Worsening of Obesity and Metabolic Status Yields Similar Molecular Adaptations in Human Subcutaneous and Visceral Adipose Tissue: Decreased Metabolism and Increased Immune Response

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Context: It is not known whether biological differences reported between sc adipose tissue (SAT) and visceral adipose tissue (VAT) depots underlie the pathogenicity of visceral fat.

Objective: We compared SAT and VAT gene expression according to obesity, visceral fat accumulation, insulin resistance, and presence of the metabolic syndrome.

Design: Subjects were assigned into four groups (lean, overweight, obese, and obese with metabolic syndrome).

Setting: Subjects were recruited at a university hospital.

Patients: Thirty-two women were included.

Main Outcome Measures: Anthropometric measurements, euglycemic-hyperinsulinemic clamps, blood analyses, and computed tomography scans were performed, and paired samples of SAT and VAT were obtained for DNA microarray-based gene expression profiling.

Results: Considering the two fat depots together, 1125 genes were more and 1025 genes were less expressed in lean compared with metabolic syndrome subjects. Functional annotation clustering showed, from lean to metabolic syndrome subjects, progressive down-regulation of metabolic pathways including branched-chain amino acid, fatty acid, carbohydrate, and mitochondrial energy metabolism and up-regulation of immune response genes involved in toll-like receptor, TNF, nuclear factor-κB, and apoptosis pathways. Metabolism and immune response genes showed an opposite correlation with fat mass, fat distribution, or insulin resistance indices. These associations were similar in SAT and VAT, although about 1000 genes showed differential expression between SAT and VAT.

Conclusions: The increase in adiposity and the worsening of metabolic status are associated with a coordinated down-regulation of metabolism-related and up-regulation of immune response-related gene expression. Molecular adaptations in SAT prove as discriminating as those in VAT. (J Clin Endocrinol Metab 96: E73–E82, 2011)

Obesity is a major risk factor for type 2 diabetes and cardiovascular disease. Insulin resistance is critical in the pathogenesis of type 2 diabetes and is associated with a constellation of disorders known as the metabolic syndrome including central obesity, atherogenic dyslipidemia and hypertension that contributes to the increased risk for cardiovascular morbidity and mortality. The mechanisms leading to an impairment of insulin sensitivity

Abbreviations: AT, Adipose tissue; BMI, body mass index; LE, lean; MS, obese with metabolic syndrome; NF, nuclear factor; OB, obese; OV, overweight; PCA, principal component analysis; PLS-DA, partial least square-discriminant analysis; SAT, sc AT; VAT, visceral AT.
are still poorly understood. Adipose tissue (AT) inflammation and metabolic disturbances have been recognized as essential in the link between an excess of fat mass and the development of insulin resistance (1). Since the pioneering work of Jean Vague, many prospective studies have shown that excess fat in the upper part of the body (i.e. abdominal obesity) is associated with increased mortality and risk for diabetes and cardiovascular complications (2). Differences in the metabolic function, especially lipolysis, and in the secretory capacity of sc and visceral fat depots have been reported (3, 4). The fat depot differences are maintained when adipocyte progenitor cells are differentiated in vitro (5–7). Genes involved in embryonic development and pattern specification may play an important role in differences between adipocytes from different depots (8). However, although transcripts with different levels of expression between fat depots have been identified, it remains unclear whether differential gene expression in sc and visceral fat explains the adverse metabolic complications associated with abdominal obesity (9–13).

The main objective of this study was to determine whether, when compared with sc abdominal AT (SAT), visceral AT (VAT) shows specific molecular signatures associated with obesity status and metabolic complications. Pan-genomic gene expression profiling of SAT and VAT was performed on thoroughly phenotyped lean (LE), overweight (OV), obese (OB), and obese with metabolic syndrome (MS) women. Gene ontology and pathway analyses were combined with measurements of body composition, fat distribution, insulin sensitivity, and other parameters of the metabolic syndrome. We found a strong inverse correlation between metabolism and immune response genes. Metabolism genes were negatively associated with fat mass, visceral fat accumulation, and insulin resistance; the opposite was found for immune response genes. Strikingly, the associations were as strong in SAT as in VAT, suggesting that molecular adaptations in the two depots have the same discriminating power with respect to abdominal obesity and metabolic syndrome.

Subjects and Methods

Subjects

Individuals who have undergone abdominal surgery (laparoscopic or laparotomic cholecystectomy and gastric banding) at the Departments of Surgery at Kravolske Vinohrady Faculty Hospital in Prague were monitored, and 53 women (age 21–66 yr, body mass index (BMI) 17.3–48.5 kg/m²) were included. Subject exclusion criteria were malignancy, inflammatory conditions, congestive heart failure, known coronary heart disease, known endocrinopathy, chronic liver or kidney disease, psychiatric disorders, treatment with antiobesity drugs, and body weight fluctuations more than 2% over the preceding 3 months. According to BMI, presence or absence of the metabolic syndrome evaluated according to the International Diabetes Federation criteria (14), and quality and quantity of total RNA isolated from SAT and VAT, 32 participants were assigned into one of the four groups (LE, OV, OB, and MS). In the selected group of women, 24 were premenopausal and eight were postmenopausal (one in LE group, one in OV group, three in OB group, and three in MS group). Five subjects in the MS group had previously diagnosed type 2 diabetes; one subject was treated with oral antidiabetic drugs. Five subjects in the MS group were on statin therapy. Five subjects (four in the MS group and one in the OB group) followed antihypertensive treatments. Each subject gave written informed consent, and the study was approved by the Ethics Committee of the Third Faculty of Medicine, Charles University, Prague.

Study protocol and statistical analysis of clinical parameters

A clinical investigation was realized 7–14 d before the surgery. Anthropometric measurements, blood sampling, and euglycemic-hyperinsulinemic clamp were performed at rest after an overnight fast. Body composition was evaluated by bioelectrical impedance (QuadScan 4000; Bodystat, Isle of Man, UK). Visceral and sc fat areas were derived from computed tomography scans at the level L4–L5. Blood samples were obtained before the clamp and plasma parameters were measured using standard procedures. Insulin sensitivity was assessed using euglycemic-hyperinsulinemic clamp. Plasma glucose, triacylglycerol, uric acid, high density lipoprotein-cholesterol, and total cholesterol levels were determined using routine laboratory procedures. Plasma insulin concentrations were measured using chemiluminescent immunometric assay (Immulite 2000; Siemens, Deerfield, IL). During the surgical procedure, paired samples of SAT and VAT were obtained by surgical excision and processed immediately. VAT was obtained from the abdominal area lateral to umbilical and VAT came from the omental fat depot defined by its anatomical location and by portal circulation venous drainage. AT was washed in physiological saline, homogenized in RLT lysis buffer (Qiagen, Valencia, CA) and stored at −80 C until total RNA extraction. To compare clinical parameters between the groups of subjects, log-transformed data were analyzed by one-way ANOVA with a Bonferroni post hoc analysis using SPSS version 17.0 statistical software and by principal component (PCA) and partial least square-discriminant analyses (PLS-DA) using SIMCA-P software (Umetrics AB, Umea, Sweden). PLS-DA is a PCA-derived method used to optimize separations between groups of subjects.

Gene expression analysis

Total RNA was isolated from AT samples with RNeasy Mini kit (Qiagen). RNA quantity and quality were checked with the Experion automated electrophoresis system (Bio-Rad Laboratories, Hercules, CA). Whole transcriptome analysis was performed using
were filtered using an average intensity of 1.5 times above the
www.bioconductor.org. Intensity ratios between Cy5 and Cy3
Loess intra-slide normalization followed by quantile inter-slide in-
scanner (Innopsys, Carbonne, France). Images were quantified us-
mendations (Agilent). Arrays were scanned using InnoScan700
ray washing were performed according to manufacturer’s recom-
human sequences and transcripts. Sample preparation and microar-
croarrays with over 41,000 60-mer oligonucleotides from unique
labeled with Cy3 dye (Applied Biosystems/Ambion, Austin, TX).
dna microarrays on SAT and VAT of the selected 32 subjects (15).
Compared with LE:
d–f
a–c
Values are means
formed using DAVID integrated knowledge base and analytic tools
(www.bioconductor.org) and completed by other data mining
tools such as Reactome (http://www.reactome.org/). For each
group of genes, the mean centroid ± SEM was calculated after nor-
malization of gene expression levels to a mean of 0 and a variance
of 1 across all individuals (15). Pearson’s correlation and poly-
nomial regression analyses of gene expression were performed be-
tween the two tissues and rs. clinical parameters. Microarray data
were deposited to Gene Expression Omnibus with GEO Series ac-
cession number GSE24883.

Results

Clinical parameters

Anthropometric and metabolic characteristics of the four
groups of subjects are shown in Table 1. Body weight, fat
mass, waist, waist to hip ratio, total and visceral fat areas,
and, insulin concentrations were lower in the lean group than
in the three other groups. Glucose disposal rate corrected for
body weight or for fat-free mass was lower in MS than in lean
and overweight patients. PLS-DA of clinical data showed
distribution of the four groups of subjects (Supplemental Fig.
1, published on The Endocrine Society’s Journals Online web
site at http://jcem.endojournals.org). Most of the data vari-
ance was explained by two principal components. Component
1 (x-axis) discriminated individuals according to the
degree of obesity. Component 2 (y-axis) separated the
two groups of obese subjects according to the presence or
absence of MS. Six parameters (glucose disposal rate, waist,
wast to hip ratio, insulin, glucose, and triacylglyc-
erol) were the most important variables for the discrimi-
nation of the MS group (contribution scores above 1).
Adipose tissue gene expression profiling

SAT and VAT gene expression profiles were determined in 32 subjects. A flow chart of gene expression analysis is depicted in Fig. 1A. PLS-DA of gene expression data showed separation of the two fat depots and, in each depot, gradation from LE to MS subjects (Fig. 1B). A total of 3019 genes had only fat depot effect, 1391 genes had only group effect, and 1581 genes had group and fat depot effects. Combining data as shown on Fig. 1A, 2972 genes had group effects, and 4600 genes had fat depot effects. Further statistical analyses were performed to identify 1) genes differential between LE and MS groups irrespective

TABLE 2. Functional groups of genes discriminating LE from MS subjects and sc from visceral fat

<table>
<thead>
<tr>
<th>Name</th>
<th>Number of genes</th>
<th>Enrichment score</th>
</tr>
</thead>
<tbody>
<tr>
<td>LE &gt; MS (789 annotated genes)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metabolic process</td>
<td>443</td>
<td>11.7</td>
</tr>
<tr>
<td>Energy, electron transport</td>
<td>65</td>
<td>9.7</td>
</tr>
<tr>
<td>Lipid and fatty acid metabolism</td>
<td>55</td>
<td>2.9</td>
</tr>
<tr>
<td>Amino acid metabolism</td>
<td>30</td>
<td>2.6</td>
</tr>
<tr>
<td>Pyruvate metabolism, tricarboxylic cycle</td>
<td>18</td>
<td>2.0</td>
</tr>
<tr>
<td>Monosaccharide metabolic process</td>
<td>28</td>
<td>2.0</td>
</tr>
<tr>
<td>MS &gt; LE (872 annotated genes)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immune response</td>
<td>188</td>
<td>7.9</td>
</tr>
<tr>
<td>Angiogenesis</td>
<td>25</td>
<td>3.3</td>
</tr>
<tr>
<td>Cell death, apoptosis</td>
<td>62</td>
<td>2.3</td>
</tr>
<tr>
<td>NF-κB cascade</td>
<td>36</td>
<td>2.2</td>
</tr>
<tr>
<td>Immune cell proliferation and activation</td>
<td>29</td>
<td>2.3</td>
</tr>
<tr>
<td>sc fat &gt; visceral fat (413 annotated genes)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lipid and fatty acid metabolism</td>
<td>42</td>
<td>3.3</td>
</tr>
<tr>
<td>Cellular carbohydrate metabolism</td>
<td>21</td>
<td>1.7</td>
</tr>
<tr>
<td>Visceral fat &gt; sc fat (422 annotated genes)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angiogenesis</td>
<td>25</td>
<td>2.2</td>
</tr>
<tr>
<td>Cell death</td>
<td>37</td>
<td>1.1</td>
</tr>
<tr>
<td>Immune and defense response</td>
<td>29</td>
<td>2.0</td>
</tr>
</tbody>
</table>

Genes with Gene Ontology (GO) annotations were analyzed using DAVID Bioinformatics Resource. Enrichment scores used to rank overall importance of annotation term groups were derived from geometric means of all the P values of each annotation term in the group. Fisher’s exact test was used with Benjamini multiple testing correction method.
of difference in the levels of expression in the two AT depots and 2) genes differential between SAT and VAT with no or similar difference in the levels of expression between the four subject groups. For group effect (1), 1025 and 1125 genes were expressed, respectively, at higher and lower levels in MS than in LE subjects (Fig. 1A and Supplemental Table 1). For fat depot effect (2), 492 and 560 genes were expressed at higher and lower levels in SAT than in VAT, respectively (Fig. 1A and Supplemental Table 2). Microarray data were confirmed by quantitative RT-PCR analysis for 51 genes with different expression profiles and ontologies (Supplemental Fig. 2).

**Functional annotation clustering of genes differential between LE and MS subjects**

Of the 1125 genes with lower expression in MS vs. LE groups, six groups of functionally related genes were found to be significantly enriched (Table 2). All the functional groups were related to metabolism and more specifically to branched-chain amino acid, fatty acid, carbohydrate, and mitochondrial energy metabolism. Arising from our previous study (15), 51% of the transcripts in metabolic process were expressed at higher levels in adipocytes compared with other cell types of human AT. Less than 3% of the mRNAs were representative of another cell type of AT. MS was associated with a general down-regulation of metabolic pathways that could lead to fat cells with depressed metabolism (Fig. 2A). Of the 1025 genes with higher expression in MS vs. LE groups, five functional groups were found to be significantly enriched (Table 2). Immune response genes showed the highest degree of enrichment. Genes involved in angiogenesis and apoptosis were represented. Reconstruction of the pathways showed coordinated up-regulation of genes linking Toll-like and TNF receptor signaling to nuclear factor (NF)-κB and apoptotic pathways (Fig. 2B) and genes involved in antigen processing and presentation (Fig. 2C). Sixteen percent of the immune response genes were expressed at higher levels in macrophages compared with other cell types of human AT (15). Mean centroids of genes involved in metabolic process (443 genes of group 1, Table 2) and immune response (188 genes of group A, Table 2) showed, respectively, a progressive decrease and increase in expression from LE to MS subjects (Fig. 3A). When individual data were analyzed, there was a strong inverse relation between metabolic process and immune response that better fitted in polynomial regression (Fig. 3B). The curvilinear regression line suggests a strong interdependence between metabolism and immunity but also that this association appears below a threshold of metabolic activity as revealed by a mean centroid of metabolic process gene expression less than 0.1 (Fig. 3B). Negative correlations existed between
LE more than MS and MS more than LE for each functional group of genes mentioned in Table 2 (r = -0.74; P < 0.0001; n = 64). Correlation between genes of the metabolic process and immune response groups and clinical parameters is shown in Table 3. Adiposity, central obesity, and other parameters that have been related to MS such as uric acid (17) were negatively correlated with metabolism genes and positively correlated with immunity genes, whereas the opposite is observed for insulin sensitivity and fat-free mass. Of note, SAT gene expression of these pathways discriminated the groups as well as VAT gene expression (Fig. 3A), an observation independently supported by PLS-DA analysis of all genes (Fig. 1B). Moreover, similar linear regressions were found in SAT and VAT between mean centroids of metabolic process or immune response genes and visceral fat areas (Fig. 3C).

**Functional annotation clustering and subject group analysis of genes differential between SAT and VAT**

Two functional groups, lipid and carbohydrate metabolism, were enriched in SAT compared with VAT, whereas three functional groups, immune response, cell death, and angiogenesis, were enriched in VAT compared with SAT (Table 2). Higher expression of genes involved in polyunsaturated fatty acid biosynthesis was a characteristic of SAT, whereas the classical complement pathway was a feature of VAT (Supplemental Fig. 3). Expression of several developmental genes suggested to play a role in the functional differences between fat depots showed SAT (Tbx15, HoxC9, and GPC4) and VAT (HoxA5, NRF2A1/COUPTFI) specificity in the present study (8). PLS-DA of fat depot-specific genes that also showed differences between groups of subjects (202 SAT and 177 VAT genes among the 1581 genes in Fig. 1A showing group and fat depot effect) revealed that SAT-enriched genes discriminated MS from LE subjects as well as VAT-enriched genes (Supplemental Fig. 4). Of note, expression of the fat depot-specific genes was as discriminating in SAT as in VAT.

**Discussion**

Excess VAT accumulation in humans is a key feature of abdominal obesity contributing to the development of the metabolic syndrome. It has been reported that VAT and SAT differ in terms of metabolic function, secretory capacity, and inflammatory response. However, it has not been demonstrated that these differences underlie the pathogenic effect of abdominal obesity. In mice, sc fat transplanted ip has a beneficial effect on insulin sensitivity compared with transplanted epididymal fat, suggesting that intrinsic properties of fat depots contribute to the different metabolic complications associated with different fat distributions (18, 19). However, human and rodent fat depots are not comparable (20). In humans, there is no anatomical equivalent of epididymal fat, and sc fat has very different body distribution and functions (e.g. in body insulation). Therefore, investigation of human fat depots in subjects with different degrees of obesity and metabolic complications is warranted. Here, we determined gene expression profiles of paired sc and visceral fat samples in four groups of carefully phenotyped subjects with different degrees of obesity and metabolic complications. The study yielded two important results. First, we found an inverse expression pattern between metabolism and immune response genes in both SAT and VAT, highlighting a strong interdependence in vivo between the two processes. Second, despite the existence of genes showing differential expression between the fat depots, SAT proved as discriminating as VAT with respect to obesity, metabolic complications, and visceral fat accumulation.

Dysfunction of AT is a mediator in the development of obesity complications (21). The main objective of our work was to identify patterns of variations in SAT and VAT mRNA levels associated with adiposity, accumulation of visceral fat, insulin resistance, and parameters of the metabolic syndrome. The progression from the lean to the obese state and further to metabolic syndrome was associated with a down-regulation of genes involved in metabolic processes. The majority of these genes are highly expressed in adipocytes. However, it cannot be ruled out that some metabolic genes are expressed at significant levels in other AT cell types. A more detailed anal-
ysis of the pathways revealed a coordinated repression of fat cell metabolism in both fat depots with diminution of fatty acid and triacylglycerol synthesis, insulin-stimulated glucose uptake, and mitochondrial energy metabolism pathways, notably the tricarboxylic acid cycle and electron transport chain. All these changes concur to evolution toward an adipocyte with low metabolic capacity that can be defined as a hypometabolic fat cell. Interestingly, branched-chain amino acid catabolism was down-regulated in OB and MS subjects as reported in monozygotic twin obese subjects (22). Metabolomic profiling revealed a positive correlation between branched-chain amino acid-related metabolites and insulin sensitivity in humans, and animal studies show that branched-chain amino acids supplemented in a high-fat diet contribute to the development of obesity-associated insulin resistance (23). Only a few adipocyte genes such as 11β-hydroxysteroid dehydrogenase 1 were up-regulated in MS subjects. This observation is in line with the potential deleterious effect of AT cortisol production in the genesis of the metabolic syndrome (24). Increase of fat mass and deterioration of the metabolic profile was also associated with up-regulation of genes involved in the immune response in both fat depots. Components of the toll-like receptor and TNF

FIG. 3. Analysis of the metabolic process and immune response genes according to obesity and metabolic complication status. Metabolic process and immune response genes correspond to functional groups (443 genes for metabolic process and 188 genes for immune response) in Table 2. A, Mean centroid (±SEM) of genes in SAT (●) and VAT (○) AT in the four groups of subjects (LE, OV, OB, and MS). B, Relation between mean centroids of metabolic process and immune response genes in the two fat depots of 32 subjects. C, Linear regression analysis of mean centroids of metabolic process and immune response genes in SAT and VAT vs. visceral fat areas. Plain and dotted lines represent SAT and VAT, respectively.
between metabolism and immunity is reminiscent of the regulation of SAT gene expression during the various phases of a dietary weight loss program (15). Both AT growth and inflammation are modulated by angiogenesis (31, 32). Angiogenic genes were up-regulated in MS subjects and notably angiopoietin-like protein 2, which has recently been shown to promote AT inflammation and systemic insulin resistance (33).

A novel observation was the lack of evidence that VAT gene expression shows better association with the obesity and metabolic profile of the subjects than SAT gene expression. This contention is supported by three lines of evidence. First, when all genes were considered, PLS-DA analysis showed that both SAT and VAT gene expression profiles separated the four groups of subjects. Second, when functional groups of genes were considered, metabolic process and immune response genes showed similar centroids in SAT and VAT in the four groups of subjects. Third, when fat depot specificity in gene expression was considered, SAT enriched genes discriminated LE, OV, OB, and MS subjects as well as VAT enriched genes. This piece of data has several important implications. SAT and VAT seem to have a comparable inflammatory and metabolically harmful profile in OB and MS subjects. Therefore, in a diagnostic perspective, microbiopsy of SAT coupled with quantitative analysis of selected subsets of transcripts may prove highly informative to capture AT dysfunction and predict the development of obesity-associated complications. Moreover, our data support the notion that the pathogenic importance of VAT may not primarily be related to intrinsic differences with SAT. However, the data do not rule out a specific role for VAT, e.g. due to its anatomical location, which leads to production of fatty acids and adipokines directly drained by the portal vein to the liver (34, 35).

However, a substantial fraction of genes showed differential expression between the fat depots. A series of studies have investigated differential gene expression between SAT and VAT (10–13, 36). Our work confirms previous findings such as high expression of components of the complement pathways in VAT and considerably expanded the number of regulated genes (10). The lower expression of lipid and carbohydrate metabolism genes and higher expression of immune response genes in VAT may partly be related to smaller fat cell size and higher number of macrophages in VAT compared with SAT (37–39). The differences in metabolic [e.g. lipolysis as shown before (7) and polyunsaturated fatty acid synthesis as shown here] and endocrine properties of adipocytes from the two depots suggest developmental heterogeneity. Our data support the evidence provided by Gestal et al. (8) of a role for genes involved in embryonic development and

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**TABLE 3.** Pearson’s correlation coefficients between clinical parameters and mean centroids of metabolic process and immune response genes in both adipose tissue depots

<table>
<thead>
<tr>
<th>Metabolic process</th>
<th>Immune response</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>−0.78</td>
</tr>
<tr>
<td>Weight</td>
<td>−0.75</td>
</tr>
<tr>
<td>Fat mass</td>
<td>−0.76</td>
</tr>
<tr>
<td>Fat-free mass</td>
<td>0.73</td>
</tr>
<tr>
<td>Waist</td>
<td>−0.83</td>
</tr>
<tr>
<td>Waist to hip ratio</td>
<td>−0.82</td>
</tr>
<tr>
<td>Total fat areas</td>
<td>−0.76</td>
</tr>
<tr>
<td>Visceral fat areas</td>
<td>−0.81</td>
</tr>
<tr>
<td>Uric acid</td>
<td>−0.64</td>
</tr>
<tr>
<td>Insulin</td>
<td>−0.80</td>
</tr>
<tr>
<td>Glucose disposal rate</td>
<td>0.58</td>
</tr>
</tbody>
</table>

Only the highest correlations are reported: $P < 0.0001; n = 64.$
pattern specification in body fat depot distribution. Interestingly, the same group recently confirmed that developmental genes have unique expression signatures in the various fat depots and showed that their expression levels showed little variation according to obesity status (40). These data in mice and our data in humans therefore strongly suggest that the molecular mechanisms underlying fat depot differences are distinct from those governing the pathogenicity of AT.

To conclude, the progression from normal-weight healthy status toward obesity, increased accumulation of visceral fat, and metabolic syndrome is associated with a coordinated down-regulation of metabolism and up-regulation of immune response gene expression. The data provide a model in which evolution toward a hypometabolic phenotype of fat cells favors the development of a remodeling phenotype of AT through modulation of inflammation and angiogenesis. Importantly, this evolution is observed both in SAT and VAT, despite the confirmation that SAT and VAT show distinct molecular signatures, thus challenging the common view that intrinsic molecular differences between the two fat depots explain the adverse effect of visceral fat accumulation. Further work is warranted to identify the factors leading to impaired adipocyte metabolism and to determine the precise kinetics of events.

Acknowledgments

We are indebted to Zuzana Parizkova (Department of Sports Medicine, Third Faculty of Medicine), Marie-Adeline Marques, and Carine Valle (Inserm Unité 858) for technical expertise.

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Disclosure Summary: The authors have nothing to disclose.

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