Impact of Bariatric Surgery on Carotid Artery Inflammation and the Metabolic Activity in Different Adipose Tissues

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Abstract: In this study, we unravel a molecular imaging marker correlated with the known reduction of cardiovascular events (most commonly related to vulnerable plaques) in morbidly obese patients after bariatric surgery (BaS).

We prospectively imaged 10 morbidly obese subjects with 18F-fluorodeoxyglucose (18F-FDG) positron emission tomography/computed tomography before and 1 year after BaS. 18F-FDG uptake—which is enhanced in inflamed, atherosclerotic vessels and in metabolically active adipose tissues—was quantified in the carotids, pericardial adipose tissue (PAT), visceral adipose tissue (VAT), as well as brown adipose tissue (BAT). The degree of carotid inflammation was compared to lean and overweight controls.

Carotid inflammation significantly declined leading to an 18F-FDG uptake comparable to the 2 control groups. Metabolic activity significantly decreased in PAT and VAT and increased in BAT.

BaS leads to a normalization of carotid artery inflammation and a beneficial impact on the metabolic activity in PAT, VAT, and BAT that is related to the metabolic syndrome observed in this patient group.

(Summary: 18F-FDG = 18F-fluorodeoxyglucose, BaS = bariatric surgery, BAT = brown adipose tissue, PAT = pericardial adipose tissue, SAT = subcutaneous adipose tissue, VAT = visceral adipose tissue.)

INTRODUCTION

Most epidemiological studies demonstrate that obesity is associated with increased cardiovascular morbidity and mortality. Unfortunately, >80% of even highly motivated obese patients are unable to achieve weight loss with dietary or lifestyle modifications alone. Furthermore, medical treatment with anti-obesity drugs has shown either no effect on primary cardiovascular end points or even an increased risk of nonfatal myocardial infarction or stroke. In contrast, several studies such as the Swedish obese subjects (SOS) trial revealed an association between bariatric surgery (BaS)-induced weight loss and a reduced number of cardiovascular events. However, there is a lack of data about a potential direct impact of BaS on atherosclerotic changes in morbidly obese patients. In contrast, it is well known that the link between adipose tissue and vascular integrity, with proinflammatory changes in fat tissue, is related to vascular endothelial dysfunction. This might at least partly explain the beneficial effects of BaS on cardiovascular events. Supporting this pathophysiologic link, it became evident that expansion of abdominal visceral adipose tissue (VAT) and peri-cardial adipose tissue (PAT) associates with the metabolic syndrome and incident cardiovascular disease, mainly coronary artery disease and vascular calcification. Additionally, recent work has better described the role and distribution of different types of fat. Human brown adipose tissue (BAT) is of special interest as it is known to be metabolically active by producing heat (thermogenesis) in response to cold conditions, which leads to enhanced energy expenditure and weight loss, with increased glucose and fatty acid uptake in BAT.

 Accordingly, obese and overweight subjects were shown to have lower BAT activity. Thus, BAT has emerged as a potential target for the treatment of obesity and obesity-associated cardiovascular diseases. However, whether BAT has a direct effect on vessel biology is not yet known. 18F-fluorodeoxyglucose (18F-FDG) positron emission tomography (PET) reflects the metabolic rate of glucose, a process known to be enhanced in inflamed vascular tissue. Accordingly, 18F-FDG uptake was shown to be significantly associated with the degree of macrophage infiltration in vascular plaques. Furthermore, 18F-FDG PET demonstrated the presence of BAT in adult humans localized to areas close to the clavicles, axilla, aorta, cervical, vertebral, as well as the supraproteral region. The presence of BAT in morbidly obese patients might at least partly explain the beneficial effects of BaS on cardiovascular events.
In this study, the $^{18}$F-FDG PET technique was used to evaluate changes of the degree of carotid artery inflammation and the metabolic activity in PAT, VAT, and BAT in morbidly obese patients as depicted by $^{18}$F-FDG-PET 1 year after BaS.

**METHODS**

**Study Design**

The study was conducted at the Maastricht University Medical Center (MUMC+), Maastricht, The Netherlands. All subjects gave written informed consent. The study was approved by the institutional review board and was performed according to the STROBE guidelines for cohort, case--control, and cross-sectional studies.\(^2\)\(^2\)

All morbidly obese patients who presented at MUMC+ for planning of BaS were consecutively screened for inclusion in the study. Based on strict inclusion criteria, 2 male and 8 female patients, with a mean body mass index (BMI, kg/m\(^2\)) of 41.7±4.34 were included in the study.\(^\text{20}\) Exclusion criteria were known cardiovascular disease and risk factors for it, including hypertension, nicotine abuse, diabetes mellitus, and/or the use of statins or β-blockers, of which the latter is known to significantly reduce the metabolic activity of BAT. To exclude any impact of medication on vascular and fat tissue $^{18}$F-FDG uptake, only patients without any change in their medications after BaS were further analyzed. However, none of the patients, except 1 patient requiring thyroid hormone substitution therapy, received any kind of medication throughout the study period. Most importantly, none of the patients received any kind of anti-inflammatory medication, either before or after BaS. The serum glucose level (5.13–5.19 mmol/L) and the intravenous injection of a mean standard dose of 78.1–83.4 MBq (2.11–2.25 mCi) $^{18}$F-FDG was followed by 2 hours of individual mild cold (t60–t180). At thermoneutral conditions (room temperature before weight loss: 0.6±0.9 °C; time (t)0–t60) was followed by 2 hours of individual mild cold (t60–t180). At the end of the first hour of cooling (t120), $^{18}$F-FDG PET/CT imaging (Gemini TF PET/CT; Philips Healthcare Nederland B.V., Eindhoven, The Netherlands) was performed to quantify metabolic activity and/or the inflamed state of fat tissue. $^{18}$F-FDG dose and the body weight of the patient. Afterward, BAT SUV\(_{\text{max}}\) were corrected by the $^{18}$F-FDG blood pool activity in the jugular veins (JVs) in order to obtain BAT target-to-background ratios (TBR\(_{\text{max}}\)). For evaluation of the blood pool activity, at least six 3 to 4-mm ROIs were placed in consecutive slices of the JV and averaged. The individual BAT TBR\(_{\text{max}}\) values obtained in each slice were then averaged to derive a mean TBR\(_{\text{max}}\) for the BAT (Figure 1C).

**Study Protocol**

$^{18}$F-FDG PET/CT

As earlier described in detail, a cooling protocol was applied to assure a standardized thermal situation for all included subjects.\(^15\),\(^19\),\(^20\) In short, 1 hour of measuring under thermoneutral conditions (room temperature before weight loss: 22.8±0.6 °C; after weight loss: 23.7±0.9 °C; time (t)0–t60) was followed by 2 hours of individual mild cold (t60–t180). At the end of the first hour of cooling (t120), $^{18}$F-FDG was injected. After the second hour of cooling, $^{18}$F-FDG PET/CT imaging (Gemini TF PET/CT; Philips Healthcare Nederland B.V., Eindhoven, The Netherlands) was performed to quantify metabolically active BAT.

The PET/CT scanning protocol included confirmation of the serum glucose level (5.13–5.19 mmol/L) and the intravenous injection of a mean standard dose of 78.1–83.4 MBq (2.11–2.25 mCi) $^{18}$F-FDG (Table 1). A low-dose noncontrast-enhanced CT scan (30 mAs) was performed for attenuation correction and localization of the $^{18}$F-FDG uptake sites, immediately followed by the PET scan.\(^15\) Total radiation dose from the PET/CT scan was approximately 2.8 mSv.

**PET Image Analyses**

An experienced reader (J.B.) who was blinded to the patient’s characteristics and the date of the scan (presurgical or postsurgical $^{18}$F-FDG PET/CT) analyzed all scans. Methodology for analysis and reproducibility of the measurements have been previously reported in part.\(^23\),\(^24\)

**Image Analysis of BAT**

Methodology for BAT analysis has been previously reported.\(^15\),\(^19\),\(^20\) In short, BAT activity measured as the maximal standardized uptake value (SUV\(_{\text{max}}\)) was quantified in the region of interest (ROI) in the BAT areas with a set threshold (SUV\(_{\text{max}}\) ≥ 1.0). The SUV is the decay-corrected tissue concentration of $^{18}$F-FDG in kBq/mL, adjusted for the injected $^{18}$F-FDG dose and the body weight of the patient. Afterward, BAT SUV\(_{\text{max}}\) were corrected by the $^{18}$F-FDG blood pool activity in the jugular veins (JVs) in order to obtain BAT target-to-background ratios (TBR\(_{\text{max}}\)). For evaluation of the blood pool activity, at least six 3 to 4-mm ROIs were placed in consecutive slices of the JV and averaged. The individual BAT TBR\(_{\text{max}}\) values obtained in each slice were then averaged to derive a mean TBR\(_{\text{max}}\) for the BAT (Figure 1C).

**Image Analysis of PAT, VAT, and Subcutaneous Adipose Tissue**

Image analysis was performed on a dedicated commercially available workstation (Extended Brilliance Workspace V4.5.3.40140; Philips Healthcare Nederland B.V., Eindhoven, The Netherlands). In order to control for the specific metabolic activity of PAT and VAT as depicted by $^{18}$F-FDG PET, we also analyzed the $^{18}$F-FDG uptake in subcutaneous adipose tissue (SAT), which is known to be less metabolically active compared to VAT.\(^25\),\(^26\) PAT, VAT, and SAT were identified based on a predefined range of Hounsfield units (−70 to −110) from CT images as previously described.\(^21\) After fusion with the PET images, standard ROIs (7–15 mm, depending on the adipose tissue region) were placed on 3 consecutive slices whenever possible and SUV\(_{\text{max}}\) values across those slices were averaged (Figure 1A and B). SAT analysis was performed by placing ROIs in the previsual SAT. PAT ROIs were placed in the subternal mediastinal region of the chest cranial of the heart and therefore as far away as possible from the myocardium and the large vessels in order to exclude overspill from the myocardial and/or vascular $^{18}$F-FDG uptake into the PAT region (Figure 1A). For VAT analysis, 3 consecutive standard ROIs were placed in the abdominal VAT above or below the kidneys to avoid overspill from the physiological $^{18}$F-FDG uptake in the kidneys (Figure 1B). Overspill from intestinal, muscle, and/or vascular uptake into the abdominal adipose tissue was widely excluded by placing the ROIs at least 2 cm away from these structures. Again, SUV\(_{\text{max}}\) values across those slices were averaged. In general, PAT and VAT ROIs were not placed at all if an overspill from surrounding structures into the respective PAT or VAT region could not be excluded to the highest possible degree. As for the BAT SUV\(_{\text{max}}\) values, PAT, VAT, and SAT SUV\(_{\text{max}}\) were corrected by the $^{18}$F-FDG blood pool activity in order to obtain PAT, VAT, and SAT TBR\(_{\text{max}}\) values, respectively, which were afterward averaged to derive mean TBR\(_{\text{max}}\) values to reflect the true metabolic activity and/or the inflamed state of fat tissue cells.
TABLE 1. PET-Related Data of the Study Population and the 2 Groups of Controls

| PET Data                              | Patients                        | Controls                        |
|---------------------------------------|---------------------------------|---------------------------------|
|                                      | Pre surgery                     | After surgery                   |
|                                      | n                               | BMI < 25                        | BMI ≥ 25 < 30                    |
| n                                     | 10                              | 7                               | 5                                |
| Fasting glucose, mmol/L              | 5.19 ± 0.32                     | 5.13 ± 0.37                     | 5.03 ± 0.49                      | 5.3 ± 0.4                      |
| 18F-FDG dose injected, MBq           | 83.4 ± 11.3                     | 78.6 ± 5.03                     | 78.1 ± 5.52                      | 78.6 ± 3.51                    |
| 18F-FDG blood pool activity (jugular vein, meanSUVmean) | 1.10 ± 0.32                     | 1.28 ± 0.57                     | 1.18 ± 0.47                      | 1.43 ± 0.12                    |
| Carotids 18F-FDG uptake meanTBRmax   | 1.92 ± 0.35                     | 1.23 ± 0.15                     | 1.39 ± 0.21                      | 1.30 ± 0.09                    |
| ΔCarotids meanTBRmax                 | −0.69 ± 0.34 (−0.32 to −1.5)    |                                 |                                  |
| PAT 18F-FDG uptake meanTBRmax        | 1.34 ± 0.49                     | 0.84 ± 0.08                     |                                  |
| ΔPAT meanTBRmax                      | −0.5 ± 0.47 (−0.03 to −1.67)    |                                  |                                  |
| VAT 18F-FDG uptake meanSUVmean       | 0.65 ± 0.19                     | 0.36 ± 0.11                     |                                  |
| ΔVAT meanSUVmean                    | −0.29 ± 0.19 (−0.03 to −0.67)   |                                  |                                  |
| SAT 18F-FDG uptake meanTBRmax        | 0.54 ± 0.3                      | 0.44 ± 0.21                     |                                  |
| ΔSAT meanTBRmax                     | −0.1 ± 0.15 (−0.31 to 0.14)     |                                  |                                  |
| BAT 18F-FDG uptake TBRmax           | 0.98 ± 2.08                     | 2.44 ± 2.97                     |                                  |
| ΔBAT meanTBRmax                     | 1.46 ± 2.76 (−1.5 to 7.33)      |                                  |                                  |

Values are mean ± SD or n (%). ΔDifference over 1 year between pre surgery and postsurgery. BAT = brown adipose tissue; BMI = body mass index; MBq = megabecquerel, n.s. = not significant, PAT = pericardial adipose tissue, PET = positron emission tomography, SAT = subcutaneous adipose tissue, SD = standard deviation, TBR = target-to-background ratio, VAT = visceral adipose tissue.

1 P = n.s. for patients pre surgery vs patients postsurgery, patients pre surgery vs both groups of controls, patients postsurgery vs both groups of controls, and between both groups of controls.

1 P = 0.0001 for patients pre surgery vs patients postsurgery; P = 0.002 for patients pre surgery vs controls BMI < 25; P = 0.001 for patients pre surgery vs controls BMI ≥ 25 < 30; P = n.s. for patients postsurgery vs both groups of controls and between both groups of controls.

1 P = 0.008.

1 P = 0.001.

1 P = n.s.

Image Analysis of the Vessels

Image analysis of the vessels was performed on the same workstation as mentioned previously. The methodology for the analysis and the excellent reproducibility of the measurements has been previously reported.23,24 Briefly, arterial 18F-FDG uptake was quantified by drawing a ROI around each common carotid artery on every slice of the coregistered transaxial PET/CT images (Figure 2A and B). By averaging the SUVmax values of all arterial slices of the left and right common carotid, a meanSUVmax value was derived for the carotid arteries. The arterial TBRmax was calculated by normalizing the SUVmax for the 18F-FDG blood pool activity by dividing the SUVmax value in the artery by the average blood mean SUV estimated from both JV as described earlier. The arterial TBRmax values were then averaged to derive a meanTBRmax for both carotid arteries. The TBR is considered to be a reflection of arterial 18F-FDG uptake and reflective of underlying macrophage activity.17

Statistical Analysis

All continuous variables are expressed as mean ± standard deviation and categorical data as absolute numbers and percentages. Normality of distribution of data was tested using the Kolmogorov–Smirnov test. Comparisons between continuous variables were performed with the independent or paired samples Student t test or the Mann–Whitney U test and correlations with the Pearson or Spearman correlation coefficient, wherever appropriate. Comparison between the groups of patients and controls was performed using analysis of variance with appropriate correction for multiple comparisons using Tukey post hoc testing.

Differences between the presurgical and postsurgical 18F-FDG uptake in the carotids, the PAT, the VAT, the SAT, the BAT, and between the presurgical and postsurgical BMI are given as delta (Δ). All statistical analyses were performed using SPSS statistical package 16.0 (SPSS Inc, Chicago, IL).

RESULTS

Population Characteristics

Characteristics of the patients as well as the healthy 7 lean and 5 overweight volunteers are given in Table 2, and PET-related methodological data is given in Table 1.15,19,20

BMI

The BMI showed a highly significant decrease 1 year after BaS in the patient group (Table 2). No significant correlation was seen between preoperative and postoperative BMI values and all of the other respective 18F-FDG uptake values in the
carotids, the PAT, VAT, SAT, and the BAT, respectively (P = n.s. for all). Also, no significant correlation was observed between the ΔBMI and the ΔCarotids, ΔVAT, ΔPAT, ΔSAT, and ΔBAT mean TBRmax, respectively (P = n.s. for all).

Vascular 18F-FDG Uptake

In BaS patients, carotids mean TBRmax before surgery (Carotids pre mean TBRmax) was significantly higher compared to the carotids mean TBRmax values in both groups of controls. However, patient’s 18F-FDG uptake in the carotids decreased 1 year after BaS leading to a significantly lower Carotids post mean TBRmax compared to the respective preoperative values (Table 1, Figure 3A). Accordingly, BaS patient’s Carotids post mean TBRmax 1 year after surgery were not significantly different from the 18F-FDG uptake parameters of the carotids in the 2 groups of controls (Table 1, Figure 3B). In BaS patients, the 18F-FDG blood pool activity within the JV was not significantly different between the presurgical and postsurgical PET (Table 1). Additionally, there were no significant differences between patient’s presurgical and postsurgical 18F-FDG blood pool activity, respectively, and both groups of controls (Table 1).

PAT, VAT, and SAT 18F-FDG Uptake

The metabolic activity of PAT and VAT considerably declined after BaS leading to a significantly lower PAT post mean TBRmax and VAT post mean TBRmax compared with the respective preoperative values (Table 1, Figure 4A and B). Furthermore, a significantly positive correlation was seen between ΔPAT and ΔVAT mean TBRmax (r = 0.674, P = 0.033) and between ΔCarotids and ΔVAT mean TBRmax (r = 0.644, P = 0.044). Accordingly, a positive correlative trend between ΔCarotids and ΔPAT mean TBRmax (r = 0.560, P = 0.093) was observed. These findings are in contrast to the control measurements of the 18F-FDG uptake in the SAT, which did not show a significant decline after BaS (Table 1). Furthermore, no significant correlation was found between ΔCarotids and ΔSAT mean TBRmax, between ΔPAT and ΔSAT mean TBRmax, and between ΔVAT and ΔSAT mean TBRmax, respectively (P = n.s. for all).
No significant correlations were found between the meanTBRmax values in VAT and PAT as well as between any of the meanTBRmax values in the 3 adipose tissues and in the carotids preoperatively and postoperatively (P = n.s. for all). However, we found a significant correlation between the preoperative meanTBRmax values in the SAT and the respective meanTBRmax values in VAT (r = 0.632, P = 0.05) and PAT (r = 0.786, P = 0.007), respectively. In contrast, no significant correlation was found between the postoperative SAT meanTBRmax and the VAT and PAT meanTBRmax, respectively (P = n.s.).

BAT Activity

Results regarding the BAT activity before and 1 year after BaS in the present patient population were previously published by our group.19,20 Briefly, before surgery, a minimal cold-induced BAT activity in supraclavicular depots was observed in 2 females. After BaS, BAT was seen in 5 of 10 subjects, including the 2 mentioned female subjects. Of these 5 BAT-positive patients, 1 subject was observed with an increased BAT activity, 3 previously BAT-negative subjects became BAT positive after surgery, and 1 subject showed a decreased BAT activity.20

We found a negative correlation between ΔPAT and ΔBAT meanTBRmax (r = −0.755, P = 0.012). A negative trend was observed between the Δcarotids and ΔBAT meanTBRmax (r = −0.239, P = 0.506) and between ΔVAT and ΔBAT meanTBRmax (r = −0.593, P = 0.071). No significant correlation was found between the ΔSAT and ΔBAT meanTBRmax (P = n.s.).

No significant correlations were seen between the preoperative and postoperative meanTBRmax values of VAT, PAT, and SAT and the respective preoperative and postoperative BAT meanTBRmax values (P = n.s. for all). Also, correlations between the preoperative and postoperative meanTBRmax values in the carotids and the respective BAT meanTBRmax values failed to show statistical significance (P = n.s. for all).

FIGURE 2. 18F-FDG PET/CT image analysis of the carotid arteries (arrows) before and after BaS. 18F-FDG PET/CT images of the neck in transaxial and coronal view (A) before and (B) after BaS. ROIs (green) drawn around the outer border of the vessel wall of the right common carotid artery (SUV_max, SUV_mean, and diameter of the ROIs) showing higher 18F-FDG uptake values before BaS (SUV_max 2.3 vs SUV_max 1.1 after BaS). SUV_max values were corrected for the blood pool activity in the JVs to derive mean TBR (meanTBRmax) values. 18F-FDG = 18F-fluorodeoxyglucose, BaS = bariatric surgery, JV = jugular vein, PET/CT = positron emission tomography/computed tomography, ROI = region of interest, SUV_max = maximal standardized uptake value, TBR = target-to-background ratio.

DISCUSSION

One year after BaS, 18F-FDG uptake in carotid arteries was dramatically decreased reflecting a reduction in carotid artery inflammation. In addition, 18F-FDG uptake in PAT and VAT significantly declined after BaS and, with regard to VAT, also showed a significant correlation with the diminished carotid wall inflammation. As was previously published by our group, BAT activity increased over the same time period.19,20 The
results of our study indicate a significant benefit within 1 year after BaS with regard to the degree of vascular inflammation and the metabolic activity in different adipose tissues. We hypothesize that these might contribute to the previously reported diminished cardiovascular risk in morbidly obese patients after BaS.2,5,7–9

Impressively, our study showed that the decrease in carotid inflammation as with the diminished carotid inflammation, the 18F-FDG uptake both in PAT and VAT significantly declined 1 year after BaS. The rationale for analyzing the metabolic activity in VATs by means of 18F-FDG PET was related to the fact that volumetric measurements with CT or magnetic resonance imaging alone may not be sufficient and could be improved by using functional imaging with PET to determine the metabolic activity in fat tissue and its relation to the cardiovascular risk.11,12,21,29 Furthermore, it is now well established that VAT is functionally more active than SAT and that its expansion, rather than that of SAT, confers a high risk for developing the metabolic syndrome as well as an increased incident of cardiovascular disease.25,26 These differences might explain the higher 18F-FDG uptake values in VAT than SAT in our study.21 In accordance, we did not find neither a significant decline of the metabolic activity of SAT 1 year after BaS nor any correlation between the decline of the 18F-FDG uptake in the carotids, in the PAT, and in the VAT and the increase of the metabolic activity of the BAT on the one hand and the delta of the SAT on the other hand. However, the underlying mechanisms are still not completely understood. In contrast, monocytes and monocyte-derived macrophages are well known to be the cellular hallmarks in the pathogenesis of atherosclerosis.30 These macrophages seem also to play a significant role in inflammatory changes of adipose tissues. Animal studies demonstrated a specific contribution of certain monocyte subsets to atherogenesis and, additionally, an obesity-associated macrophage accumulation in adipose tissue.31–34 As it is known that the 18F-FDG uptake reveals a highly significant correlation with the degree of macrophage density in the arterial wall as depicted by histological CD 68 staining, it is not unlikely that 18F-FDG uptake in adipose tissue is also attributed to the macrophage density of adipose tissues.17 Therefore, our study seems to further support potentially inflammatory changes of

### TABLE 2. Characteristics of the Study Population and the 2 Groups of Controls

| Characteristics | Patients | Controls |
|-----------------|----------|----------|
|                 | Pre surgery | After Surgery | BMI < 25 | BMI ≥ 25 < 30 |
| n               | 10        | 5         |          |            |
| Age, y          | 40 ± 9    | 41 ± 9    | 25 ± 4   | 26 ± 4     |
| Sex             | Male      | Female    |          |            |
|                 | 2 (20.0)  | 8 (80.0)  | 6 (85.7) | 5 (100)    |
|                 | 2 (20.0)  | 8 (80.0)  | 1 (14.3) | 0 (0)      |
| Weight, kg      | 127.3 ± 17.5 (98.2–155.0) | 90.8 ± 16.5 (74.0–120.0) | 77.6 ± 7.2 (70.3–90.3) | 91.5 ± 4.7 (85.6–95.5) |
| Height, m       | 1.75 ± 0.09 (1.63–1.91) | 1.75 ± 0.09 (1.63–1.91) | 1.83 ± 0.06 (1.77–1.92) | 1.84 ± 0.02 (1.82–1.88) |
| BMI, kg/m²      | 41.7 ± 4.34 (34.3–48.4) | 29.7 ± 4.15 (24.3–35.9) | 23.2 ± 1.20 (21.3–24.4) | 27.1 ± 1.25 (23.9–28.6) |
| < 25            | 0         | 1 (10.0)  | 7 (100)  | 0          |
| ≥ 25 < 30       | 0         | 3 (30.0)  | 0        | 5 (100)    |
| ≥ 30            | 10 (100)  | 6 (60.0)  | 0        | 0          |
| ΔBMI            | −12.0 ± 3.0 (−7.2 to −15.6) |                      |            |            |

Values are mean ± SD or n (%). ΔDifference over 1 year between pre surgery and postsurgery. BMI = body mass index, n.s. = not significant, SD = standard deviation.

* P = 0.001 for patients pre surgery vs controls BMI < 25, and P = 0.003 for patients pre surgery vs controls BMI ≥ 25 < 30; P > 0.0001 for patients postsurgery vs controls BMI < 25, and P = 0.002 for patients postsurgery vs controls BMI ≥ 25 < 30.

† P = 0.0001 for patients pre surgery vs patients postsurgery, for patients pre surgery vs controls BMI < 25, and for patients pre surgery vs controls BMI ≥ 25 < 30; P = n.s. for patients postsurgery vs both groups of controls, and between both groups of controls.

‡ P = 0.0001 for patients pre surgery vs patients postsurgery, for patients pre surgery vs controls BMI < 25, and for patients pre surgery vs controls BMI ≥ 25 < 30; P = n.s. for patients postsurgery vs controls BMI < 25; P = n.s. for patients postsurgery vs controls BMI ≥ 25 < 30 and between both groups of controls.
adipose tissues underlying the metabolic activity in PAT and VAT as depicted by the $^{18}$F-FDG uptake. Our study revealed interesting clues on the role of BAT on inflammatory changes in the carotid arteries 1 year after BaS. There is emerging evidence that activation of BAT increases energy expenditure and that obese and overweight subjects have lower BAT activity. Moreover, animal studies and more recent clinical evidence argue that decreasing adiposity by activating BAT and potently oxidizing fatty acids would, in most settings, indirectly benefit the vasculature. In fact, in humans, cervical BAT size is negatively correlated with BMI and the degree of coronary atherosclerosis. BAT has therefore emerged as an attractive target for the treatment of obesity and associated cardiovascular disease. In the current study, we observed a negative trend between the decline of carotid wall inflammation and the increase of BAT activity 1 year after BaS. It could thus be hypothesized that increasing BAT activity leads to an anti-inflammatory effect in the vasculature, as depicted by the decreasing $^{18}$F-FDG uptake in the carotids. A fact, which might further elucidate the anti-inflammatory properties of BAT, is the significant association between the decline of the metabolic activity of PAT with the increase in BAT activity, which we observed after BaS. This might be explained by declining inflammatory changes in PAT due to the observed increase of BAT activity. This effect was previously described in an animal model with BAT-transplanted mice.

FIGURE 3. (A) Vascular $^{18}$F-FDG uptake in the carotids in patients before and 1 year after BaS. (B) Comparison of the preoperative and postoperative vascular $^{18}$F-FDG uptake between patients and the 2 groups of controls. Arterial $^{18}$F-FDG uptake in the carotids ($\text{mean TBR}_{\text{max}}$) significantly decreased 1 year after BaS (A). Patients’ preoperative $^{18}$F-FDG uptake in the carotids was significantly higher as compared to lean (BMI $< 25$; $P = 0.002$) and overweight controls (BMI $\geq 25 < 30$; $P = 0.001$). One year after BaS, no significant differences between patients’ carotids $\text{mean TBR}_{\text{max}}$ compared with both groups of controls can be observed (B). $^{18}$F-FDG = $^{18}$F-fluorodeoxyglucose, BaS = bariatric surgery, BMI = body mass index, TBR = target-to-background ratio.

FIGURE 4. Comparison between the (A) PAT and the abdominal (B) VAT $^{18}$F-FDG uptake of the patients before and 1 year after BaS. Both PAT and VAT $\text{mean TBR}_{\text{max}}$ shows a highly significant decline over a time period of 1 year after BaS. $^{18}$F-FDG = $^{18}$F-fluorodeoxyglucose, BaS = bariatric surgery, BMI = body mass index, PAT = pericardial adipose tissue, TBR = target-to-background ratio, VAT = visceral adipose tissue.
Although some might argue that the limited number of patients in our study could hamper interpretation, we believe the number of patients to be sufficient because of the depth of our investigations combined with the fact that every person has been his/her own control. As we only included healthy patients and excluded all patients with any kind of comorbidities, only a limited number of patients was feasible for inclusion. This was mainly due to the fact that most of patients in question for inclusion suffered from diabetic or prediabetic disease. Furthermore, the patients group consisted of more females and much older subjects compared with the 2 groups of controls. Again, because every person has been his/her own control and the differences were the same before and after BaS, age and/or gender-related bias is unlikely.

As we applied an imaging protocol including cold stimulation appropriate to disclose BAT activity,\(^5\)\(^,\)\(^9\)\(^,\)\(^10\) we could not take advantage of methods that have been employed to optimize the arterial \(^{18}\)F-FDG signal, for example, a longer \(^{18}\)F-FDG circulation time. However, the same imaging protocol was applied to the subjects in all groups. Furthermore, we, because of restrictions due to radiation protection of the patients, were not able to apply a weight-adapted FDG dose. Instead we chose a standard dose of the tracer. However, previously published data indicated no significant impact of the injected FDG dose on the degree of FDG uptake in the vasculature. In addition, we used TBR with for the underlying blood pool corrected SUV values of the carotids.\(^37\) Therefore, the impact of the low FDG standard dose in the current study should not lead to a significant impact on our study results.

Obviously, we were not able to retain biopsies to compare histology of vascular and adipose tissues with the imaging parameters and have, with that regard, to rely on previously published data.\(^21\)\(^,\)\(^34\) Intentionally, we decided not to evaluate biomarkers in the patient group because of the known fact that inflammatory biomarkers such as CRP, IL-6, or TNF-\(\alpha\) show significant, weight-independent reductions after BaS.\(^5\)\(^,\)\(^27\)\(^,\)\(^28\) Therefore, repetitive evaluation of the biomarkers within the context of the current study would not have added any significant new information with that regard.

We demonstrated that in morbidly obese patients, the degree of carotid inflammation normalizes already 1 year after BaS. This is intriguing as our results indicate that vascular inflammation as part of the atherosclerotic disease process may be almost completely reversed, even within that rather short time period. This effect appeared not to be completely related to only the degree of weight loss per se and, intriguingly, one might speculate on anti-inflammatory effects induced by BaS itself. In addition, a significantly reduced metabolic activity of PAT and VAT as well as an increased degree of BAT was observed 1 year after BaS. We hypothesize the latter to possibly have contributed to the observed beneficial changes in vascular inflammation and the metabolic activity in PAT and VAT.

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