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Visceral fat adipokine secretion is associated with systemic inflammation in obese humans

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Short running title: Visceral Fat and Inflammation

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ABSTRACT

Although excess visceral fat is associated with non-infectious inflammation, it is not clear whether visceral fat is simply associated with, or actually causes metabolic disease in humans.

To evaluate the hypothesis that visceral fat promotes systemic inflammation by secreting inflammatory adipokines into the portal circulation that drains visceral fat, we determined adipokine arteriovenous concentration differences across visceral fat, by obtaining portal vein and radial artery blood samples, in 25 extremely obese subjects (body mass index [BMI] 54.7±12.6 kg/m^2) during gastric bypass surgery at Barnes-Jewish Hospital in St.Louis, MO.

Mean plasma IL-6 concentration was ~50 % greater in portal vein than in radial artery in obese subjects (P=0.007). Portal vein IL-6 concentration correlated directly with systemic C-reactive protein concentrations (r=0.544, p=0.005). Mean plasma leptin concentration was ~20% lower in portal vein than in radial artery in obese subjects (P=0.0002). Plasma TNFα, resistin, MCP-1, and adiponectin concentrations were similar in portal vein and radial artery in obese subjects.

These data suggest that visceral fat is an important site for IL-6 secretion, and provide a potential mechanistic link between visceral fat and systemic inflammation in persons with abdominal obesity.

Excessive visceral fat (i.e mesenteric and omental fat) is associated with insulin resistance and diabetes (1, 2). Accordingly, waist circumference, which correlates with visceral fat mass (3), has been recommended as a clinical marker to identify patients at increased risk for metabolic diseases (4), and large waist circumference is one of the criteria used to diagnose the *metabolic syndrome* (5). However, the mechanism(s) responsible for the relationship between visceral fat and metabolic abnormalities is not known, and, it is not clear whether visceral fat is simply associated with, or actually causes, metabolic disease.

It has been hypothesized that large amounts of visceral fat causes insulin resistance, because lipolysis of visceral adipose tissue triglycerides releases free fatty acids (FFA) directly into the portal vein, which are then transported to the liver (2). Increased delivery of FFA to the liver impairs insulin's ability to suppress hepatic glucose production, and increased systemic FFA concentration inhibits insulin-mediated glucose disposal in skeletal muscle (6). However, data from studies that examined FFA kinetics in human subjects, suggest it is unlikely that lipolytic activity in visceral fat is a major contributor to insulin resistance (7). On average, about 20% of portal vein FFA and 14% of total FFA that appear in the systemic circulation are derived from lipolysis of visceral fat in obese subjects (7, 8). Therefore, fatty acids released from visceral fat represent only a small percentage of total FFA delivered to liver and muscle tissues.

Visceral fat could cause metabolic abnormalities by secreting inflammatory adipokines, such as interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), macrophage chemoattractant protein 1 (MCP-1) and resistin, which induce insulin resistance and diabetes (9, 10). In contrast, visceral fat might have beneficial metabolic effects by producing adiponectin (11), which increases insulin sensitivity and decreases glucose intolerance and diabetes (12). However, the importance of adipokine production by visceral fat in the pathogenesis of the metabolic abnormalities associated with obesity has not been carefully studied.

The purpose of the present study was to evaluate the relative contribution of inflammatory adipokine (IL-6, TNF-α, MCP-1, resistin, leptin) and adiponectin secretion from visceral fat in insulin-resistant subjects with abdominal obesity. Portal vein and peripheral artery plasma concentrations of adipokines were determined in insulin-resistant extremely obese subjects who had large amounts of visceral fat. We hypothesized that the concentration of inflammatory adipokines would be greater in portal vein than peripheral artery in obese subjects.

RESEARCH DESIGN AND METHODS

Study subjects. Twenty-five subjects with class III upper body obesity (6 men and 19 women; BMI 54.7 ± 12.6 kg/m^2; waist circumference 150± 10 cm, age 42± 9 y), who were scheduled to undergo open gastric bypass surgery, participated in this study. Subjects completed a comprehensive medical evaluation, which included a history and physical examination, an electrocardiogram, and standard blood and urine tests. All obese subjects had evidence of insulin resistance, based on either a history of type 2 diabetes or high homeostasis model assessment (HOMA) score (13). All women who participated in this study were pre-menopausal. Six obese subjects had type 2 diabetes and were treated with insulin and metformin; none were being treated with thiazolidinediones. Each subject provided written informed consent before enrolling in the study, which was approved by the Human Studies Committee of Washington University School of Medicine in St. Louis.

Study Design. Open gastric bypass surgery and upper gastrointestinal tract surgery were performed in the morning at Barnes-Jewish Hospital, after subjects had fasted overnight. During the operation, blood samples were obtained simultaneously from the radial artery and portal vein before gastric stapling or intestinal resection was initiated. Blood samples were immediately transferred to sterile glass EDTA tubes (BD Vacutainer™; BD Biosciences, Oxford, UK), placed on ice, and centrifuged at 2200 *g* for 10 min at 4°C. Aliquots of plasma were then placed in sterile cryovials, snap-frozen in liquid nitrogen and stored at -80°C until subsequent analyses were performed.

Sample Analyses

Commercial RIA kits were used to measure plasma total adiponectin (Linco Research, St.Louis, MO), and commercial ELISA kits were used to measure IL-6, TNF-α, resistin, MCP-1 (Quantakine High Sensitive - R&D Systems, Minneapolis, MN) and plasma CRP (ALPCO Diagnostics, Windham, NH) concentrations. Plasma high molecular weight (HMW) and low molecular weight (LMW) adiponectin was determined by velocity sedimentation and quantitative Western blot analysis (14). Plasma insulin and leptin concentrations were measured by radioimmunoassay (Linco Research, St.Louis, MO).

Statistical Analyses

The statistical significance of differences between blood sampling sites was evaluated by using a Student's *t*-test for paired samples for data that was normally distributed with approximately equal standard deviation values. The statistical significance of differences between groups that were not normally distributed or that had unequal standard deviations was evaluated by using the Wilcoxon two-samples test for variables. Pearson correlation was used to assess associations between continuous variables. Correlation data were log transformed when the data were not normally distributed. A p-value <0.05 was considered statistically significant. All data were analyzed by using SPSS FOR WINDOWS software, version 12.0 (SPSS Inc, Chicago). All values are expressed as means±SD.

RESULTS

Portal vein and peripheral artery blood samples were obtained simultaneously from 25 subjects with extreme obesity (body mass index [BMI] 54.7 ± 12.6 kg/m^2) and large visceral fat mass (waist circumference 150 ± 10 cm) during open gastric bypass surgery. All obese subjects had evidence of insulin resistance based on the homeostasis model assessment (HOMA) of insulin resistance (HOMA-IR) (13).

In obese subjects, mean plasma insulin concentration was more than two-fold greater in the portal vein than in the peripheral artery (34.4±21 and 15.2±8 μU/ml, respectively; p=0.0004). Plasma IL-6 concentration was ~50% higher in portal vein than in peripheral artery (Table 1). Plasma leptin concentration was ~20% lower in portal vein than in peripheral artery (P=0.0002). In contrast, portal vein plasma TNFα, MCP-1, resistin, and total adiponectin concentrations were not significantly different from their peripheral artery concentrations. The percent of adiponectin present as the high molecular weight (HMW) form in portal vein and radial artery were evaluated in a subset of 10 obese subjects; no significant difference in percent HMW adiponectin was found between portal vein (33.1±11%) and artery (28.6±17%). Portal vein IL-6 concentrations correlated directly with arterial C-reactive protein (CRP) concentrations (Figure 1).

DISCUSSION

The importance of adipokines released from visceral fat in the pathogenesis of insulin resistance and systemic inflammation has not been carefully studied in human subjects, because of the difficulty in gaining access to portal vein blood. The portal vein, which drains visceral fat, is the major source of blood supply to the liver and is responsible for approximately 80% of total liver blood flow (15). In the present study, we obtained blood samples from the portal vein and radial artery during open gastric bypass surgery in morbidly obese subjects who had a large amount of intra-abdominal fat. Plasma IL-6 concentrations were much higher in portal vein than in peripheral artery blood in obese, demonstrating that visceral fat is an important source of IL-6 production in obese persons. These data are consistent with previous *ex vivo* findings that IL-6 secretion is greater in omental than in subcutaneous adipose tissue samples (16, 17). Moreover, portal vein IL-6 concentrations correlated directly with arterial CRP concentrations in obese subjects. These results provide the first evidence of a potential mechanistic link between visceral fat mass and systemic inflammation in human subjects.

The direct secretion of IL-6 into the portal vein has important metabolic consequences, because IL-6 stimulates hepatic acute-phase reactant production (18), impairs insulin-mediated glycogenesis (19), and stimulates hepatic gluconeogenesis (20). Increased serum IL-6 concentration is also associated with an increased risk of developing type 2 diabetes and cardiovascular disease (21-23). In our obese subjects, portal vein IL-6 concentrations correlated directly with systemic CRP concentrations, suggesting that IL-6 delivery to the liver contributes to the regulation CRP production. This observation provides a potential mechanism for the relationship between visceral fat and systemic insulin resistance, and supports the possibility that visceral fat is involved in regulating the hepatic production of acute-phase reactants that activate inflammatory pathways (24). These findings are consistent with data obtained from LIKK mice, which found that a localized increase in NF-κB and inflammation in the liver can cause peripheral insulin resistance in skeletal muscle (25). In addition, we have previously found that there is a considerable net release of interleukin-6 from subcutaneous abdominal fat *in vivo*, and this release is greater in obese than in lean subjects (26). Therefore, both visceral and subcutaneous fat depots in obese persons produce a large portion of circulating IL-6 during basal conditions.

Plasma leptin concentrations were lower in portal vein than in peripheral artery blood in our subjects. The decrease in portal vein leptin concentration is consistent with data obtained *in vitro* from isolated adipose tissue, which found that the expression of the *ob* gene, which produces leptin, and leptin secretion are lower in omental than subcutaneous fat (27, 28).

In contrast to IL-6 and leptin, the plasma concentrations of other potential inflammatory adipokines, such as TNF-α, and resistin, were similar in portal vein peripheral artery. These results are not surprising, based on what is known about the production and breakdown of these adipokines. Although TNF-α production is upregulated in visceral fat (29), it is likely that this cytokine acts locally and is not primarily released into the bloodstream. In fact, we have previously found there is no net release of TNF-α from subcutaneous abdominal fat *in vivo* (26). Resistin is exclusively produced by adipocytes in mice (30), but resistin expression in humans is more prominent in monocytes and macrophages (31). Adiponectin circulates in plasma primarily as a low molecular weight (LMW) hexamer and as a larger, multimeric, high molecular weight (HMW) complex (32). The HMW protein, but not the LMW form, has direct beneficial metabolic effects in the liver by increasing hepatic insulin sensitivity and decreasing hepatic glucose production (33-34). In addition, treatment with recombinant adiponectin has been shown to decrease hepatomegaly, steatosis, hepatic inflammation, and serum transaminase concentrations in a mouse model of nonalcoholic steatohepatitis (35). Therefore, preferential production of HMW adiponectin by visceral fat could have direct beneficial metabolic effects on the liver, which might not be identified by only measuring total adiponectin concentrations. However, we found no differences between portal and systemic total, HMW or LMW adiponectin concentrations. These findings suggest that visceral fat is not a major site for adiponectin production.

Fasting plasma insulin concentration was more than two-fold greater in the portal vein than in the peripheral artery blood in the obese subjects, consistent with data reported previously (36). This observation underscores the important strategic anatomical location of both the pancreas and visceral fat, as endocrine organs that regulate hepatic glucose and lipid metabolism. Both tissues are drained by the portal circulation, which provides an efficient system for delivering protein hormones (e.g. insulin) and inflammatory cytokines (e.g. IL-6) directly to the liver, where they can modulate endogenous glucose production and the production of acute-phase inflammatory reactants.

Our study has several important limitations. First, our study was conducted in subjects during postabsorptive conditions, which might not reflect adipose tissue adipokine secretion into the systemic or portal circulations during postprandial conditions. Second, blood samples were obtained during surgery which could have affected plasma adipokine concentrations. General anesthesia can decrease portal blood flow (37), which could increase portal vein adipokine concentrations. However, a decrease in blood flow should have simultaneously affected all adipokines secreted by visceral fat, whereas we found that portal vein IL-6 concentrations were higher and leptin concentrations were lower than in radial artery blood. Third, our study subjects were limited to extremely obese subjects (BMI >40 kg/m^2), who had massive amounts of intra-abdominal fat. Therefore, these results might not necessarily apply to obese persons who have lower BMI values and lesser amounts of intra-abdominal fat. However, we did not find any significant correlation among BMI or waist circumference and portal vein or arterial adipokine concentrations. Fourth, the association we observed between portal vein IL-6 and systemic CRP concentrations does not prove a causal relationship. Additional and very complex studies, involving portal vein infusion of IL-6 inhibitors and recombinant portal vein IL-6, will be needed to prove that portal IL-6 is a major regulator of CRP production.

The results of the present studies support the notion that visceral fat is an important endocrine organ, which is involved in the complex interrelationship between obesity and systemic inflammation. Our findings suggest that increased IL-6 secretion from visceral fat into the portal circulation is involved in the pathogenesis of systemic metabolic abnormalities associated with abdominal obesity.

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access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Figure Legends

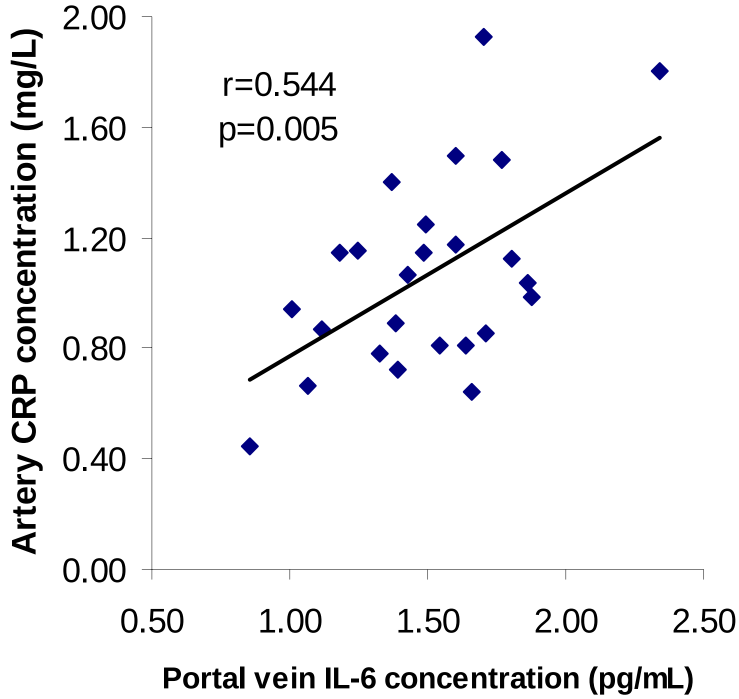
Figure 1. Relationship between portal vein interleukin-6 and systemic C-reactive protein concentrations in extremely obese subjects. Data are log transformed.

Table 1. Radial artery and portal vein plasma adipokine concentrations in obese subjects

Adipokine	Sample site		
	Radial artery	Portal vein	Difference (range)
IL-6 (pg/ml)	28.5 ± 27.6	42.1 ± 41.8*	13.6 ± 23.3 (-16.0–60.4)
TNF-α (pg/ml)	1.87 ± 0.8	1.93± 0.8	0.06 ± 0.2 (-0.4–0.6)
MCP-1 (pg/ml)	205 ± 88	190 ± 99	-14.7 ± 82.2 (-202–198)
Resistin (pg/ml)	18.5 ± 11	18.1 ± 11	-0.4 ± 2.6 (-8.1–4.2)
Leptin (ng/ml)	101 ± 51	81 ± 42**	-19 ± 21 (-80.0–16.0)
Total adiponectin (μg/ml)	14.3 ± 10	14.7 ± 11	0.4 ± 3.1 (-7.0–7.1)

Values are means ± SD
Significantly different from corresponding radial artery value, **P*=0.007; **P=0.0002

Figure 1


Artery CRP concentration (mg/L)
2.00
1.60
1.20
0.80
0.40
0.00
r=0.544
p=0.005
0.50
1.00
1.50
2.00
2.50
Portal vein IL-6 concentration (pg/mL)