

# Physical Activity Associates with Muscle Insulin Sensitivity Postbariatric Surgery

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## ABSTRACT

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**Purpose:** Bariatric surgery is considered as an effective therapeutic strategy for weight loss in severe obesity. Remission of type 2 diabetes is often achieved after the surgery. We investigated whether increase in self-reported habitual physical activity associates with improved skeletal muscle insulin sensitivity and reduction of fat depots after bariatric surgery. **Methods:** We assessed self-reported habitual physical activity using Baecke questionnaire in 18 diabetic and 28 nondiabetic patients with morbid obesity (median age, 46 yr; body mass index, 42.0 kg·m<sup>-2</sup>) before and 6 months after bariatric surgery operation. Insulin-stimulated femoral muscle glucose uptake was measured using fluorodeoxyglucose positron emission tomography method during hyperinsulinemia. In addition, abdominal subcutaneous and visceral fat masses were quantified using magnetic resonance imaging and liver fat content using magnetic resonance spectroscopy. Also, serum proinflammatory cytokines were measured. **Results:** Patients lost on average 22.9% of weight during the follow-up period of 6 months ( $P < 0.001$ ). Self-reported habitual physical activity level increased ( $P = 0.017$ ). Improvement in skeletal muscle insulin sensitivity was observed only in those patients who reported increase in their physical activity postoperatively ( $P = 0.018$ ). The increase in self-reported physical activity associated with the loss of visceral fat mass ( $P = 0.029$ ). Postoperative self-reported physical activity correlated also positively with postoperative hepatic insulin clearance ( $P = 0.02$ ) and tended to correlate negatively with liver fat content ( $P = 0.076$ ). Postoperative self-reported physical activity also correlated negatively with serum TNF $\alpha$ , methyl-accepting chemotaxis protein and interleukin 6 levels. **Conclusions:** Self-reported physical activity is associated with reversal of skeletal muscle insulin resistance after bariatric surgery as well as with the loss of visceral fat content and improved postoperative metabolism in bariatric surgery patients. **Trial registration:** Clinicaltrials.gov, NCT00793143 (SLEEVEPASS), NCT01373892 (SLEEVEPET2). **Key Words:** BARIATRIC SURGERY, PHYSICAL ACTIVITY, INSULIN SENSITIVITY, VISCERAL FAT TISSUE, MRI, PET

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Obesity is a disease with increased morbidity due to several conditions including type 2 diabetes, cardiovascular disease and cancer, and it is associated with increased risk of overall mortality (1). It is a chronic condition often difficult to treat as weight loss requires intense lifestyle interventions such as dieting and regular physical exercise, and resulting weight change may not be permanent.

Bariatric surgery is considered as a highly effective treatment option for severe to morbid obesity, some form or variation of gastric bypass being the most common procedure after unsuccessful conservative treatments. Besides weight loss, decrease in mortality and increase in quality of life, the remission of type 2 diabetes mellitus (T2DM) is an important outcome of bariatric surgery. T2DM remission is achieved in most of the diabetic patients after Roux-en-Y gastric bypass operation (2–4), and it may be due to a decrease in hepatic

and peripheral insulin resistance or improvement in insulin secretion and glycemic control. We have previously shown tissue-specific improvements in insulin sensitivity after laparoscopic Roux-en-Y gastric bypass and gastric sleeve operations (5–7).

Until recently, the role of physical activity has been considered minimal in bariatric surgery patients (8,9), and at the moment, there are no physical activity guidelines for bariatric surgery patient population. However, recent clinical intervention studies have shown postoperative exercise training to induce several health benefits by improving muscle mitochondrial dysfunction (10), whole-body insulin sensitivity and cardiorespiratory fitness (11) as well as glucose tolerance (12) in bariatric surgery patients after operation. Although bariatric surgery decreases both fat mass and lean body mass (13), postoperative exercise training can maintain skeletal muscle mass (14), suggesting that postoperative body composition could be positively affected by regular exercise. Moreover, a recent study showed that exercise training after 12 to 24 months of surgery, suggested as time point of potential weight regain, improves body composition and functional walking ability (15). Thus, physical exercise could potentially be successful adjunct therapy for surgery-induced caloric restriction and produce further tissue-specific metabolic benefits in addition to surgery. The effects of physical activity and exercise on postoperative fat distribution and the loss of fat in different depots, especially decrease in visceral fat, are currently unclear (16).

As skeletal muscle is a major site of glucose usage and peripheral insulin resistance, the aim of the current study was to investigate whether self-reported habitual physical activity associates with improved insulin sensitivity in whole-body level and especially in skeletal muscle tissue after bariatric surgery. We also investigated whether postoperative self-reported physical activity is associated with the reduction of specific fat depots, especially visceral adiposity and liver fat content, both ectopic fat storages associated within chronic inflammation, lipid-induced insulin resistance and metabolic dysfunction.

The current study is part of two larger bariatric surgery data collections (SLEEVEPASS study, NCT00793143, described previously by Helmiö and colleagues (17) and SleevePET study, NCT01373892) and the results of muscle positron emission tomography imaging with radiotracer  $^{18}\text{F}$ -fluorodeoxyglucose positron emission tomography ( $^{18}\text{F}$  FDG PET) and liver magnetic resonance spectroscopy (MRS) have been published earlier in a subset of patients (5–7).

## MATERIALS AND METHODS

**Subjects.** Forty-six subjects (4 males, 42 females) were recruited among patients undergoing surgical procedure as part of their obesity treatment at the Hospital District of Southwest Finland. Twenty-five age-matched, healthy and normal weight volunteers (2 males, 23 females, median body mass index [BMI],  $23.2 \text{ kg}\cdot\text{m}^{-2}$ ) were recruited via local

newspaper ads. The inclusion criteria were age 18 to 60 yr, BMI over 40 or  $35 \text{ kg}\cdot\text{m}^{-2}$  with an additional risk factor and failure of previous, carefully planned conservative treatments for severe obesity. Individuals with excessive use of alcohol or poor compliance, severe mental disorder, eating disorder or diabetes mellitus requiring insulin treatment were excluded. Due to imaging device weight limitation, patients with body weight over 150 kg were also excluded. At the baseline, 18 (39%) of the 46 obese patients fulfilled American Diabetes Association classified T2DM criteria (18). Eleven (39%) of the 28 non-T2DM patients had prediabetic condition (three impaired fasting glucose [IFG] and eight impaired glucose tolerance [IGT]), 17 (61%) were normoglycemic. Patients were treated with metformin only ( $n = 10$ ), and with metformin combined to additional gliptins ( $n = 3$ ), glitazones ( $n = 2$ ), sulphonylurea ( $n = 1$ ), and DPP4 inhibitors ( $n = 3$ ).

**Study design.** The study protocol was approved by the Ethics Committee of the Hospital District of Southwest Finland and was conducted by the principles of the Declaration of Helsinki. Written informed consent form was obtained prior the study from each study participant. Patients were randomized to undergo either laparoscopic Roux-en-Y gastric bypass ( $n = 21$ ) or laparoscopic gastric sleeve ( $n = 25$ ) operation.

At the screening stage, the medical history of prior conservative treatments for obesity was assessed and blood tests and oral glucose tolerance test were performed for all study subjects. The criteria of American Diabetes Association were used for screening of impaired fasting blood glucose level and for IGT. Patients were instructed to withhold from glucose-lowering medications 24 to 72 h before the metabolic studies. The postoperational phase was conducted 6 months after the operation, when the greatest average weight loss is observed according to the study by the Longitudinal Assessment of Bariatric Surgery Consortium (19), and all studies were repeated similarly as before the operation. Healthy participants were studied once. The study design is illustrated in Figure 1.

**Physical activity questionnaire.** The assessment of habitual physical activity was performed using a self-report questionnaire by Baecke et al. (20) for all participants. Baecke questionnaire has been widely used in physical activity research and has been validated in a population with obesity by Tehard et al. (21). It consists of 16 questions divided into three sections: physical activity at work, during leisure time (sport excluded) and during sport. Three indices measuring the level of habitual physical activity are derived (work, leisure and sport index). The data was collected during face-to-face interviews conducted by research personnel under supervision of an exercise physiologist.

**PET study and euglycemic hyperinsulinemic clamp.** Insulin-stimulated skeletal muscle glucose uptake was measured in 23 patients and in 10 healthy participants with  $^{18}\text{F}$ FDG PET method during euglycemic hyperinsulinemic clamp after an overnight fast. The euglycemic hyperinsulinemic clamp technique was used as previously described (22,23).

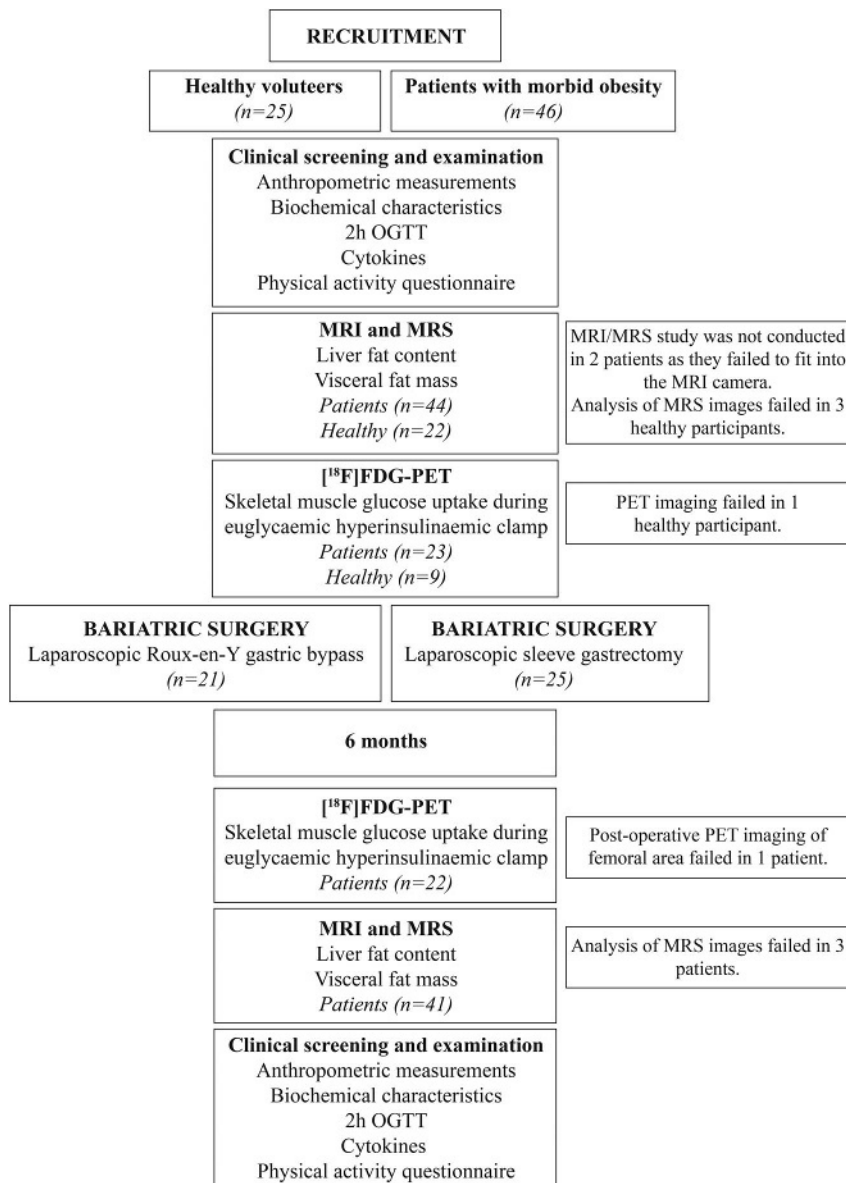


FIGURE 1—Study flowchart.

**Image acquisition and processing.** The synthesis of [<sup>18</sup>F]FDG was performed as described by Hamacher et al. (24). Patients lay in supine position in an integrated PET scanner (GE Discovery ST System, General Electric Medical Systems, Milwaukee, WI) and a transmission scan was performed. Thereafter, a [<sup>18</sup>F]FDG bolus (187 ± 10 MBq) was injected intravenously at the time point of 110 ± 10 min from the start of euglycemic hyperinsulinemic clamp. Dynamic scanning (frames, 3 × 300 s) of femoral region started 127 ± 10 min after the [<sup>18</sup>F]FDG injection. Arterialized blood samples were drawn throughout the study, and plasma radioactivity was measured with an automatic gamma counter (Wizard 1480 3", Wallac, Turku, Finland).

**Measurement of m. quadriceps femoris and whole-body glucose uptake.** Plasma and muscle tissue [<sup>18</sup>F]FDG time-activity data were analyzed graphically using three compartment model of [<sup>18</sup>F]FDG kinetics (25). Regional

glucose uptake was assessed with Carimas 2.0.2 (PET Centre, Turku, Finland), an in-house image analysis software, by drawing volumes of interests manually on m. quadriceps femoris using magnetic resonance imaging (MRI) images as anatomical reference. Regional tissue time-activity curves were obtained from the volumes of interests. A regional fractional uptake rate ( $K_i$ ) was then calculated using each regional time-activity curves and the plasma radioactivity curve. The rate of tissue glucose uptake was calculated by multiplying the fractional rate of tracer uptake ( $K_i, \text{min}^{-1}$ ) by the mean plasma glucose concentration ( $\text{mmol}\cdot\text{L}^{-1}$ ) sampled during the PET scanning. Lumped constant of 1.2 was used for skeletal muscle tissue. Insulin-stimulated skeletal muscle glucose uptake is expressed as micromoles (glucose) per minute per kilogram.

**MRI and MRS.** Abdominal fat masses and liver fat content (LFC) were assessed using a 1.5-T MR imager (Gyrosan Intera CV Nova Dual; Philips Medical Systems,

Best, the Netherlands) with flexible surface and body coils. MRI was performed to obtain abdominal visceral and subcutaneous adipose tissue masses in 44 patients and 25 healthy participants. Axial T1-weighted dual fast field echo images (TE 2.3 and 4.6 ms, TR 120 ms, slice thickness 10 mm without gap), covering thorax and abdomen were acquired. SliceOmatic software version 4.3 was used to calculate the abdominal adipose tissue volumes (<http://www.tomovision.com/products/sliceomatic.htm>). The regions of interest were drawn semi-automatically using Morpho-mode for subcutaneous fat and Region Growing-mode for visceral fat depots. Fat volume was calculated automatically by SliceOmatic. LFC was measured with MRS as previously described by Borra et al. (26) in 41 obese and in 22 healthy participants. Cutoff value of 5.1% was used for the determination of elevated LFC (26).

**Body composition.** Body composition was measured using bioelectric impedance (Omron BF400). Although the hydration of the soft tissues in obese subjects may cause errors in the bioelectric impedance analysis, it has been shown to be a reasonable method to assess body composition among bariatric surgery patients in group level (27,28). Height, weight, and waist circumference were measured using standard procedures.

**Biochemical and immunological analyses.** Plasma glucose concentrations were measured in the laboratory of the Turku PET Centre in duplicate using the glucose oxidase method (Analox GM7 or GM9; Analox Instruments Ltd., London, UK). Fasting plasma insulin and C-peptide levels were determined by time-resolved immunofluorometric assay (AutoDELFIA; PerkinElmer Life and Analytical Sciences) in Turku University Hospital central laboratory. HOMA-IR index (29), the rate of insulin secretion (30), and the rate of insulin clearance (insulin secretion/concentration) (31) were calculated from oral glucose tolerance test data as previously described.

Serum concentrations of proinflammatory cytokines were measured using standard methods and performing quality control. The Luminex 200 and the Luminex XYPTM platform were from Luminex Corp. (Luminex, Austin, TX). The software, Bio-PlexTM Manager version 4.1 was from Bio-Rad (Bio-Rad Laboratories AB, Sweden). The array reader was

calibrated by using Bio-Plex Calibration kit (kit cat no. 171-203060; Bio-Rad Laboratories AB, Sweden). The calibration curves for each analyte were calculated by the Bio-Plex 4.1 software. Serum samples were analyzed in duplicate by using Milliplex Human Serum Adipokine (panel A) kit (cat. no: HADK1-61 K-A containing resistin, methyl-accepting chemotaxis protein (MCP), interleukin one  $\beta$  (IL1 $\beta$ ), interleukin 6 (IL6), interleukin 8 (IL8) and tumor necrosis factor alpha (TNF $\alpha$ ) as recommended by the manufacturer (Millipore Corporation, USA).

**Statistical analyses.** The normality of variables was assessed by Shapiro–Wilk criteria and by visual evaluation. Data are presented as median and interquartile range (anthropometrics, metabolic variables and cytokines) or as mean and standard deviation (physical activity indices). Nonnormally distributed data were transformed by taking natural logarithm to achieve normal distribution assumption. Comparisons between study groups were made using Student's *t* test for nonpaired data. In addition, Pearson correlation coefficients were calculated. Association between the anthropometrics, glucose profile and self-reported physical activity in preoperative and postoperative time points, and time–physical activity interaction were performed with hierarchical linear mixed modeling using the compound symmetry covariance structure for time. *P*-values less than 0.05 (two-tailed) denoted statistical significance. Statistical analyses were performed using SAS (Version 9.3 for Windows; SAS Inc., Cary, NC).

## RESULTS

**Before bariatric surgery.** At the baseline, fasting concentrations of glucose and insulin were higher ( $P \leq 0.001$  for both) and the rate of hepatic insulin clearance was lower in patients with morbid obesity ( $P = 0.001$ ) (Table 1). Twenty (49%) of the 41 patients had elevated LFC preoperatively. Hepatic insulin clearance correlated negatively with LFC ( $r = -0.383$ ,  $P = 0.013$ ), abdominal subcutaneous fat mass ( $r = -0.455$ ,  $P = 0.002$ ), and positively with insulin-stimulated whole-body (0.448,  $P = 0.032$ ) and skeletal muscle glucose uptake ( $r = 0.532$ ,  $P = 0.009$ ). Waist

TABLE 1. Anthropometric and metabolic characteristics of the study participants.

	Healthy, <i>n</i> = 25	Patients, <i>n</i> = 46		<i>P</i> (Time)
		Preoperative	Postoperative	
Age (yr)	47 (39.5, 53.0)	46 (37.8, 54.0)		
Height (cm)	169.2 (160.6, 173.5)	166.3 (161.4, 170.0)		
Weight (kg)	63.7 (58.5, 67.9)	115.5 (106.1, 125.0)*	86.7 (81.3, 96.3)*	<0.001
BMI (kg·m <sup>-2</sup> )	23.2 (21.5, 24.7)	42.0 (39.5, 43.8)*	31.9 (29.6, 34.0)*	<0.001
Waist (cm)	77 (70, 80)	119 (112, 128)*	100 (94, 109)*	<0.001
Percentage of body fat (%)	32.6 (27.2, 36.6)	51.2 (47.8, 53.5)*	43.1 (39.8, 46.1)*	<0.001
Abdominal subcutaneous fat mass (kg), <i>n</i> = 20/44	4.2 (3.3, 6.0)	18.5 (15.5, 22.0)*	11.7 (9.3, 14.6)*	<0.001
Visceral fat mass (kg), <i>n</i> = 20/44	0.96 (0.7, 1.62)	4.00 (2.98, 4.84)*	2.25 (1.23, 2.95)*	<0.001
LFC (%), <i>n</i> = 22/41	1.28 (0.90, 2.06)	5.07 (3.13, 12.62)*	1.53 (0.84, 2.89)	<0.001
Fasting glucose (mmol·L <sup>-1</sup> )	5.5 (5.2, 5.7)	6.0 (5.5, 7.1)*	5.3 (5.0, 5.8)	<0.001
Fasting insulin (mU·L <sup>-1</sup> )	5.0 (3.0, 8.0)	12.5 (8.0, 20.0)*	7.0 (4.0, 8.0)	<0.001
HOMA-IR	1.2 (0.7, 2.0)	3.4 (2.1, 5.9)*	1.5 (1.0, 2.1)	<0.001
Insulin clearance (mL·min <sup>-1</sup> ·m <sup>-2</sup> )	1.87 (1.52, 3.20)	1.29 (0.99, 1.97)*	1.72 (1.20, 2.40)**	0.002
Whole-body glucose uptake (μmol·min <sup>-1</sup> ·kg <sup>-1</sup> ), <i>n</i> = 10/23	39.9 (33.7, 46.1)	11.4 (8.0, 18.2)*	21.6 (17.9, 29.6)*	<0.001
Skeletal muscle glucose uptake (μmol·min <sup>-1</sup> ·kg <sup>-1</sup> ), <i>n</i> = 9/23	66.1 (43.5, 96.8)	12.7 (9.2, 20.7)*	34.2 (15.4, 51.4)***	0.002

Data are expressed as median and quartiles (Q<sub>1</sub>, Q<sub>3</sub>), *n* = healthy/patients. *P* (time) indicates the *P* value for time effect (preoperative vs postoperative values).

\* $P \leq 0.001$ , \*\* $P \leq 0.05$ , \*\*\* $P \leq 0.01$  for bariatric surgery patients compared to healthy subjects.



TABLE 2. Levels of serum proinflammatory cytokines.

	Healthy, <i>n</i> = 25	Patients, <i>n</i> = 46		<i>P</i> (Time)
		Preoperative	Postoperative	
IL1 beta (pg·mL <sup>-1</sup> )	0.21 (0.11, 0.40)	0.11 (0, 0.28)	0.18 (0, 0.39)	0.323
IL6 (pg·mL <sup>-1</sup> )	1.75 (1.12, 3.1)	2.60 (1.69, 3.78)	1.76 (1.15, 2.40)	<0.001
IL8 (pg·mL <sup>-1</sup> )	4.30 (3.25, 5.65)	5.69 (3.87, 8.00)	5.97 (4.2, 7.56)	0.275
TNFα (pg·mL <sup>-1</sup> )	3.44 (2.26, 5.75)	5.20 (3.93, 7.30)*	4.88 (3.62, 7.14)*	0.589
MCP (pg·mL <sup>-1</sup> )	233.4 (146.0, 329.0)	258.8 (191.5, 423.4)**	274.5 (174.7, 396.5)*	0.792
Resistin (pg·mL <sup>-1</sup> )	13,998 (10,656, 15,987)	16,581 (13,015, 21,314)***	17,321 (14,598, 20,516)***	0.491

Data are expressed as median and quartiles (Q<sub>1</sub>, Q<sub>3</sub>). *P* (time) indicates the *P* value for time effect (preoperative vs postoperative values).

\**P* ≤ 0.05, \*\**P* = 0.067, \*\*\**P* ≤ 0.01 for bariatric surgery patients compared to healthy subjects.

circumference correlated negatively with insulin-stimulated whole-body glucose uptake ( $r = -0.536, P = 0.008$ ) and with skeletal muscle glucose uptake ( $r = -0.473, P = 0.023$ ).

Preoperatively, serum levels of proinflammatory cytokines TNFα ( $P = 0.026$ ) and resistin ( $P = 0.01$ ) were elevated in patients with morbid obesity, also serum level of MCP ( $P = 0.067$ ) tended to be higher in patients compared to healthy participants (Table 2). IL1β correlated positively with waist circumference ( $r = 0.518, P = 0.006$ ). IL8 levels correlated negatively with insulin-stimulated whole-body glucose uptake ( $r = -0.591, P = 0.003$ ), positively with HOMA-IR index ( $r = 0.347, P = 0.018$ ), negatively with hepatic insulin clearance ( $r = -0.372, P = 0.011$ ) and positively with LFC

( $r = 0.355, P = 0.023$ ) in patients with morbid obesity. In addition, TNFα levels correlated negatively with insulin-stimulated whole-body ( $r = -0.498, P = 0.016$ ) and skeletal muscle glucose uptake ( $r = -0.426, P = 0.016$ ) before bariatric surgery. MCP levels correlated positively with waist circumference ( $r = 0.337, P = 0.02$ ), LFC ( $r = 0.379, P = 0.014$ ), and fasting glucose levels ( $0.403, P = 0.005$ ).

Compared with healthy participants, leisure time ( $P ≤ 0.001$ ), sport ( $P ≤ 0.001$ ) and total physical activity ( $P ≤ 0.001$ ) indices were lower in patients with morbid obesity at the baseline (Fig. 2A). Self-reported total physical activity index correlated positively ( $r = 0.415, P = 0.049$ ) with insulin-stimulated glucose uptake in skeletal muscle (Fig. 3A) and

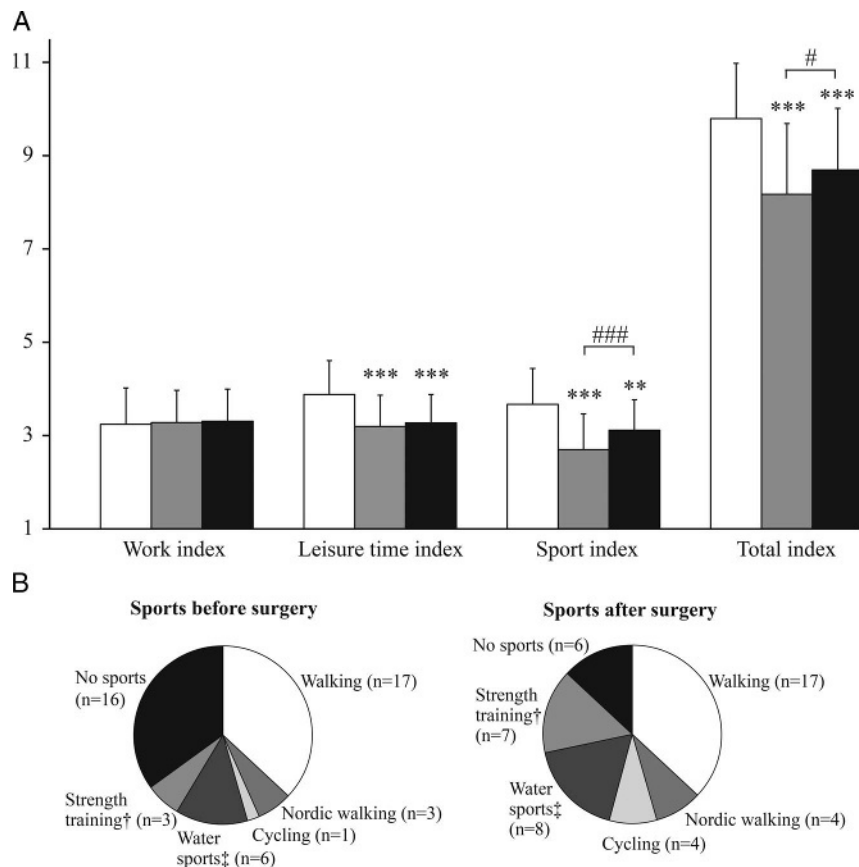
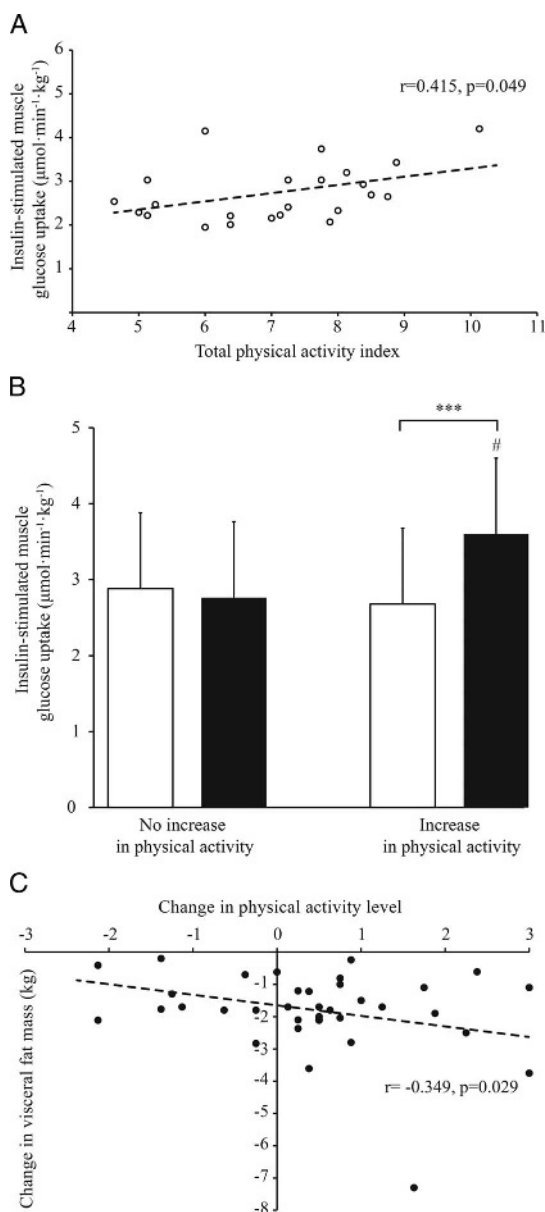


FIGURE 2—A, Baecke physical activity indices in healthy participants (white bars) and in patients pre (gray bars) and post (black bars) bariatric surgery. Data expressed as mean (+SD). Preoperative vs postoperative sport index ( $P = 0.0096$ ) and total index ( $P = 0.0168$ ) increased significantly. \*\* $P ≤ 0.01$ , \*\*\* $P ≤ 0.001$ . Patients compared to healthy. # $P ≤ 0.05$ , ### $P ≤ 0.001$ . Preoperative vs postoperative values. B, Most frequently played sports according to Baecke physical activity questionnaire (item 9) before and after bariatric surgery in patients. †Strength training either at gym or at home, ‡Swimming, aqua jogging or aqua gymnastics.



**FIGURE 3**—A, Preoperative total physical activity index correlated with higher rate of insulin-stimulated skeletal muscle glucose uptake in bariatric surgery patients ( $r = 0.415$ ,  $P = 0.049$ , logarithm transformed glucose uptake values). B, Only patients who had increase in the total physical activity index postoperatively had increase in the rate of insulin-stimulated skeletal muscle glucose uptake 6 months after bariatric surgery.  $***P \leq 0.001$ . Paired  $t$  test for preoperative (white bars) vs postoperative (black bars) glucose uptake values with logarithm transformation.  $\#P \leq 0.05$ . Increase in the physical activity index vs no increase postoperatively. C, Change in the total physical activity index correlated with the loss of visceral fat mass ( $r = -0.349$ ,  $P = 0.029$ ) 6 months after bariatric surgery.

with the rate of hepatic insulin clearance ( $r = 0.345$ ,  $P = 0.02$ ) and negatively with  $\text{TNF}\alpha$  levels ( $-0.418$ ,  $P = 0.004$ ) and abdominal subcutaneous fat mass ( $r = -0.334$ ,  $P = 0.029$ ).

**After bariatric surgery.** Surgery resulted in weight loss of 26.5 (8.0) kg within follow-up period of 6 months; however, patients' weight remained in obese range at the postoperative study visit (Table 1). Abdominal subcutaneous

and visceral fat masses decreased but were still over twice as high as in lean participants. Outcomes were similar with both surgical methods (data not shown). LFC decreased by 6.2 (6.3) percentage points and was normalized to the level of healthy participants in 17 (85%) of the 20 patients with preoperatively elevated LFC levels.

Diabetes was in full remission in 12 (67%) of 18 diabetic participants, one patient had IGT and three IFG after surgery. Three T2DM patients still used medication (2 metformin and one sitagliptin). HOMA-IR index was normalized to the level of healthy participants. The rate of hepatic insulin clearance improved and correlated negatively with abdominal subcutaneous fat mass ( $r = -0.516$ ,  $P = 0.001$ ) and LFC ( $r = -0.502$ ,  $P = 0.001$ ). Also, insulin-stimulated whole-body glucose uptake increased significantly ( $P \leq 0.001$ ) and correlated negatively with waist circumference ( $r = -0.431$ ,  $P = 0.04$ ), but remained low compared with healthy participants.

IL6 level decreased and correlated negatively with insulin-stimulated whole-body ( $r = -0.551$ ,  $P = 0.006$ ) and skeletal muscle glucose uptake ( $r = -0.477$ ,  $P = 0.025$ ) postoperatively. IL8 correlated negatively with the rate of hepatic insulin clearance ( $r = -0.400$ ,  $P = 0.006$ ).  $\text{TNF}\alpha$  correlated positively with LFC ( $r = 0.339$ ,  $P = 0.032$ ), visceral fat mass (0.359,  $P = 0.025$ ) and negatively with hepatic insulin clearance ( $r = -0.390$ ,  $P = 0.008$ ). Also, MCP correlated positively with LFC ( $r = 0.387$ ,  $P = 0.014$ ) and negatively with hepatic insulin clearance ( $r = -0.327$ ,  $P = 0.028$ ) both.

Six months after bariatric operation, 31 (76%) of 46 patients reported increased habitual physical activity level. Increase of self-reported physical activity was inferred for those patients whose change in total physical activity index was larger than zero. Only six patients did not play any sports after surgery, and more patients reported to engage in strength training, water sports, cycling, and Nordic walking postoperatively than preoperatively (Fig. 2B). Walking was the most frequently reported sports mode both before and after the surgery. Sport index ( $P = 0.0096$ ) and total physical activity index ( $P = 0.0168$ ) increased, surgical method had no effect on physical activity outcome (data not shown). On average, patients reported to play sports 1 to 2  $\text{h}\cdot\text{wk}^{-1}$  before surgery and increased sports to 2 to 3  $\text{h}\cdot\text{wk}^{-1}$  postoperatively. No significant differences were found in the degree of work related physical activity, neither between study groups nor between baseline and postsurgery values. Furthermore, postoperative leisure time related physical activity level excluding sport did not increase and self-reported leisure time ( $P \leq 0.001$ ), sport ( $P = 0.002$ ), and total physical activity ( $P = 0.001$ ) indices were still lower in patients compared to healthy participants.

Interestingly, only patients who reported increase in total physical activity index postoperatively had increase in the rate of insulin-stimulated skeletal muscle glucose uptake thus higher absolute rate 6 months after bariatric surgery ( $P = 0.018$ ) (also in Fig. 3B). This finding was confirmed using

hierarchical linear mixed modeling in which postoperative self-reported total physical activity index had an effect explaining improvement in the rate of insulin-stimulated glucose uptake in skeletal muscle ( $P = 0.036$ ). However, the rate of whole-body glucose uptake increased similarly in postoperatively active and nonactive patients.

Postoperative self-reported total physical activity correlated positively with hepatic insulin clearance ( $r = 0.345$ ,  $P = 0.02$ ) and showed tendency to correlate negatively with LFC ( $r = -0.286$ ,  $P = 0.076$ ). Furthermore, change in total physical activity index correlated with the loss of abdominal visceral fat mass postoperatively ( $-0.349$ ,  $P = 0.029$ ) (Fig. 3C). Loss of abdominal visceral fat mass also tended to be higher in patients who reported increased total physical activity index postoperatively compared to patients whose index remained the same ( $-2.04$  [1.35] kg vs  $-1.26$  [0.89] kg;  $P = 0.078$ ). Self-reported total physical activity index also correlated negatively with levels of proinflammatory cytokines TNF $\alpha$  ( $-0.318$ ,  $P = 0.031$ ), IL6 ( $-0.353$ ,  $P = 0.023$ ) and MCP ( $-0.300$ ,  $P = 0.043$ ) after bariatric surgery (Fig. 4).

Finally, self-reported physical activity index showed no association to body weight loss nor decrease in whole-body adiposity or loss of abdominal subcutaneous fat mass postoperatively.

## DISCUSSION

In the present study, preoperative and postoperative physical activity level was investigated using a validated self-report questionnaire, and insulin sensitivity as well as body composition using noninvasive imaging methods in bariatric surgery patients. We found that postoperative self-reported physical activity was associated with the improvement of skeletal muscle insulin sensitivity as quadriceps muscle glucose uptake under insulin stimulation increased only in those patients who reported increase in their physical activity level 6 months after bariatric surgery operation. Self-reported physical activity was also associated with lower LFC postoperatively and change in physical activity with the loss of visceral fat mass. Our data suggest that physical activity may facilitate the

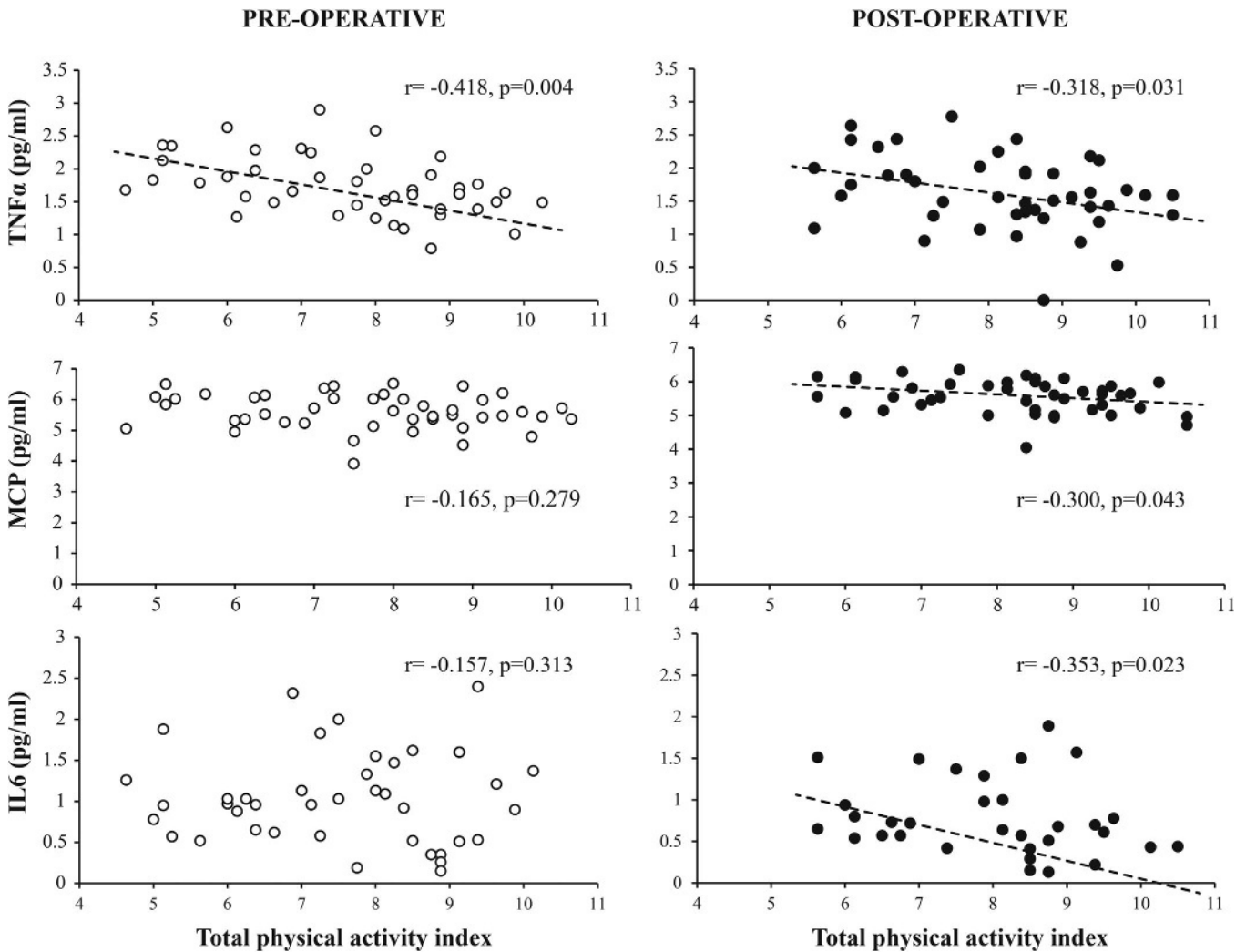


FIGURE 4—Correlations between total physical activity index and serum proinflammatory cytokines TNF  $\alpha$ , MCP and IL6 prebariatric and postbariatric surgery.

amelioration of peripheral insulin resistance after surgery and that bariatric surgery alone might not increase skeletal muscle insulin sensitivity.

In our data, using hyperinsulinemic euglycemic clamp method, a moderate increase in whole-body insulin sensitivity was seen in all patients 6 months after the bariatric surgery, and this increase was probably related to surgery-induced caloric restriction and weight loss. However, the increase in insulin-stimulated skeletal muscle glucose uptake reflecting improvement in muscle insulin sensitivity happened only in patients who reported increased physical activity postoperatively. In the current study, the rate of insulin-stimulated glucose usage was quantified using PET with [ $^{18}$ F]-FDG radiotracer which is highly sensitive noninvasive molecular imaging method.

Our data are consistent with previous studies reporting increased insulin action in the skeletal muscle tissue after bariatric surgery (8,9,32–34). An exercise intervention study by Coen et al. (11) found that 120 min of moderate intensity exercise per week for 6 months after bariatric surgery improved not only whole-body insulin sensitivity, but also muscle mitochondrial oxidative capacity only in exercising and not in sedentary patients although both groups experienced mitochondrial remodeling (10). Our data support the results of these studies, as increase in skeletal muscle insulin sensitivity was seen only in patients who reported increased habitual physical activity after bariatric surgery.

In our data set, self-reported physical activity level showed no association to body weight loss or decrease in percentage of whole body fat after bariatric surgery which is in line with several previous results (11,12,35). Furthermore, we did not find any connection between self-reported physical activity level and the loss of abdominal subcutaneous fat mass. In a previous study, Woodlief et al. (36) reported greater loss of abdominal subcutaneous fat mass after high volume ( $286 \pm 40 \text{ min}\cdot\text{wk}^{-1}$ ) structured exercise program after Roux-en-Y gastric bypass operation. However, in our data set, increase in self-reported physical activity was associated with the loss of visceral fat mass, fat depot linked to cardiovascular risk factors, insulin resistance, and low-grade systemic inflammation. Thus, physical exercise could potentially affect visceral obesity and the distribution of body fat after bariatric surgery as speculated previously (16). In our data set, self-reported postoperative physical activity also showed a tendency to correlate with lower LFC, suggesting that physical activity has effect decreasing ectopic fat accumulation as reported previously in normal weight males (37). In addition, self-reported postoperative physical activity associated inversely with serum levels of inflammatory markers TNF  $\alpha$ , MCP and IL6. Regular exercise has been reported to decrease resting levels of TNF  $\alpha$ , IL6, and to suppress TNF  $\alpha$  sustained, stress related, IKK/NF- $\kappa$ B-mediated signaling pathway causing insulin resistance in skeletal muscle tissue and accumulation of LFC (38).

Diabetes relapses have been reported to happen in every third patient in five year's time after the initial T2DM remission

(39), and in half of the patients after 12 yr (4). One could speculate that physically active lifestyle could possibly help in preventing the weight regain and delay the recurrence of T2DM in the long run by maintaining and enhancing insulin sensitivity. Our data suggest that postoperative improvement in the peripheral insulin sensitivity is due to voluntary physical activity modifications in daily living – not only surgically induced caloric restriction.

There are some considerations to our study design. First, study participants were given no advice on physical activity and therefore all changes were voluntary. However, due to local surgical guidelines and patient selection criteria, participants were recruited among patients motivated to lose weight and to modify lifestyle, thus most sedentary persons were excluded. Also, insulin-dependent T2DM patients were excluded from the study; therefore, our results might not apply to the most severe cases of insulin resistance in morbid obesity. We also did not assess intra muscular fat content, lipid storage associated with mitochondrial dysfunction and muscle tissue insulin resistance. As we did not find differences between Roux-en-Y and gastric sleeve operations in the outcome measures of the present study, the results are pooled. Postsurgery measurements were performed 6 months after surgery, and it is possible that insulin sensitivity data may be confounded by dynamic phase of weight loss at that time point. We controlled the weight of the patients also after 1 yr of the surgery, and the median weight loss between 6 months and 1 yr was 2.8 kg. Hence, the major weight loss occurred during the first 6 months after surgery and slowed greatly thereafter. Finally, physical activity questionnaire was used to estimate physical activity level instead of objective measurement of energy expenditure or guided exercise training intervention. Questionnaires are practical and low cost method to assess changes in physical activity, but their sensitivity, validity and reliability could be limited (40). Furthermore, bariatric surgery patients have been shown to over-report their activities (41). Baecke questionnaire, however, is widely used in epidemiological studies, and has been validated in population with obesity (21). Although the gold standard for evaluation of physical activity in bariatric surgery patients is still lacking, it has been shown that self-reported changes in physical activity measured by Baecke questionnaire are predictive of postoperative weight loss after bariatric surgery (42,43). However, it is possible that the results of the present study may have been affected by the within variability of the questionnaire. For instance, all changes in total physical activity index greater than zero were inferred as increase in physical activity. Also, increase in sports index may have been affected by leisure time physical activity which has been shown to contribute to weight loss and body composition after bariatric surgery (14). Further research with objectively measured physical activity and supervised exercise interventions are needed to study the role of exercise training among bariatric surgery patients.

To conclude, increase in self-reported habitual physical activity is associated with the improvement of skeletal muscle



insulin sensitivity and the distribution of body fat after bariatric surgery. Recommendations of habitual physical activity and physical exercise training should be included in the postoperational treatment of bariatric surgery patients to help the patients to maximize and in the future to maintain the surgery-induced metabolic health benefits.

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A. M. S. analyzed and interpreted the data and wrote the article. J. C. H., A. K., M. S., T. P., V. S., H. I., A. M., T. L., M. H. and P. S. acquired and analyzed data and edited the article. E. L. did the statistical work. P. N. designed and supervised clinical trials NCT00793143 and NCT01373892, interpreted the data, and edited the manuscript. P. N. is the guarantor of this work and, as such, has full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors had access to the study data and have reviewed and approved the final article.

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