Acylation stimulating protein reduction precedes insulin sensitization after BPD-DS bariatric surgery in severely obese women

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OBJECTIVE: The mechanisms involved in early resolution of insulin resistance and type 2 diabetes mellitus after biliopancreatic diversion with duodenal switch (BPD-DS) surgery are still unknown. We evaluated early effects of BPD-DS on plasma acylation stimulating protein (ASP), an adipokine involved in lipid and glucose metabolism.

SUBJECTS: 32 non-diabetic and 22 diabetic severely obese women (BMI >40 kg m⁻²) were evaluated for body composition and plasma parameters before, 24 h, 5 days, 6 and 12 months after surgery.

RESULTS: Within the early postoperative period (24 h), ASP decreased 25 and 30% in non-diabetic and diabetic women, respectively (P < 0.001). Twenty-four hours after surgery, triglyceride, cholesterol, HDL-Chol, LDL-Chol and C3 also decreased, while glucose, insulin and high-sensitivity C-reactive protein (hsCRP) increased (all P < 0.001). By 5 days, without significant weight loss, the decreases in ASP, cholesterol, HDL-Chol and LDL-Chol levels were all maintained. At this time, glucose, insulin and HOMA-IR also decreased 11 to 52% (all P < 0.001). At 6 and 12 months, with pronounced weight loss and decreased per cent fat mass, there were further decreases in ASP (maximal — 56% non-diabetic, — 61% diabetic, P < 0.001), as well as in glucose, insulin, HOMA-IR, triglyceride, cholesterol, LDL-Chol, HDL-Chol and hsCRP levels. Improved insulin resistance/diabetes at 5 days was predicted by 24 h changes as follows: per cent change ASP, HDL-Chol, hsCRP and total cholesterol predicted HOMA-IR (5 days) (r² = 0.454, P < 0.001), and per cent change ASP, HDL-Chol and hsCRP predicted change (5 days vs baseline) in HOMA-IR (r² = 0.351, P < 0.001).

CONCLUSION: Acute postoperative decreases in ASP are associated with early improvement of insulin resistance/diabetes after BPD-DS surgery.

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Keywords: C3adesArg; adipokine; complement C3; Insulin resistance; obesity

INTRODUCTION

Bariatric surgery has become a common strategy used in the treatment of severely obese patients with a body mass index (BMI) > 40 or > 35 kg m⁻² with severe co-morbidities. The effectiveness in improving abnormalities in insulin and glucose metabolism ranges from 48% with gastric banding to 99% in biliopancreatic diversion (BPD) with or without duodenal switch (DS). As early as 1995, RYGB bariatric surgery was recognized as a ‘cure’ for diabetes. In restriction/malabsorption procedures, improved insulin sensitivity occurs before any significant weight loss, with studies reporting 80–100% remission rate within days (1 week) of surgery. Even performing a duodenal-jejunal bypass in non-obese patients with type 2 diabetes (T2D) leads to disease remission in a majority of patients. Information on factors to predict an improvement in insulin sensitivity would provide biomarkers and contribute to understanding the mechanisms involved.

Little is known regarding the exact mechanisms involved, but several have been proposed: (i) physical (anatomical) changes, (ii) hormonal changes (gastro-intestinal or other hormones) and, (iii) postoperative caloric restriction. The ‘foregut’ hypothesis proposes that bypass of the proximal small intestine results in inhibition of a putative signal responsible for insulin resistance, and explains the more rapid diabetes resolution in those undergoing malabsorptive bariatric surgery vs procedures that are solely restrictive. The ‘hindgut’ hypothesis suggests that early contact of the distal bowel with relatively undigested food enhances signals (such as hormones including incretins) that improve glucose metabolism. Postoperative caloric restriction may also contribute to the early resolution. Changes in gastrointestinal and pancreatic hormones, including incretins as well as adipokines and cytokines, are reported over weeks to years, during which there are weight changes. Few studies have examined changes within days, where there is no weight change. Most attention has focused on the incretins GLP-1 and GIP, which alter insulin secretion (entero-insular axis) and peripheral postprandial lipid and glucose clearance. Results are controversial with both early increases in GLP-1 and decreases in GIP (consistent with improved insulin sensitivity), and the converse reported. Further, animal studies are inconclusive. A proposed link to the gut-adipo-insular axis has also been suggested. The links between adipose tissue function, fatty acid metabolism, and glucose uptake into insulin-sensitive tissues (such as muscle) are now well established in healthy, obese and

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diabetic subjects. Adipose tissue is also an active endocrine organ secreting a variety of adipokines including leptin, adiponectin, acylation stimulating protein (ASP) and many others.19,20 Over the past decade, the concept that hypertrophic adipose tissue is a promoter of type 2 diabetes progression owing to changes in adipokines and proinflammatory molecules, and their effects on impairment of insulin sensitivity has become accepted.21 With respect to bariatric surgery, 1 week after BPD, reductions of plasma leptin have been observed before any weight changes,14,16 although not all agree.22 By contrast, there was no short-term change in adiponectin.23,14,16 However, neither of these hormones has been directly suggested to be responsible for the rapid improvement in insulin sensitivity in these studies.25 ASP (aka C3adesArg) is a lipogenic adipokine produced by adipose tissue through the interaction of the precursor proteins of the alternative complement pathway C3, factor B, and adipsin.19 ASP is linked to obesity through its action to enhance triglyceride (TG) synthesis and storage in the adipocyte, via its receptor CSL2. ASP increases both glucose uptake as well as fatty acid esterification, independently of and additively to insulin.19 Plasma ASP levels are increased in a number of metabolic disorders associated with obesity including insulin resistance, hypothyroidism, type 2 diabetes, polycystic ovary syndrome and cardiovascular disease.19,24–27 With weight loss, either diet- or surgery-induced, plasma ASP decreases.19 Interestingly, obesity is not an essential feature of elevated ASP levels, as ASP is increased in subjects with type 2 diabetes, polycystic ovary syndrome, and lipoprotein lipase deficiency, even in the absence of obesity.24,26,27 suggesting that it may be a compensatory increase associated with adipose tissue dysfunction or insulin resistance.28

In the present study, we conducted a comprehensive investigation of short-term and long-term endocrine and metabolic changes following BPD-DS. Our aim was to evaluate potential acute changes in ASP levels, and the association with improvement of insulin resistance and diabetes before weight loss, (1 day and 5 days postoperatively) to evaluate ASP as a predictive factor for improved insulin sensitivity in the absence of weight loss. Further, we evaluated whether the short term and long-term ASP changes (6 months and 12 months) after BPD-DS surgery were present and similar in non-diabetic and diabetic women.

MATERIALS AND METHODS

Subjects

Subjects scheduled to undergo bariatric surgery (BPD-DS) were recruited through the bariatric surgery clinic of the Institut universitaire de cardiologie et de pneumologie de Québec (IUCPQ). Subjects were randomly selected (in chronologic order of surgeries, regardless of diabetic status or current medication) for participation based on inclusion criteria: women, >18 years of age, BMI ≥ 30 kg m⁻² with associated comorbidities, and were collected from surgeries performed between July 2006 to May 2008. Subjects who had previously undergone bariatric surgery or those bearing a pacemaker were excluded (patients with a pacemaker cannot undergo electrical bioimpedance assessment). Only subjects who completed the study (5 time periods, with blood samples collected and available) were included for subsequent biochemical analysis. Laboratory procedures were completed before statistical analysis was performed. The experimental protocol was approved by the ethics committee of the IUCPQ and all patients gave their written informed consent.

Anthropometric and biochemical measurements

Women were assessed preoperatively (within 3 months of surgery) and postoperatively (24 h, 3 days, 6 months and 12 months). Blood samples were collected between June 2006 to May 2009. Height was measured using a stadiometer (SECA, 216 1814009, Brooklyn, NY, USA). Total body mass, BMI, lean and fat masses were evaluated by electrical bioimpedance balance using standard formulas (Tanita TBF-310, Tokyo, Japan) following a 12-h fast. BMI was calculated as weight (kgs)/height (m²). Medical history was collected for diabetes, hypertension, coronary artery disease and dyslipidemia as well as the corresponding pharmacological therapy. The information provided by the patient was confirmed by consulting clinical files.

Venous blood was collected following a 12-h fast into EDTA containing tubes. Glycated hemoglobin (HbA1c) was evaluated in a fresh sample by turbidimetric inhibition immunoassay. All other tubes were rapidly placed on ice, centrifuged within 15 min, plasma collected and frozen in aliquots at -80°C until analysis. Assays were measured in the hospital clinical biochemistry laboratory using standard methodology or in the research laboratory (CRP, C3, ASP and NEFA). High-sensitive C-reactive protein (hsCRP) and apolipoprotein B (apoB) levels were measured by immunoturbidimetric method (Integra 800 System, Roche Diagnostics, IN, USA). Complement C3 was measured by immunoturbidimetry (Kamiya Biochemical Company, Seattle, WA, USA). Plasma ASP was measured by ELISA.29 Non-esterified fatty acid (NEFA) was analyzed by colorimetric enzymatic assay (Wako Pure Chemicals, Richmond, VA, USA). All other biochemical assays were performed using a Modular system (Roche Diagnostics). LDL-cholesterol concentration was calculated with Friedewald’s formula (no subjects had triglyceride values >4.5 mM).30 Homeostatic model assessment of insulin resistance (HOMA-IR) was calculated from fasting plasma insulin and glucose levels as (insulin x glucose)/22.5, where insulin concentration is reported as milliunits per liter and glucose as millimolar concentrations.

Statistical analyses

All results are expressed as mean ± s.d. or s.e.m. as indicated. The fasting data values were compared between non-diabetic and diabetic women using unpaired Student’s t-test. Comparison across different times were analyzed by repeated measures ANOVA followed by Holm Sidak post-hoc test. Correlations of selected parameters were analyzed by linear regression (Forward Stepwise regression). GraphPad Prism (San Diego, CA, USA) and SigmaStat (San Rafael, CA, USA) software programs were used for graph and statistical analyses. Significance was set at P < 0.05, where NS indicates ‘not significant’.

RESULTS

Pre-operative body weight and composition

Subjects were randomly selected (in chronologic order of surgeries, regardless of diabetic status or current medication) for participation based on inclusion criteria: women, >18 years of age, BMI ≥ 40 or BMI ≥ 35 kg m⁻² with associated comorbidities, and were collected from surgeries performed between July 2006 to May 2008. Only subjects who completed the study (5 time periods, with blood samples collected and available) were included for subsequent biochemical analysis. Of the 54 women, 32 were non-diabetic, and the women were separated into two groups for analysis based on diabetic status. Twenty-two women had been previously diagnosed as diabetic and were being treated accordingly with diet, biguanides, sulfonylureas, thiazolidinediones and/or insulin as indicated in Table 1. Eighteen diabetics were being treated with lipid-lowering therapy. Pre-operative body composition and biochemical measurements are shown in Table 1. Diabetic and non-diabetic women were of similar age, body size and per cent fat mass. Plasma triglyceride levels and ASP were significantly higher in diabetic women compared with non-diabetic women (P < 0.05) as were glucose, HbA1c and fructosamine. However, plasma C3 and hsCRP were not significantly different.

Changes in BMI and body composition following BPD-DS surgery

Postoperatively, women were followed up at 24 h (1 day), 5 days, 6 months and 12 months. Acutely (5 days), there was no significant change in body composition (Table 2), but in both non-diabetic and diabetic women, respectively, at 6 months, there was a 26 and 25% decrease in BMI, reflecting a decrease in both fat mass (−39% and −40%) and lean mass (−12% and −10%), with an overall decrease in per cent body fat (Table 3). This was also true at 12 months, with further decreases in fat mass (−58% and −55%), although the patients still remained within the obese range based on BMI.
Acute and long-term lipid, lipoprotein and liver enzyme responses
Preoperatively, plasma cholesterol, HDL-cholesterol and LDL-cholesterol decreased at 1 and 5 days in both non-diabetic and diabetic women, at which point none were on lipid-lowering therapy (Table 2). Over the long-term, there was a significant reduction of fasting cholesterol, HDL-cholesterol and LDL-cholesterol in both non-diabetic and diabetic women, while plasma TG and apoB levels decreased only in the non-diabetic women (Table 3).

### Table 1. Pre-operative characteristics of BPD-DS surgery women

| Variables                  | Non-diabetic | Diabetic |
|----------------------------|--------------|----------|
| Demographics and treatment | 32           | 22       | P       |
| Age (years)                | 38.3 ± 10.3  | 42.0 ± 10.6 | NS     |
| Diabetic medication (%)    | 0/32 (0%)    | 20/22 (91%) | <0.001 |
| Lipid medication           | 4/32 (13%)   | 18/22 (82%) | <0.001 |
| Body composition           |              |          |         |
| BMI (kg m⁻²)               | 48.6 ± 7.4   | 49.8 ± 7.9 | NS     |
| Fat mass (kg)              | 66.9 ± 13.5  | 66.2 ± 14.8 | NS     |
| Lean mass (kg)             | 59.3 ± 8.1   | 61.0 ± 9.5 | NS     |
| Fat percentage (%)         | 52.8 ± 2.6   | 51.7 ± 3.6 | NS     |
| Biochemical measures       |              |          |         |
| ASP (nmol l⁻¹)             | 30.0 ± 15.7  | 38.4 ± 21.0 | <0.05 |
| C3 (mg dl⁻¹)               | 1.99 ± 0.34  | 2.09 ± 0.4 | NS     |
| hsCRP (mg dl⁻¹)            | 14.1 ± 24.2  | 10.8 ± 8.1 | NS     |
| Glucose (mmol l⁻¹)         | 5.76 ± 1.67  | 8.28 ± 3.28 | <0.001 |
| HbA1c (%)                  | 5.62 ± 0.88  | 6.81 ± 1.03 | <0.001 |
| Insulin (mmol l⁻¹)         | 149 ± 71     | 193 ± 119 | NS     |
| Fructosamine (µmol l⁻¹)    | 202 ± 33     | 230 ± 47  | <0.01  |
| Lipid parameters           |              |          |         |
| TG (mmol l⁻¹)              | 1.38 ± 0.57  | 1.81 ± 0.82 | <0.05 |
| Cholesterol                | 4.80 ± 0.68  | 4.53 ± 1.04 | NS     |
| HDL-Chol (mmol l⁻¹)        | 1.40 ± 0.30  | 1.26 ± 0.35 | NS     |
| LDL-Chol (mmol l⁻¹)        | 2.78 ± 0.59  | 2.45 ± 0.77 | NS     |
| Apo-B (mmol l⁻¹)           | 0.79 ± 0.16  | 0.75 ± 0.20 | NS     |
| NEFA (µmol l⁻¹)            | 0.55 ± 0.12  | 0.53 ± 0.17 | NS     |

**Abbreviations:** ASP, acylation stimulating protein; BMI, body mass index; Chol, cholesterol; hsCRP, high-sensitivity C-reactive protein; NEFA, non-esterified fatty acid; TG, triglyceride; The values are presented as mean ± s.d. and significant differences analyzed by Student’s t-test for non-diabetic women vs diabetic women where pNS indicates not significant.

### Table 2. Early changes in plasma values in non-diabetic and diabetic patients following BPD-DS surgery

| Variables                  | Non diabetic women | Diabetic women |
|----------------------------|--------------------|----------------|
|                            | Pre-operative     | 24 h          | 5 days | P-value | Pre-operative | 24 h          | 5 days | P-value |
| BMI (kg m⁻²)               | 48.6 ± 7.4        | 48.6 ± 7.4    | NS     |         | 49.8 ± 8     | 49.8 ± 8      | NS     |
| Fat mass (kg)              | 66.9 ± 13.5       | 66 ± 14.9     | NS     |         | 66.2 ± 14.9  | 62.7 ± 13.9   | NS     |
| Lean mass (kg)             | 59.3 ± 8          | 60 ± 7.9      | NS     |         | 61 ± 9.5     | 64.1 ± 11.6   | <0.05 |
| Fat percentage (%)         | 52.8 ± 2.6        | 52 ± 3.8      | NS     |         | 51.7 ± 3.6   | 49.3 ± 3.9    | <0.05 |
| TG (mmol l⁻¹)              | 1.38 ± 0.57       | 1.16 ± 0.31*  | 1.48 ± 0.33 | <0.05  | 1.81 ± 0.82  | 1.64 ± 0.99   | <0.05 |
| Apo-B (mmol l⁻¹)           | 0.79 ± 0.16       | 0.75 ± 0.2    | NS     |         | 0.75 ± 0.2   | 0.72 ± 0.18   | <0.001 |
| NEFA (µmol l⁻¹)            | 0.55 ± 0.12       | 0.67 ± 0.3*   | 0.65 ± 0.23 | <0.05  | 0.53 ± 0.17  | 0.56 ± 0.18   | <0.05 |
| Chol (mmol l⁻¹)            | 4.8 ± 0.68        | 3.34 ± 0.62*  | 3.73 ± 0.75* | <0.001 | 4.53 ± 0.43  | 3.1 ± 0.71*   | 3.66 ± 0.72* | <0.001 |
| HDL-Chol (mmol l⁻¹)        | 1.4 ± 0.3         | 1.09 ± 0.23*  | 0.79 ± 0.2* | <0.001 | 1.26 ± 0.35  | 0.94 ± 0.26*  | 0.72 ± 0.18* | <0.001 |
| LDL-Chol (mmol l⁻¹)        | 2.78 ± 0.59       | 1.72 ± 0.5*   | 2.27 ± 0.64* | <0.001 | 2.45 ± 0.77  | 1.39 ± 0.56*  | 2.1 ± 0.61*  | <0.001 |
| Fructosamine               | 202 ± 5.0         | 160 ± 3.1***  | 165 ± 3.3*** | <0.001 | 230 ± 9.9    | 173 ± 6.1***  | 181 ± 7.1*** | <0.001 |
| hsCRP (g l⁻¹)              | 10.1 ± 1.5        | 133 ± 8.9***  | 68.4 ± 6.9*** | <0.001 | 10.8 ± 1.7   | 148 ± 14.7*** | 86.5 ± 16.4*** | <0.001 |

**Abbreviations:** BMI, body mass index; Chol, cholesterol; hsCRP, high-sensitivity C-reactive protein; NEFA, non-esterified fatty acid; TG, triglyceride. The values are presented as mean ± s.d. and significant differences were analyzed by repeated measures ANOVA followed by Holm–Sidak post-hoc test (*P < 0.05) vs preoperative state.
ASP and complement C3 correlate with diabetes and insulin resistance improvement

The rapid changes in plasma ASP and C3 at 1 day precede the improvement in glucose- treatment insulin homeostasis that was only evident by 5 days. Using HOMA-IR as an index of glucose-insulin homeostasis, we evaluated which early changes in factors are still increased. This suggests that the changes in ASP may be more related to metabolic improvement than to an inflammatory response.

Interestingly, the rapid decreases in ASP that are maintained at 5 days, as with the improved insulin sensitivity by 5 days, are independent of body weight changes (which only occur later). It has been suggested that the mechanism of rapid resolution of diabetes may be due to physical (anatomical) changes, hormonal changes (gastro-intestinal or other) or postoperative caloric restriction. Data from this study support the concept that hormonal changes, such as changes in ASP, may contribute to improved insulin sensitivity, but also raise the question of what mediates the changes in plasma ASP.

Plasma ASP increases in obesity and decreases with weight loss, correlating with various indices of body size (such as BMI). Further, plasma ASP correlates in a number of studies with indices of insulin-glucose metabolism (such as HOMA-IR) and various lipid parameters. However, independent of obesity, plasma ASP is increased in non-obese subjects, including those with diabetes, polycystic ovary syndrome, hypothyroidism, cardiovascular disease and dyslipidemia, suggesting other regulatory mechanisms. In particular, dietary intake, especially the dietary lipoproteins chylomicrons, stimulate production of ASP in vitro in adipocytes, and in vivo in human studies. In the present context, while acute caloric restriction at 1 day (fasting state) may explain a decreased ASP level, at 5 days, fasting TG and NEFA are comparable to preoperative levels.

Potential changes in adipose tissue function post-BPD-DS surgery, could impact on ASP production. Thiazolidinedione treatment in type 2 diabetics, which alters adipose tissue function, decreases ASP production in adipose tissue in humans, which might explain why diabetics in adipose tissue in humans, which might explain why diabetics
Decreased plasma ASP suggests a change in subsequent ASP function. Increased insulin and glucose are indicative of insulin resistance, while a decrease indicates improved insulin function. By analogy, an increased plasma ASP may suggest compensation, indicative of an ‘ASP resistant’ state. \(^{38}\) ASP resistance is demonstrated in vitro by reduced specific binding and response to ASP in cells from subjects with high ASP levels. \(^{38}\) Hypothetically, a decrease in plasma ASP could be reflective of increased ASP sensitivity, although this remains to be demonstrated experimentally. ASP has effects on TG storage and glucose transport in adipocytes, effects that are both additive and independent to those of insulin. \(^{19}\) ASP has been shown to stimulate insulin secretion. \(^{39}\) The rapid decreases in plasma ASP may contribute to the decreased insulin, having a supportive role, as with the incretins.

In conclusion, acute down regulation of ASP and C3 levels are associated with early improvement of insulin resistance and diabetes after BPD-DS surgery evidenced by a normalization of both glucose and insulin levels. Whether the increased ASP levels contribute to the insulin resistance, or are increased to compensate for the insulin resistance remains to be determined.
| Table 4. Correlation of acute changes with improvement in HOMA-IR at 5 days |
|-----------------|-----------------|
| Dependent variable | HOMA-IR (5 days) |
| R² (P-value) | 0.454 (P<0.0001) |
| Independent variables (24h) | %Δ-ASP (P<0.0001) | Δ-HDL (P<0.0001) | hsCRP (P=0.020) |
| Model 1 | Model 2 |
| HDL (P<0.0001) | hsCRP (P=0.036) |

For dependent variables, HOMA-IR at 5 days and ΔHOMA-IR (5-day value — preop. value) were used. Independent variables included all variables shown in Tables 1 and 2 and Figure 1 at 24h, or the change in these variables at 24h (24h value — preop. value). Forward stepwise regression analysis was used, with the model explaining the greatest variability presented.

Figure 3. Graphical representation of time frame of changes in ASP, HOMA-IR and bodyweight. Changes in ASP initiate at an early time point (1 day), before changes in HOMA-IR (5 days), and in the absence of any change in body weight, which only occurs in the months following bariatric surgery. ↓ decrease, ↔ no change, BW body weight.

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REFERENCES

1 Buchwald H, Avidor Y, Braunwald E, Jensen MD, Pories W, Fahrbach K et al. Bariatric surgery and cardiovascular risk factors: a scientific statement from the American Heart Association. Circulation 2011; 123: 1638–1701.
2 Poirier P, Cornier MA, Mazzone T, Stiles S, Cummings S, Klein S et al. Bariatric surgery and cardiovascular risk factors: a scientific statement from the American Heart Association. Circulation 2011; 123: 1638–1701.
3 Pories WJ, Swanson MS, MacDonald KG, Long SB, Morris PG, Brown BM et al. Would you have thought it? An operation proves to be the most effective therapy for adult-onset diabetes mellitus. Ann Surg 1995; 222: 339–350.
4 Nandagopal R, Brown RJ, Rother CI. Resolution of type 2 diabetes following bariatric surgery: implications for adults and adolescents. Diabetes Technol Ther 2010; 12: 671–677.
5 Thomas S, Schauer P. Bariatric surgery and the gut hormone response. Nutr Clin Pract 2010; 25: 175–182.
6 Yang J, Li C, Liu H, Gu H, Chen P, Liu B. Effects of subtotal gastrectomy and Roux-en-Y gastrojejunoanastomosis on the clinical outcome of type 2 diabetes mellitus. J Surg Res 2010; 164: e67–e71.
7 DePaula AL, Stival AR, DePaula CC, Halpern A, Vêncio S. Impact on dyslipidemia of the laparoscopic ilial interposition associated to sleeve gastrectomy in type 2 diabetic patients. J Gastrointest Surg 2010; 14: 1319–1325.
8 Brandt ML, Harmon CM, Helmraith MA, Inge TH, McKay SJ, Michalsky MP. Morbid obesity in pediatric diabetes mellitus: surgical options and outcomes. Rev Endocrinol 2010; 6: 637–645.
9 Lifante JC, Inabnet WB. Early improvement in type 2 diabetes in obese patients following gastric bypass and bili-pancreatic diversion: the role of the enteroinsular axis. J Clin Endocrinol Metab 2008; 93: 2479–2485.
10 Laffèrène B, Teixeira J, McGinity J, Tran H, Hyger JR, Colarusso A et al. Effect of weight loss by gastric bypass surgery versus hypocaloric diet on glucose and insulin levels in patients with type 2 diabetes. J Clin Endocrinol Metab 2008; 93: 2479–2485.
11 Rao RS, Kini S. GIP and bariatric surgery. Obes Surg 2011; 21: 244–252.
12 Beck B. Gastric inhibitory polypeptide: a gut hormone with anabolic functions. J Mol Endocrinol 1989; 2: 169–174.
13 Sancho V, Trigo MV, Martin-Duce A, Gonz-Lez N, Acitores A, Arnes-L et al. Effect of GLP-1 on D-glucose transport, lipolysis and lipogenesis in adipocytes of obese subjects. Int J Mol Med 2006; 17: 1133–1137.
14 Guidone C, Manco M, Valera-Mora E, Iaconelli A, Gniuli D, Mari A et al. Mechanisms of recovery from type 2 diabetes after malabsorptive bariatric surgery. Diabetes Metab 2006; 35: 2025–2031.
15 Kashyap SR, Daud S, Kelly KR, Gastaldelli A, Win H, Brethauer S et al. Acute effects of gastric bypass versus gastric restrictive surgery on beta-cell function and insulinotropic hormones in severely obese patients with type 2 diabetes. Int J Obes (Lond) 2010; 34: 462–471.
16 Isbell JM, Tamboli RA, Hansen EN, Saliba J, Dunn JP, Phillips SE et al. The importance of caloric restriction in the early improvements in insulin sensitivity after Roux-en-Y gastric bypass surgery. Diabetes Care 2010; 33: 1438–1442.
17 Pacheco D, de Luis DA, Romero A, González Sagrado M, Conde R, Izazola O et al. The effects of duodenal-jejunal exclusion on hormonal regulation of glucose metabolism in Goto-Kakizaki rats. Am J Surg Pathol 2007; 194: 221–224.
18 Robertson MD, Bickerton AS, Dennis AL, Vidal H, Jewell DP, Frayn KN. Enhanced metabolic cycling in subjects after colonic resection for ulcerative colitis. Int J Endocrinol Metab 2005; 90: 2747–2754.
19 Cianflone K, Xia Z, Chen LY. Critical review of acylation-stimulating protein physiology in humans and rodents. Biochim Biophys Acta 2003; 1609: 1273–1279.
20 Lago F, Gómez R, Gómez-Reino JJ, Dieguez C, Guallilo O. Adipokines as novel modulators of lipid metabolism. Trends Biochem Sci 2009; 34: 500–510.
21 Athyros VG, Tziomalos K, Karagiannis A, Anagnostis P, Mikhailidis DP. Should adipokines be considered in the choice of the treatment of obesity-related health problems? Curr Drug Targets 2010; 11: 122–135.
22 Maruna P, Gurlich R, Fried M, Frasko R, Chachkhiain I, Haluzik M. Leptin as an acute phase reactant after non-adjustable laparoscopic gastric banding. Obes Surg 2001; 11: 609–614.
23 Couce ME, Cottam D, Esplen J, Schauer P, Burguerba B. Is ghrelin the culprit for weight loss after gastric bypass surgery? A negative answer. Obes Surg 2006; 16: 870–878.
24 Yang Y, Lu HL, Zhang J, Yu HY, Wang HW, Zhang MX et al. Relationships among acylation stimulating protein, adiponectin and complement C3 in lean vs obese type 2 diabetes. Int J Obes (Lond) 2006; 30: 439–446.
25 Yu H, Yang Y, Zhang M, Lu H, Zhang J, Wang H et al. Thyroid status influence on adiponectin, acylation stimulating protein (ASP) and complement C3 in hyperthyroid and hypothyroid subjects. Nutr Metabol (Lond) 2006; 3: 13.
26 Pagilalunga S, Julien P, Tahiri Y, Cadelis F, Bergeron J, Gaudet D et al. Lipoprotein lipase deficiency is associated with elevated acylation stimulating protein plasma levels. J Lipid Res 2009; 50: 1109–1119.
27 Wu Y, Zhang J, Wen Y, Wang H, Zhang M, Cianflone K. Increased acylation-stimulating protein, C-reactive protein, and lipid levels in young women with polycystic ovary syndrome. Fertil Steril 2009; 91: 213–219.

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28 St-Pierre DH, Cianflone K, Smith J, Caderre L, Karelis AD, Imbeault P et al. Change in plasma acylation stimulating protein during euglycaemic-hyperinsulinaemic clamp in overweight and obese postmenopausal women: a MONET study. Clin Endocrinol (Oxf) 2009; 70: 539–546.
29 Maslowska M, Vu H, Phelis S, Sniderman AD, Rhode BM, Blank D et al. Plasma acylation stimulating protein, adipisin and lipids in non-obese and obese populations. Eur J Clin Invest 1999; 29: 679–886.
30 Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem 1972; 18: 499–502.
31 Faraj M, Havel PJ, Phelis S, Blank D, Sniderman AD, Cianflone K. Plasma acylation-stimulating protein, adiponectin, leptin, and ghrelin before and after weight loss induced by gastric bypass surgery in morbidly obese subjects. J Clin Endocrinol Metab 2003; 88: 1594–1602.
32 Swarbrick MM, Stanthope KL, Austreheim-Smith IT, Van Loan MD, Ali MR, Wolfe BM et al. Longitudinal changes in pancreatic and adipocyte hormones following Roux-en-Y gastric bypass surgery. Diabetologia 2008; 51: 1901–1911.
33 Maslowska M, Scantlebury T, Germinario R, Cianflone K. Acute in vitro production of acylation stimulating protein in differentiated human adipocytes. J Lipid Res 1997; 38: 1–11.
34 Scantlebury T, Maslowska M, Cianflone K. Chylomicron-specific enhancement of acylation stimulating protein and precursor protein C3 production in differentiated human adipocytes. J Biol Chem 1998; 273: 20903–20909.
35 Saleh J, Summers LK, Cianflone K, Fielding BA, Sniderman AD, Frayn KN. Coordinated release of acylation stimulating protein (ASP) and triacylglycerol clearance by human adipose tissue in vivo in the postprandial period. J Lipid Res 1998; 39: 884–891.
36 Kalant D, Phelis S, Fielding BA, Frayn KN, Cianflone K, Sniderman AD. Increased postprandial fatty acid trapping in subcutaneous adipose tissue in obese women. J Lipid Res 2000; 41: 1963–1968.
37 Tahiri Y, Karpe F, Tan GD, Cianflone K. Rosiglitazone decreases postprandial production of acylation stimulating protein in type 2 diabetics. Nutr Metab (Lond) 2007; 4: 11.
38 Zhang XJ, Cianflone K, Genest J, Sniderman AD. Plasma acylation stimulating protein (ASP) as a predictor of impaired cellular biological response to ASP in patients with hyperapoB. Eur J Clin Invest 1998; 28: 730–739.
39 Ahren B, Havel PJ, Pacini G, Cianflone K. Acylation stimulating protein stimulates insulin secretion. Int J Obes Relat Metab Disord 2003; 27: 1037–1043.