeptidyl peptidase 4 · morbid obesity · lipids · liver
effects on glucose homeostasis, DPP4 has been shown to directly impair insulin signaling in adipocytes, skeletal muscle cells as well as in hepatocytes in vitro (7, 9). Pharmacological DPP4 inhibitors are now frequently prescribed for glycemic control in patients with type 2 diabetes mellitus (10).

Bariatric surgery is an effective treatment for morbid obesity leading to the improvement of its cardiometabolic sequelae such as type 2 diabetes mellitus, arterial hypertension, and hyperlipidemia (11, 12). Changes in a wide range of hormones have been proposed to mediate the metabolic benefits seen with bariatric surgery such as changes in postprandial incretin response or altered bile acid metabolism (13). Studies investigating the potential involvement of plasma DPP4 activity in bariatric surgery-associated metabolic improvements are, however, scarce. Thus, the aim of this study was to investigate the impact of bariatric surgery-induced weight loss on circulating DPP4 activity and whether changes in DPP4 activity are associated with the observed metabolic improvements.

Methods

The patients were recruited in an ongoing observational study at the obesity outpatient clinic of the Department of Medicine I of Klinik Landstraße, formerly known as Krankenanstalt Rudolfstiftung, in Vienna, Austria. We recruited all consenting consecutive patients who were evaluated for bariatric surgery. Medical history, blood draws and anthropometric measures were taken before and at each routine follow-up visit after surgery. The patients either underwent laparoscopic Roux-en-Y gastric bypass surgery or sleeve gastrectomy. 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 performed were in accordance with institutional guidelines and all subjects gave written informed consent before the study. For this sub-study, we selected 68 patients without previously known type 2 diabetes for whom pre- and post-operative serum samples were available. We excluded patients with previously known and already treated diabetes to exclude confounding due to changes in antidiabetic medications after surgery. Normal glucose metabolism, prediabetes and overt type 2 diabetes mellitus were diagnosed according to current guidelines (14). In a subset of 34 participants, results of an oral glucose tolerance tests (OGTT), performed after the ingestion of 75g glucose diluted in 300ml water with insulin and glucose measurements at 0, 60, 120 minutes, were available both before as well as after surgery.

All patients with severe renal or liver disease or patients on a systemic corticosteroid drug therapy were excluded from this study. In addition, all patients with acute psychiatric illnesses were excluded.

Laboratory measurements

Peripheral venous blood samples were collected from all patients after an overnight fast for determination of basic laboratory characteristics. Routine laboratory measurements were performed at the institution’s central laboratory. Homeostasis model assessment insulin resistance (HOMA-IR) index and Matsuda insulin sensitivity index were calculated using published formulae (15, 16). The Matsuda insulin sensitivity index is calculated from fasting as well as post-load glucose and insulin levels during an OGTT and has been shown to be highly correlated with whole-body glucose disposal during a hyperinsulinemia euglycemic clamp, the gold standard for the assessment of whole body insulin sensitivity (16). HOMA-IR, on the other hand, which is derived from fasting glucose and insulin measurements is thought to primarily reflect hepatic insulin resistance (15). Serum samples for the determination of DPP4 activity were centrifuged between 30 - 60 minutes after the blood draw and stored at -80°C. Serum DPP4 activity was assayed by a commercially available kit measuring the fluorescence of the cleaved fluorogenic DPP4 substrate H-Gly-Pro-AMC using a microplate reader (Enzo Life Sciences, Inc., Lausen, Switzerland).

Statistics

The data are presented as count, median (25th - 75th percentile), or mean ± standard deviation, as appropriate. Accordingly, within-groups differences were tested using Student’s paired t-test or Wilcoxon signed-rank test. To investigate associations between two continuous variables, Spearman’s rank correlation coefficient was used. To investigate longitudinal associations, change scores (Δ) were calculated by subtracting the baseline value from the follow-up value of each respective variable.

We used multiple linear regression to adjusted associations between change scores for their respective baseline values and other variables of interest. Effect size is given as standardized regression coefficients (beta). All analyses were performed using SPSS 25 (IBM Corp., Armonk, NY). Two-sided p-values ≤0.05 were deemed statistically significant.

Results

This study included 68 individuals with morbid obesity of which 53 (78%) were female with a mean age of 42 ± 12 years and a mean BMI of 46.9 ± 7.7 kg/m². The median baseline HbA1c value was 5.8 (IQR: 5.5 - 6.3) % indicating an impaired glucose metabolism in more than half of the participants: 31 (45.6%) fulfilled the diagnostic criteria for prediabetes and 14 (20.6%) for diabetes. The remaining baseline characteristics are depicted in table 1. Among the baseline
clinical variables depicted in table 1, baseline DPP4 activity correlated with the hepatic markers alanine aminotransferase (ALAT) (rho=0.274, p=0.026) and gamma-glutamyltransferase (GGT) (rho=0.280, p=0.002) while there were no significant correlations with BMI (rho=0.082, p=0.508) or the marker of insulin resistance HOMA-IR (rho=0.172, p=0.175).

Sleeve gastrectomy and laparoscopic Roux-en-Y gastric bypass surgery were performed in 58 (85.3%) and 10 (14.7%) patients, respectively. After a median follow-up of 12 (IQR 11–17) months, mean weight loss was 43 (95%CI: 40 - 47) kg of body weight corresponding to a change in BMI from 46.9 ± 7.7 to 30.3 ± 9.3 kg/m². As expected, this was accompanied by relevant improvements in cardio-metabolic risk markers, and liver parameters (table 1). At the same time, DPP4 activity declined from 230 (IQR: 194 - 273) to 193 (164 - 252) pmol/min (p = 0.012, Figure 1).

The decrease in DPP4 activity did not significantly differ between normoglycemic, prediabetic or diabetic patients after adjusting for baseline DPP4 activity (p=0.125). When investigating the associations between postoperative changes, the decrease in DPP4 activity correlated significantly with the changes in BMI (rho=0.410, p=0.001), total cholesterol (rho=0.383, p=0.003), ALAT (rho=0.380, p=0.003), ASAT (rho=0.295, p=0.034), GGT (rho=0.276, p=0.034) but not with the change in HOMA-IR (rho=0.094, p=0.503). In the subset of participants who underwent an oral glucose tolerance test, ΔDPP4 activity correlated with ΔMatsuda index (rho=-0.475, p<0.001).

We used multivariable linear regression to investigate whether the associations between ΔDPP4 activity and the beneficial changes in metabolic markers were independent of the loss of body mass. After adjusting for baseline DPP4 activity, baseline BMI, change in BMI, and the baseline values of the respective independent variable, ΔDPP4 activity was associated with Δtotal cholesterol (beta=0.341, p=0.025), ΔLDL cholesterol (beta=0.350, p=0.019), ΔGGT (beta=0.323, p=0.040), and ΔMatsuda index (beta=-0.386, p=0.045) but not with ΔALAT (beta=0.118, p=0.357), ΔASAT (beta=-0.028, p=0.827).

Table 1. Patients’ characteristics before and after bariatric surgery

|                | baseline              | post surgery          | p    |
|----------------|-----------------------|-----------------------|------|
| BMI (kg/m²)    | 46.9 ± 7.7            | 30.3 ± 9.3            | < 0.001|
| Glucose (mg/dL)| 100 ± 19              | 91 ± 20               | 0.001|
| Insulin (μU/mL)| 25 (16 - 35)          | 9 (6 - 15)            | < 0.001|
| HOMA-IR        | 6.2 (3.8 - 8.1)       | 2 (1.2 - 3.3)         | < 0.001|
| Matsuda index  | 1.56 (1.02 - 2.78)    | 5.22 (3.41 - 7.78)    | < 0.001|
| HbA1C (%)      | 5.8 (5.5 - 6.3)       | 5.3 (5 - 5.5)         | < 0.001|
| Triglycerides  | 136 (96 - 178)        | 81 (65 - 119)         | < 0.001|
| Cholesterol    | 200 ± 33              | 185 ± 32              | 0.001|
| LDL cholesterol| 123 ± 30              | 110 ± 29              | 0.001|
| HDL cholesterol| 47 ± 11               | 56 ± 14               | < 0.001|
| GGT (U/L)      | 28 (18 - 36)          | 15 (9 - 20)           | < 0.001|
| ALAT (U/L)     | 29 (22 - 41)          | 19 (16 - 27)          | < 0.001|
| ASAT (U/L)     | 22 (19 - 29)          | 20 (16 - 23)          | 0.020|
| C-reactive protein (mg/L) | 6.9 (4 - 1.1) | 2 (1 - 4.6) | < 0.001|

ASAT: aspartate aminotransferase; ALAT: alanine aminotransferase; BMI: body mass index; GGT: gamma-glutamyltransferase; HbA1C: glycated hemoglobin; HOMA-IR: homeostasis model assessment of insulin resistance index; HDL: high-density lipoprotein; LDL: low-density lipoprotein. Data are depicted as counts, medians (25th - 75th percentile), or mean ± standard deviation. Between group comparisons were performed Student’s paired sample t-test or Wilcoxon signed-rank test, as appropriate.

Discussion

In the present study, we found that plasma DPP4 activity is significantly reduced after weight loss induced by bariatric surgery. As bariatric surgery is associated with loss of a large portion of excess body fat (17), this finding is in accordance with the notion that a substantial part of circulating DPP4 levels are derived from adipose tissue. Previous data indicate that decreased DPP4 levels after weight loss not only reflect the reduction in adipose tissue mass per se but also an ameliorated adipocyte hypertrophy (7). Other studies investigating the impact of gastric bypass surgery on circulating DPP4 activity rather than serum levels reported divergent results. In small cohorts, Alam et al. reported a decrease in DPP4 activity by 11.6% one month after gastric bypass (n=16) while Sarkar et al. found no differences in DPP4 activity 4–6 weeks after gastric bypass surgery (n=20) (18, 19). Studies investigating
Fig. 1. Boxplot for the comparison between pre- and post-surgical values of serum DPP4 activity. * p≤0.005; °outlier

early, sometimes transient, metabolic changes are important to assess mechanisms independent of weight loss contributing to diabetes remission. The longer follow-up period of our study reflected the persistent changes in metabolism after weight stability is usually achieved. We can however draw no conclusions about the weight-loss independent effects on DPP4 activity. At the same time, our findings are not confounded by transient metabolic alterations observed within the first months after surgery owing to a catabolic state with an excessively negative energy balance characterized by a metabolism mostly relying on lipid oxidation and ketogenesis (20).

Interestingly, the decrease in DPP4 activity was not associated with improved fasting insulin resistance, as indicated by HOMA-IR, but rather with increasing post-prandial insulin sensitivity, as estimated by the Matsuda index. However, our study lacks insulin resistance measures derived from the gold standard, the hyperinsulinemic euglycemic clamp, and thus replication using this technique is needed. Still, this finding hints towards a potential contribution of weight loss-induced decrease in DPP4 to improved incretin response. Lower circulating DPP4 activity following bariatric surgery could, besides hypertrophy of intestinal L-cells, be an additional explanatory factor for the large increase in post-prandial GLP-1 levels after bariatric surgery (21, 22). Augmented incretin response is believed to be an important contributor to the amelioration of glycemic control achieved by bariatric surgery (23). However, the association between changes in DPP4 activity and GLP-1 levels could not be addressed in the present study due to the lack of post-prandial serum samples. We further found that the decreasing DPP4 activity after surgery is associated with an improved atherogenic lipid profile, especially with decreasing atherogenic LDL cholesterol levels, independently of weight loss. It is a well observed fact that bariatric procedures significantly reduce levels of cholesterol and LDL cholesterol (24). Among the hypothesized mechanisms contributing to reduced cholesterol levels after bariatric surgery are a decreased intestinal cholesterol absorption, an increased trans-intestinal cholesterol excretion as well as an increased flux of cholesterol into bile acid synthesis due to augmented fecal excretion of bile acids (25, 26). Interestingly, there are studies suggesting a direct role of DPP4 in the regulation of cholesterol levels. A study in mice showed that the DPP4 inhibitor sitagliptin increases fecal cholesterol loss by reducing intestinal cholesterol absorption and increasing macrophage-to-feces reverse cholesterol transport (27). Two other mouse studies with sitagliptin and anagliptin, respectively, provide divergent conclusions as to whether this effect depends on increased GLP-1 signaling (28, 29). A clinical trial in patients with type 2 diabetes, however, found no effect of anagliptin on cholesterol absorption markers. After one month of treatment, anagliptin significantly decreased the cholesterol synthesis marker lathosterol while no changes in the absorption markers campesterol, sitosterol or cholesterol could be observed (30). Accordingly, our study provides evidence that decreased DPP4 activity after weight loss surgery might contribute to the improvement in dyslipidemia.

Another finding in our study was an association of the decline of the DPP4 activity with the early liver marker GGT. Bariatric surgery has already been proven to lead to a histological resolution of non-alcoholic steatohepatitis (NASH) (31). NASH is a common comorbidity observed in morbidly obese patients and the consequence of excessive hepatic triglyceride accumulation secondary to visceral fat expansion and insulin resistance (32). Few clinical studies reported elevated circulating DPP4 activity in patients with NAFLD and NASH (9, 33–36). Circulating DPP4 activity correlated significantly with caspase-cleaved keratin-18, a hepatic apoptosis marker, with liver stiffness, as assessed by transient elastography, and the histological fibrosis stage (35). Additionally, DPP4 expression in hepatocytes has been shown to be correlated with histopathological grading of NASH (33). Interestingly, treatment with the DPP4 inhibitor des-fluoro-sitagliptin resulted in an amelioration of diet-induced visceral obesity and hepatic steatosis. On a molecular level, the authors described a reduced expression of the master transcriptional regulator of lipid synthesis sterol regulatory element-binding protein-1c as well as a reduced expression of the lipogenic enzymes stearoyl-CoA desaturase-1 and fatty acid synthase (37). Current literature further provides evidence for a causative rather than a purely consequential role of DPP4 in NAFLD/NASH. Hepatic overexpression of DPP4 in mice on a high-fat diet led to hepatic insulin resistance accompanied by hepatic steatosis and liver damage as well as increased body weight, fat mass, adipose tissue inflammation, and hypercholesterolemia. In vitro, treatment of human hepatocyte lines with DPP4 in the physiological range resulted in an impaired insulin sensitivity (9). Taken together, these data point towards a reciprocal relationship between DPP4 and metabolic hepatic disease. A contribution of increased GLP-1 signaling to the
observed effects cannot be excluded as studies have shown that direct treatment of hepatocytes with GLP-1 analogues suppresses lipogenesis and induces lipolysis (38). Taken together, reduced DPP4 activity after bariatric surgery could both be a marker of as well as a contributor to improvement in NAFLD at the same time.

The study has, however, some limitations. Due to the observational design, we cannot distinguish an association from a causal role. In addition, the measurement of GLP-1 levels, especially after a mixed-meal challenge, could have provided insights whether the observed findings were independent of GLP-1 signaling.

A strength of this study is the sample size, which is substantially larger than previously reported studies. Due to the exclusion of individuals with previously known and treated diabetes, we can rule out the effects of antidiabetic medications on DPP4 activity. Compared to previous studies, we chose a longer follow-up period after which patients usually are weight stable and thus lets us draw conclusions about the long-term metabolic effects of the intervention.

To summarize, we described a significant reduction in DPP4 activity following surgically induced weight loss which was associated both with an ameliorated dyslipidemia as was as an improvement in the liver marker GGT as an indicator for improved NAFLD/ NASH. The independence of the changes in weight and the lack of association with insulin resistance point towards direct involvements of DPP4 independent of the well-described effects on glucose metabolism.

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Compliance with Ethical Standards

Conflict of Interest CTH, JMB, BL, GS, and GHS declare that they have no conflict of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from all individual participants included in the study.

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