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Greater Omentectomy Improves Insulin Sensitivity in Nonobese Dogs

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Greater Omentectomy Improves Insulin Sensitivity in Nonobese Dogs

**Abstract**
Visceral adiposity is strongly associated with insulin resistance; however, little evidence directly demonstrates that visceral fat *per se* impairs insulin action. Here, we examine the effects of the surgical removal of the greater omentum and its occupying visceral fat, an omentectomy (OM), on insulin sensitivity ($S_I$) and β-cell function in nonobese dogs. Thirteen male mongrel dogs were used in this research study; animals were randomly assigned to surgical treatment with either OM ($n = 7$), or sham-surgery (SHAM) ($n = 6$). OM failed to generate measurable changes in body weight (+2%; $P = 0.1$), or subcutaneous adiposity (+3%; $P = 0.83$) as assessed by magnetic resonance imaging (MRI). The removal of the greater omentum did not significantly reduce total visceral adipose volume ($-7.3 \pm 6.4\% ; P = 0.29$); although primary analysis showed a trend for OM to increase $S_I$ when compared to sham operated animals ($P = 0.078$), further statistical analysis revealed that this minor reduction in visceral fat alleviated insulin resistance by augmenting $S_I$ of the periphery ($+67.7 \pm 35.2\% ; P = 0.03$), as determined by the euglycemic-hyperinsulinemic clamp. Insulin secretory response during the hyperglycemic step clamp was not directly influenced by omental fat removal (presurgery $6.82 \pm 1.4$ vs. postsurgery: $6.7 \pm 1.2$ pmol/l/mg/dl, $P = 0.9$). These findings provide new evidence for the deleterious role of visceral fat in insulin resistance, and suggest that a greater OM procedure may effectively improve insulin sensitivity.

**Disciplines**
Medical Sciences

**Comments**
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Greater omentectomy improves insulin sensitivity in non-obese dogs

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Abstract
Visceral adiposity is strongly associated with insulin resistance; however little evidence directly demonstrates that visceral fat per se impairs insulin action. Here we examine the effects of the surgical removal of the greater omentum and its occupying visceral fat, an omentectomy, on insulin sensitivity ($S_I$) and $\beta$-cell function in non-obese dogs. Thirteen male mongrel dogs were used in the present research study; animals were randomly assigned to surgical treatment with either omentectomy ($n=7$), or sham-operation ($n=6$). Omentectomy failed to generate measurable changes in body weight (+2%; $P=0.1$), or subcutaneous adiposity (+3%; $P=0.83$) as assessed by magnetic resonance imaging. The removal of the greater omentum did not significantly reduce total visceral adipose volume (-7.3 ± 6.4%; $P=0.29$); while primary analysis showed a trend for omentectomy to increase $S_I$ when compared to sham operated animals ($P=0.078$), further statistical analysis revealed that this minor reduction in visceral fat alleviated insulin resistance by augmenting $S_I$ of the periphery (+67.7 ± 35.2%; $P=0.03$), as determined by the euglycemic-hyperinsulinemic clamp. Insulin secretory response during the hyperglycemic step clamp was not directly influenced by omental fat removal (pre-surgery 6.82 ± 1.4 vs. post-surgery: 6.7 ± 1.2 pM · mg⁻¹ · dl⁻¹, $P=0.9$). These findings provide new evidence for the deleterious role of visceral fat in insulin resistance, and suggest that a greater omentectomy procedure may effectively improve insulin sensitivity.

Keywords
visceral fat; insulin sensitivity; in vivo studies; omental; visceral obesity; body fat distribution

INTRODUCTION
Obesity is strongly associated with insulin resistance, a risk factor for a number of chronic diseases, including type 2 diabetes, cardiovascular disease, and some forms of cancer1. As first suggested by Vague2, visceral adiposity appears to be a more important determinant of insulin resistance than subcutaneous adiposity or even overall obesity. Beyond the reported association, there is limited evidence directly implicating visceral fat per se as a cause of insulin resistance. Furthermore, the pathophysiologic mechanisms that associate visceral adiposity with impaired insulin action remain poorly understood.

The deleterious effects of visceral fat may be explained by its unique metabolic properties as it exhibits substantially higher rates of lipolysis compared with other fat tissue, resulting in
increased mobilization of free fatty acids (FFAs) directly to the liver. In vivo studies reveal that FFAs impair hepatic glucose production and insulin-mediated glucose uptake by skeletal muscle in humans, and thus appear to be an important signal interceding visceral fat accumulation and insulin resistance. Alternatively, visceral adipocytes are known to variably secrete numerous proteins and cytokines, including tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and/or reduced adiponectin, and one or more of these latter molecules may impair insulin action.

Several investigators have attempted to establish a cause and effect relationship between central adiposity and insulin resistance by demonstrating that the surgical removal of visceral fat alleviates insulin resistance. Barzilai et al. reported that surgical removal of 2 intra-abdominal fat pads, the epididymal and perirenal depots, reversed hepatic insulin resistance in elderly, obese rats. However, it is problematic to relate these results to other species, including man, given that adipose drainage of these depots don’t enter the portal circulation. Therefore, in the present study we have performed a surgical procedure that specifically removes intra-abdominal fat with portal drainage.

Omentectomy refers to the surgical removal of the whole greater omentum and its constituent fat. A 2002 study investigating this surgery as a possible treatment for obesity reported that obese patients undergoing simultaneous adjustable gastric binding (AGB) plus omentectomy saw a greater, long-term improvement in fasting insulin and glucose than those who received AGB alone. However, the specific fluctuations in insulin sensitivity (S_t) and fat redistribution resulting from the surgery remain unclear due to the difficulty in obtaining frequent, accurate measurements in humans.

Thus, our approach to studying the putative role of visceral fat in the pathogenesis of insulin resistance is the implementation of an omentectomy in the dog, an animal model reminiscent of human adiposity and its sequelae. To date, we have described that dogs develop insulin resistance in response to increased adiposity similarly to humans. Furthermore, this large animal model allows for repetitive metabolic measurements using the most accurate diagnostic and imaging techniques. The present study is a metabolic characterization of the in vivo relationship between visceral fat and insulin action in non-obese dogs.

**METHODS**

**Animals**

Thirteen male mongrel dogs (30.5 ± 1.0 kg) were used in the present research study. Dogs were housed under controlled kennel conditions in the University of Southern California (USC) Medical School Vivarium and were accepted into the study only if determined to be in good health. Dogs were presented daily with a diet consisting of 825 grams dry chow (Prolab Canine/Laboratory High-Density Canine Diet; PMI Nutrition, Brentwood, MO) and 1 can Purina Pro-Plan Puppy (Nestle Purina PetCare Company, St. Louis, MO). The experimental procedure was approved by the USC Institutional Animal Care and Use Committee.

**Study Design**

Experiments began following two weeks of acclimation to the standard diet and familiarization with the Pavlov sling. Metabolic assessments were made prior to any surgical treatment at baseline (pre-surgery) in all dogs to determine adiposity, S_t, and β-cell function. Following pre-testing, dogs underwent omentectomy (OM) or sham-surgery (SHAM), and a minimum of 16 days were allowed for complete medical recovery, after which all experimental procedures were repeated (post-surgery). All experiments were randomly performed with a minimum of 2 days between each protocol.
Surgery

Dogs were randomly assigned to an experimental group: OM (n=7) or SHAM (n=6) operation. Surgeries were conducted under general anesthesia, initially induced with intravenous sodium pentobarbital (0.44 mL/kg; Western Medical, Arcadia, CA) and maintained with isofluorane (Western Medical).

The omentectomy surgery consisted of two components; implantation of chronic catheters into the jugular and portal vein, and excision of the whole greater omentum. The sham surgery consisted of catheter implantation only, but was altogether matched with omentectomy procedure in surgical incisions, treatment, and length of time. The jugular catheter was first advanced into the right atrium for sampling of mixed venous blood. Immediately following an abdominal laparotomy, another catheter was secured in the portal vein. Subsequently in the omentectomy-animals only, the greater omentum was fully exposed, blood vessels were ligated and cauterized, and the membrane was excised. The excised omentum was weighed and frozen for future analysis.

Magnetic resonance imaging (MRI)

Prior to each scan, pre-anesthesia was induced with a subcutaneous injection of Acepromazine (0.04mg/kg; Bio-ceutic, St. Joseph, MO) and Atropine Sulfate (0.1mg/kg; Western Medical). Dogs then received intravenous anesthesia consisting of Ketamine HCL (10mg/kg; Bioniche-Pharma, Lake Forest, IL) and Diazepam (0.2mg/kg; Hospira; Lake Forest, IL). Thirty 1-cm axial images were obtained using a General Electric 1.5 Tesla Horizon Magnet (version 5.7) for assessment of body composition. The excised omenta were similarly scanned; membranes were lined up in series on a head coil, and 0.5-cm axial slices were obtained over the entire omentum for analysis.

Euglycemic-hyperinsulinemic clamps

With the exception of one dog that did not receive a post-OM clamp, each dog was tested in a longitudinal manner. Beginning at t=−120 min, a primed intravenous infusion of high-performance liquid chromatography-purified [3-3H]-D-glucose was started (25μCi bolus + 0.25μCi/min; DuPont-NEN, Boston, MA). At t=0, intravenous insulin (0.75mU*min⁻¹*kg⁻¹; Lilly, Indianapolis, IN) and somatostatin (1.0μg*min⁻¹*kg⁻¹; Bachem California, Torrance, CA) was started. A 50% dextrose infusion labeled with [3-3H]-D-glucose (2.0μCi/g) was variably infused to maintain euglycemia and specific activity. Steady-state was defined as the final 30 minutes of the clamp. Insulin and [3-3H]-D-glucose samples were collected in heparinized tubes coated with lithium fluoride (Brinkmann Instruments; Westbury, NY) containing 50μl EDTA. FFA samples were collected in tubes containing 50μl EDTA and methyl-paraoxon to suppress in vitro lipolysis. Following centrifugation, plasma was aliquoted into microcentrifuge tubes and stored as necessary.

Hyperglycemic step clamp

Glucose concentrations were clamped at three sequential steps: 100 mg/dl between t=0 and 60 min, 150 mg/dl between t=60 to 150 min, and 200 mg/dl between t=150 and 240 min. Plasma samples were obtained every 10 minutes for the entirety of the experiment, and a variable dextrose infusion was used to clamp glucose at the desired level. Steady-state was defined as the final 30 minutes of each glycemic step.

Assays

Plasma glucose was measured using the YSI-2700 auto-analyzer (Yellow Springs Instruments; Yellow Springs, OH). To determine [3-3H]-D-glucose concentration, samples were counted in Ready-Safe scintillation solution (Beckman liquid scintillation counter,
Fullerton, CA). Insulin was measured using an enzyme-linked immunoassay kit adapted for dog plasma in our laboratory (Millipore, St. Charles, MO). FFA concentrations were analyzed using an in vitro calorimetric assay (NEFA HR-2; Wako Pure Chemical Industries, Richmond, VA).

Analysis and calculations

Each slice obtained from MRI was analyzed using Scion Image (Version Beta 4.0.2; Scion Corporation, Frederick, MD), which quantifies fat tissue (pixel values 121-254) and non-fat tissue (pixel values 20-120). The area of fat tissue in each slice was calculated by dividing total pixels of fat by the ratio of the total pixels to the known area of each slice. Visceral fat was defined as the area of fat tissue located within the peritoneal cavity in an 11-cm region of the thorax identified by the central landmark slice where the left renal artery branches from the abdominal aorta. Subcutaneous fat was calculated as the total fat in the assessment region less the visceral fat volume. Greater omental images were similarly analyzed.

The timecourse of endogenous glucose production (EGP) and glucose uptake (Rd) was calculated using Steele’s model modified with a labeled glucose infusion as detailed in Finegood et al.10. SI-CLAMP was defined as the steady-state exogenous glucose infusion rate (Ginf) divided by the difference between basal and steady-state plasma insulin times the steady-state plasma glucose concentration. SI-Rd and SI-EGP were calculated by substituting the difference between basal and steady-state period Rd and EGP timecourse, respectively for \( \Delta G_{\text{inf}} \) in the above formula.

\( \beta \)-cell function was defined as the slope of the line relating steady state plasma glucose to plasma insulin concentrations of each glyceamic step period. Disposition index (DI) was calculated as the product of SI and the area-under-the-curve of insulin secretion during the step clamp11.

The Kruskal-Wallis equality-of-populations rank test was used to compare changes in SI between treatment groups using STATA. We analyzed the effect of treatment (OM or SHAM) in individual animals by comparing to pre-surgery data using paired t-tests, and the effect of OM-treatment as compared to SHAM-treatment using unpaired t-tests statistics. Due to the small sample size, Wilcoxon matched pairs test was additionally performed to verify the effect of each treatment on SI. All other statistics were performed using Prism 4.03 (Graphpad Software Inc., San Diego, CA). Data are reported as the mean ± SE. Statistically significance was set at P ≤ 0.05.

RESULTS

Body composition

Neither OM or SHAM significantly altered animals’ body weights (pre- vs. post-surgery; OM: 28.0±0.8 vs. 28.5±0.7kg, P=0.10. SHAM: 33.6±1.3 vs. 33.2±1.3kg, P=0.5); however, there was by chance a difference in baseline body weights between treatment groups (P<0.01; animals were randomly assigned to procedures). To account for this difference, all relevant calculations account for body weight, and changes in individual animals were compared to the pre-surgery data. In accordance with the lack of change found in body weight, MRI analysis revealed that there was no overall significant change in adiposity resulting from either treatment following surgical recovery (Figure 1A). MRI assessment revealed that visceral fat in SHAM-treated animals increased 5% (pre: 433.7±44.9, post: 454.0±54.8cm³, P=0.53), while subcutaneous fat did not change (pre: 324.2±50.4, post: 325.7±68cm³, P=0.95; Figure 1B). OM-treated animals exhibited a 3% accumulation of subcutaneous fat (pre: 224.5±50.0, post: 230.7±2.8 cm³, P=0.83, Figure 1B). It is important to note that the excision of 122.9 ± 11.7g of greater omental tissue resulted in a small
7.3±6.4% average reduction in the total MRI-measured visceral adipose compartment (pre-OM: 353.4±46.0, post-OM: 327.5±45.7cm³, P=0.29). Thus, greater omentectomy surgery in lean dogs produced virtually no measured change in body composition, signifying the relatively modest nature of this surgical intervention.

Although we observed an insignificant reduction in the visceral fat depot of OM-treated dogs, direct quantification of the excised omental membranes revealed that they were composed of 121.4±11.4cm³ fat tissue. Therefore, although the overall MRI-observed alteration in adiposity was subtle, the greater omentum scan images confirm that a noticeable volume of fat was in fact removed (Figure 1C) and the amount was variable among dogs.

**Insulin sensitivity**

Dogs exhibited a wide variability in insulin sensitivity (S_I) prior to treatment at baseline, and there were no differences between treatment groups (P>0.25). Kruskal-Wallis equality-of-populations test revealed a tendency for S_I to increase with OM, and to decrease with SHAM (P=0.078). Despite this negative result, further testing was performed using both parametric and non-parametric analysis. There was a 63.6±31.5% increase in S_I.CLAMP associated with the removal of greater omental fat (pre-OM: 4.55±0.85, post-OM: 7.45±1.18×10⁴ dl·kg⁻¹·min⁻¹·pM⁻¹, P=0.04, Figure 2A), with an upward trend in each omentectomized dog. In contrast, we observed no change in S_I.CLAMP with SHAM-treatment (pre-SHAM: 6.42±0.75, post-SHAM: 6.33±1.75×10⁴ dl·kg⁻¹·min⁻¹·pM⁻¹, P=0.95, Figure 2A). These findings were supported by non-parametric analysis; Wilcoxon revealed increased S_I with OM-treatment from basal (P=0.031), and no change with SHAM-treatment (P=0.56). Any individual variability in S_I following either OM- or SHAM-surgery was accounted for by a corresponding alteration in visceral fat volume (linear regression analysis, P=0.025, Figure 2B).

Hepatic S_I (S_I.EGP) as assessed from EGP suppression during the clamp did not significantly change with either treatment (pre- vs. post-surgery; OM: 0.9±0.2 vs. 1.2±0.5×10⁴ dl·kg⁻¹·min⁻¹·pM⁻¹, P=0.5. SHAM: 1.2±0.2 vs. 1.1±0.2×10⁴ dl·kg⁻¹·min⁻¹·pM⁻¹, P=0.40, Figure 3B). Despite the lack of change in hepatic sensitivity, we observed improvement in the ability of insulin to augment glucose utilization in the periphery in the OM-treated animals only; steady-state R_d levels had a tendency to increase (pre: 10.1±2.1, post: 12.4±1.8mg·kg⁻¹·min⁻¹, P=0.08, Figure 3A). When taken in combination with decreased steady-state insulin levels (pre-OM: 282.2±24.0, post-OM: 229.1±22.4, P=0.17, Figure 3C), S_I.Rd was improved 67.7±35.2% by the surgical removal of omental fat (from 3.5±0.9 to 5.9±1.3×10⁴ dl·kg⁻¹·min⁻¹·pM⁻¹, P=0.03). As expected, there was no effect of SHAM-treatment on R_d timecourse (Figure 3A), plasma insulin (Figure 3C), or S_I.Rd (pre: 5.3±0.5, post: 5.1±1.6×10⁴ dl·kg⁻¹·min⁻¹·pM⁻¹, P=0.87). There was no observed effect of either treatment on FFA suppression by insulin during the clamp (Figure 3D).

**Fasting parameters**

In the pre-surgery state, there were no differences in fasting insulin or FFAs (P>0.2; Table 1) between treatment groups, and there were no corresponding alterations to OM- vs. SHAM-treatment in any dog. Baseline levels of glucose uptake and glucose production were similar between groups (R_d: 2.4±0.1 and 2.4±0.2 mg·kg⁻¹·min⁻¹ in OM and SHAM, respectively, P=0.48). Fasting glucose values only approached significance using the Kruskal-Wallis test (pre-OM: 101±2, post-OM: 97±2, pre-SHAM 93±1, post-SHAM 94±2), all remained within normal physiologic range. Portal
Vein catheters were implanted for the purpose of measuring fasting plasma markers, but had poor patency.

**β-cell function and DI**

We found no measurable effect of omentectomy on β-cell functionality (pre-OM: 6.8±1.4, post-OM: 6.7±1.2pM·mg⁻¹·dl⁻¹, P=0.9, Figure 4A), and only a tendency for DI to increase from 41.8±7.7 to 59.5±10.8 (P=0.12; Figure 4C). SHAM-treatment had no effect on β-cell function (pre: 3.5±0.7, post: 4.4±0.77pM·mg⁻¹·dl⁻¹, P=0.23, Figure 4B), or DI (pre-SHAM: 38.4±5.9, post-SHAM: 45.3±14.5, P=0.55, Figure 4D).

**DISCUSSION**

A number of epidemiological studies have reported visceral fat per se confers a greater risk for metabolic and cardiovascular disease than obesity per se12. In spite of the strong association, the concept that visceral fat is particularly deleterious remains controversial due to the lack of evidence directly implicating visceral fat in insulin resistance. Abate et al13 contends that truncal fat, whether visceral or subcutaneous, is responsible for the pathogenesis of insulin resistance, yet it was clearly demonstrated that the surgical liposuction of abdominal subcutaneous fat failed to improve insulin action14 disputing this latter claim. Still, animal studies aimed at substantiating the especially detrimental role of visceral adiposity in insulin action have been unsuccessful due to the challenging nature of surgically removing “true” visceral fat6 – the mesenteric fat depot-- in rodents. Thus, it remains to be demonstrated whether visceral fat per se is causative of insulin resistance.

Unlike for the rodent, it is not difficult to surgically remove a “true” visceral fat depot in large animals, such as by performing an omentectomy in the dog. The amount of fat stored in the greater omentum can vary widely in normal animals -- from thin and transparent in lean animals, to thick and solidified with adipose tissue in obese ones. Therefore, in contrast to other models of extreme weight loss and generalized adipose reduction- bariatric surgery, low-calorie diets, or pharmacologic supplementation15–omentectomy results in a targeted, diminutive loss of intra-abdominal fat in non-obese dogs. While the initial analysis of the S1 data only approached significance, on further analysis we found that excision of visceral fat increased S1 by 67% - despite the seemingly small 7% reduction of the visceral fat compartment. Interestingly, all OM-animals had a net upward rise in S1, although the change was highly variable among individuals. Sham surgeries in which animals were exposed to similar surgical stress and treatment had no such overall effect on S1.

Our study uniquely demonstrates that a surgical excision of a mere 122 cm³ of omental fat improves insulin sensitivity, lending support to the hypothesis that it is the specific localization of adipose tissue, attributing distinct metabolic significance to fat. The importance of regional adiposity in determination of insulin action has growing evidentiary support; it was previously shown that an implantation of adipose cells into the subcutaneous region of lipoatrophic mice significantly improved insulin action16, while implantation of adipose cells into the visceral region of nude mice increased TNF-α concentrations, resulting in insulin resistance17. Despite the accumulating evidence favoring the harmful nature of visceral fat, we cannot discount that there is communication occurring between the visceral and subcutaneous fat depots that may be responsible for alterations in insulin action. For instance, the removal of epididymal and perirenal fat pads in rats has been shown to alter gene expression in other fat depots18.

We were surprised to find that the excision of omentum enhanced glucose utilization in the periphery, as indicated by a significant increase in the Rₜₕ timecourse during the glucose clamp, but did not appear to alter insulin’s ability to suppress glucose output. While
unexpected, the improvement in peripheral but not hepatic $S_I$ may be explained in several ways. The insulin dose given to these normal animals was sufficient to completely suppress EGP in the omentectomy as well as the sham-operated animals. The liver is more sensitive to insulin than is skeletal muscle, and by performing a dose-response experiment at lower insulin concentrations we might have observed a difference in liver sensitivity. Also, it has been shown by several investigators that much of the effect of insulin to control EGP is indirect, mediated through lipolysis and/or controlled by the central nervous system\textsuperscript{19-20}; therefore omentectomy may not be particularly effective in altering insulin’s indirect effect. It is also feasible that changes in hepatic $S_I$ would have been detectable previous to the three weeks allowed for recuperation from surgery, and that the resulting improvement in peripheral insulin action was a secondary modification. Finally, our data shows that greater omental fat content \textit{per se}, versus other intraabdominal fat tissue (i.e. mesenteric, retroperitoneal), may perhaps directly influence skeletal muscle, though as yet a mechanism for this is not clear.

It is possible that alterations in $S_I$ associated with central adiposity are a result of intricate communication between the insulin-sensitive organs, and a number of moieties secreted by visceral adipocytes may mediate changes in insulin action. Among such secretagogues, it is widely believed that FFAs intercede visceral fat accumulation and insulin resistance\textsuperscript{21}, as FFA elevations have been shown to stimulate tyrosine-kinase activity, and reduce autophosphorylation of the insulin receptor in liver and muscle in animals\textsuperscript{22}. In our study, we did not observe a change in fasting FFA, or insulin-mediated suppression of FFA during the clamp associated with an omentectomy.

Other secretory products of adipocytes, including TNF-$\alpha$, interleukin-6, and MCP-1, are believed to link inflammation and insulin resistance\textsuperscript{23}, and although the mechanism is poorly understood, activation through JNK, IKK$\beta$, and NF-$\kappa$B pathways have been suggested\textsuperscript{24}. Karin and colleagues\textsuperscript{25} have recently shown that disabling the inflammatory pathway by knocking out JNK-1, and inducing obesity with a high-fat diet, attenuated the development of insulin resistance in mice, proving that obesity without inflammation will not produce insulin resistance. The greater omentum is a highly vascularized membrane abundant with macrophages and lymphoid structures\textsuperscript{26}, and therefore it is possible that its excision may reduce the inflammatory response by occupying immune cells, profoundly improving $S_I$ without a change in adiposity. Animals in the present study had chronic indwelling catheters that were exteriorized at the neck, and the persistent opening in the skin potentially causes an elevated inflammatory response that confounds measurements of inflammation. Future studies will investigate the role of adipokines in insulin resistance. Other possibilities that should be investigated include elevated portal vein FFAs and altered secretion of incretin moieties. One or a number of these factors may be involved in the improvement of peripheral insulin action associated with visceral adipose reduction.

Some investigators believe that visceral obesity impairs insulin secretion, purportedly due to elevated portal vein FFA concentrations that may overload the $\beta$-cell and impair fatty acid oxidation\textsuperscript{27}. Our study demonstrated that a rather modest reduction in visceral fat does not alter the insulin secretory response in healthy individuals, indicating no significant direct effect of visceral fat removal on pancreatic $\beta$-cell function. Conversely, it is possible that we did not extract sufficient visceral fat to prompt a response from the $\beta$-cell, or that measurements of glucose-stimulated insulin secretion may have been taken too shortly after surgical treatment. Jimenez \textit{et al}\textsuperscript{28} previously showed that $S_I$, secretion, and clearance all reverted to healthy levels following gastric restrictive surgery, but that the change in insulin secretion occurred subsequent to all other changes.
In conclusion, our findings indicate that the regional distribution of fat per se may be a critical feature conferring the metabolic consequence of adipose tissue, and that a rather minimal reduction in visceral fat by an omentectomy may result in an improvement in $S_I$, suggesting that visceral fat may indeed cause insulin resistance.

Acknowledgments

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References


FIGURE 1. Effect of surgical treatment on adiposity
(A): Abdominal MRI images of representative dogs from OM and SHAM treatment groups. Fat tissue appears yellow while all other tissue appears red. Visceral fat is located within the peritoneal cavity, while subcutaneous fat is outside of the peritoneum. (B): Relative changes in visceral and subcutaneous adiposity in OM and SHAM-treated dogs. (C) Axial MRI images of excised omentum from OM-treated dogs.
FIGURE 2. Effect of surgical treatment on insulin sensitivity
(A) Insulin sensitivity ($\times 10^4$ dl·kg$^{-1}$·min$^{-1}$·pM$^{-1}$) by individual dogs and means ± SE pre- and post-omentectomy (left panel) and sham (right panel) surgery. (B) Linear regression depicting the relationship between change in the visceral adipose volume vs. the change in insulin sensitivity with omentectomy and sham-surgery. *P < 0.05 compared to pre-surgery by paired t-tests.
FIGURE 3. Euglycemic- hyperinsulinemic clamp parameters
Time-course data of glucose uptake (A), glucose production (B), plasma insulin (C), and plasma FFA (D) pre- and post-omentectomy and sham-surgery, respectively. Pre-surgery: closed symbols. Post-surgery: open symbols. *P ≤0.05 compared to pre-surgery by paired t-tests.
FIGURE 4. Pancreatic β-cell function
Pre- and post- omentectomy (A) and sham (B) surgery. The disposition index with omentectomy (C) and sham-treatment (D). Pre-surgery: closed symbols and solid lines; post-surgery: open symbols and dashed lines.
Table 1

Effect of surgical treatment on basal parameters

<table>
<thead>
<tr>
<th></th>
<th>Pre-OM</th>
<th>Post-OM</th>
<th>Pre-SHAM</th>
<th>Post-SHAM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose (mg/dl)</td>
<td>100.2 ± 1.9</td>
<td>97.6 ± 2.4 *</td>
<td>92.6 ± 1.2</td>
<td>94.6 ± 1.6</td>
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<tr>
<td>Insulin (pmol/l)</td>
<td>48.6 ± 8.7</td>
<td>48.8 ± 8.2</td>
<td>42.7 ± 8.8</td>
<td>48.9 ± 7.4</td>
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<td>Glucose uptake (mg/kg/min)</td>
<td>2.4 ± 0.1</td>
<td>2.5 ± 0.2</td>
<td>2.4 ± 0.2</td>
<td>2.3 ± 0.2</td>
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<tr>
<td>Glucose production (mg/kg/min)</td>
<td>2.2 ± 0.1</td>
<td>2.3 ± 0.2</td>
<td>2.4 ± 0.2</td>
<td>2.2 ± 0.1</td>
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<tr>
<td>FFA (mmol/l)</td>
<td>0.86 ± 0.1</td>
<td>0.84 ± 0.1</td>
<td>0.64 ± 0.1</td>
<td>0.7 ± 0.1</td>
</tr>
</tbody>
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Data are mean ± SE.

* P <0.05 vs. pre-surgery.