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Abdominal subcutaneous and omental adipocyte morphology and its relation to gene expression, lipolysis and adipocytokine levels in women☆

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ABSTRACT

Objective. We tested the hypothesis that women with adipocyte hypertrophy in either omental (OM) or subcutaneous (SC) adipose tissue are characterized by alterations in adipocyte lipolysis and adipose tissue expression of genes coding for proteins involved in adipocyte metabolism or inflammation, independent of overall adiposity and fat distribution.

Methods. OM and SC fat samples were obtained surgically in 44 women (age: 47.1 ± 5.0 years, BMI: 27.7 ± 5.3 kg/m^2). In a given depot, women with larger adipocytes than predicted by the regression of adipocyte size vs. total and regional adiposity measurements were considered as having adipocyte hypertrophy, whereas women with smaller adipocytes than predicted were considered as having adipocyte hyperplasia.

Results. Women with OM adipocyte hypertrophy had significantly lower SC GLUT4 mRNA abundance ($p \le 0.05$), higher SC CEBPB mRNA expression ($p \le 0.05$) as well as higher mRNA expression of OM PLIN ($p \le 0.05$), CD68 ($p \le 0.10$), CD14 ($p \le 0.10$), CD31 ($p \le 0.05$) and vWF ($p \le 0.05$) compared to women with OM adipocyte hyperplasia. OM adipocyte isoproterenol- (10^{-10} to 10^{-5} mol/L), forskolin- (10^{-5} mol/L) and dibutyryl cAMP- (10^{-3} mol/L) stimulated lipolysis was higher in women with hypertrophic OM adipocytes ($p \le 0.05$, for all). Women with SC adipocyte hypertrophy had lower SC mRNA expression of GLUT4 ($p \le 0.10$), higher SC mRNA expression of CEBPB ($p \le 0.05$), lower plasma adiponectin concentrations ($p \le 0.05$) and higher SC adipocyte isoproterenol- (10^{-9} to 10^{-5} mol/L) stimulated lipolysis ($p \le 0.05$) compared to women with SC adipocyte hyperplasia.

Abbreviations: IL-6, Interleukin-6; DXA, dual energy x-ray absorptiometry; BMI, body mass index; HDL, high-density lipoprotein; PPARγ, the nuclear hormone receptor peroxisome proliferator-activated receptor γ; CEBP, CCAAT/enhancer binding protein; PLIN, perilipin; GLUT4, glucose-transporter 4; IRS-1, insulin receptor substrate-1; vWF, von Willebrand Factor; CD31, PECAM-1 (platelet/endothelial cell adhesion molecule 1).

☆ All authors have read and agree to the publication of the manuscript.The authors attest that the manuscript is not currently under consideration, in press, or published elsewhere.

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Conclusion. Hypertrophic adipocytes in both fat compartments are characterized by alterations in adipocyte lipolysis and adipose tissue expression of genes coding for proteins involved in adipocyte metabolism or inflammation.

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1. Introduction

Excess adipose tissue accumulation on the greater omentum and mesentery is strongly related to metabolic complications such as insulin resistance, hyperinsulinemia, hypertriglyceridemia, hypertension and low HDL-cholesterol concentrations [1,2]. Although the overall amount of adipose tissue and central body fat distribution are both associated with metabolic disorders, the size of adipocytes within adipose tissue compartments is also an important predictor of these complications [3–5].

Fat gain under a positive energy imbalance results in adipocyte hypertrophy, which is the enlargement of mature adipocytes, and/or in adipocyte hyperplasia, which is the proliferation and differentiation of preadipocytes [3,6,7]. Large inter-individual variations in adipocyte size are noted as a function of the amount of adipose tissue [8], although average adipocyte size generally increases with fat mass values [3,4,9,10]. Several studies previously reported that subcutaneous and omental adipocyte sizes are strongly related to body composition and fat distribution [3,4,10]. In this context, total and regional adiposity as well as fat cell size seems to be closely associated with adipocyte function and the metabolic alterations of obesity [3,11–13].

Previous studies reported that subcutaneous adipocyte hypertrophy was linked to altered glucose homeostasis [11–13]. More specifically, Arner et al. demonstrated using a detailed characterization of subcutaneous adipocyte cellularity that adipose tissue hypertrophy is related to low insulin sensitivity and high circulating insulin levels independent of body fat mass [3]. Our laboratory demonstrated that only omental adipocyte hypertrophy is associated with altered blood lipids independent of body composition and fat distribution [4]. Adipocyte hypertrophy from both fat compartments also seems to be related to hypertension [14]. These previous associations between adipocyte size and metabolic complications independent of body composition might result from changes in the function of hypertrophied adipocytes in both fat compartments. Very few studies using techniques to separate small from large adipocytes within the same adipose tissue depot have examined the effect of fat cell size on adipocyte regulation. These studies suggested that large fat cells have an increased lipolytic response, altered adipokine secretion patterns and altered gene expression compared to small adipocytes from the same individual [15–19]. However, most of these studies did not examine visceral adipose tissue morphology. To our knowledge, whether omental and subcutaneous adipocyte hypertrophy is related to adipocyte lipolytic rates and markers of adipose tissue metabolism independent of overall and regional adiposity remains unclear in the lean-to-obese range of BMI values.

The aim of the study was to examine if abdominal subcutaneous and omental adipocyte hypertrophy is associated with alterations in gene expression, lipolysis and plasma adipocytokine levels, independent of body fatness and fat distribution. We tested the hypothesis that women with adipocyte hypertrophy in either omental or subcutaneous adipose tissue are characterized by increased adipocyte lipolysis and altered adipose tissue expression of genes coding for proteins involved in adipocyte metabolism or inflammation, independent of adiposity and fat distribution.

2. Materials and Methods

2.1. *Subject recruitment*

The study included 44 healthy women (age 39.6–61.7 years) who elected for total (n = 43) or subtotal (n = 1) abdominal hysterectomies, some with salpingo-oophorectomy of one (n = 6) or two (n = 17) ovaries. Women were recruited through the elective surgery schedule of the Gynecology Unit at Laval University Medical Center. The study was approved by the Research Ethics Committees of Laval University Medical Center. All subjects provided written informed consent before their inclusion in the study.

2.2. *Body fatness and body fat distribution measurements*

Body fatness and body fat distribution measurements were performed on the morning of or within a few days before or after the surgery. Measurements of total body fat mass were determined by dual-energy X-ray absorptiometry (DXA) using a Hologic QDR-4500A densitometer and the whole body fan beam software V8.26a:3 (Hologic Inc., Bedford, MA). Abdominal subcutaneous and visceral adipose tissue cross-sectional areas at the L4–L5 vertebrae were obtained by computed tomography (CT) using a GE Light Speed 1.1 CT scanner (General Electric Medical Systems, Milwaukee, WI), as previously described [20,21].

2.3. *Plasma adipocytokines*

Blood samples were collected on the morning of the surgery after a 12 h fast. Plasma adiponectin levels were measured by a commercially available radioimmunoassay (Linco Research, Missouri, USA). Plasma interleukin-6 (IL-6) levels were measured by a commercially available enzyme-linked immunosorbent assay (R&D Systems, Minneapolis, MN).

2.4. *Adipose tissue sampling*

Subcutaneous and omental adipose tissue samples were collected during the surgical procedure at the site of incision (lower abdomen) and at the distal portion of the greater omentum, respectively. The samples were immediately

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