Impact of Physical Inactivity on Adipose Tissue Low-Grade Inflammation in First-Degree Relatives of Type 2 Diabetic Patients

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OBJECTIVE—First-degree relatives (FDRs) of patients with type 2 diabetes may exhibit a disproportionately elevated risk of developing insulin resistance, obesity, and type 2 diabetes when exposed to physical inactivity, which to some unknown extent may involve low-grade inflammation. We investigated whether subjects who are nonobese FDRs show signs of low-grade inflammation before or after exposure to short-term physical inactivity.

RESEARCH DESIGN AND METHODS—We studied 13 healthy FDR subjects and 20 control (CON) subjects matched for age, sex, and BMI before and after 10 days of bed rest (BR). Insulin sensitivity was measured by the hyperinsulinemic-euglycemic clamp. Key low-grade inflammation mediators were measured in arterial blood and microdialysate from subcutaneous abdominal (SCAAT) and femoral adipose tissue. Adipokine mRNA expression was determined in SCAAT.

RESULTS—Before BR, FDR subjects displayed insulin resistance, elevated plasma C-reactive protein, leptin, and monocyte chemoattractant protein (MCP)-1, high interleukin (IL)-6, and MCP-1 expressions, as well as low adiponectin and leptin expressions. FDR subjects responded to BR by decreasing plasma adiponectin and IL-10 expression and increasing plasma expression of IL-10 and tumor necrosis factor-α. In contrast, CON subjects responded to BR by increasing plasma adiponectin and adiponectin expression and by decreasing SCAAT microdialysate leptin.

CONCLUSIONS—Young and nonobese FDR of patients with type 2 diabetes exhibit low-grade inflammation, which is further and disproportionately aggravated when exposed to physical inactivity. The study provides support for the notion that people at increased risk of type 2 diabetes should avoid even short periods of physical inactivity.

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Human adipose tissue produces a variety of inflammatory mediators that act locally in the adipose tissue and systemically, leading to obesity-associated low-grade inflammation. Many of the inflammatory mediators can regulate insulin action in skeletal muscle and adipose tissue (1,2) and form putative links between adipose tissue and systemic metabolism (3). Chronic low-grade inflammation is pathophysiologically related to the development of type 2 diabetes and atherosclerosis.

Physical inactivity contributes to a positive energy balance and the induction of obesity, but the relation between physical inactivity and low-grade inflammation may be independent of obesity. In a cross-sectional design, a low level of physical activity was associated with elevated plasma levels of interleukin (IL)-6 and C-reactive protein (CRP) independently of obesity (4). A review by Hamer (5) found an inverse association between the level of physical activity and one or more inflammatory markers in 27 of 40 observational studies after adjusting for measures of fitness. Furthermore, physically active individuals consistently demonstrated low concentrations of CRP. Recent intervention studies found that exercise training downregulated markers of chronic inflammation such as IL-6 and alanine aminotransferase (6,7). However, it is not known if physical inactivity per se in a longitudinal design upregulates inflammatory markers and changes molecular mechanisms relevant to the development of type 2 diabetes.

First-degree relatives (FDRs) of type 2 diabetic patients bear a high lifetime risk of developing insulin resistance and represent a genetic model for studies into the cause of type 2 diabetes. Individuals who progress to type 2 diabetes display features of low-grade inflammation years before onset of the disease, suggesting that low-grade inflammation is involved in the pathogenetic processes (6,8). The objective of the current study was to investigate adipose tissue and systemic markers of low-grade inflammation in healthy, nonobese FDR and control (CON) subjects and in a longitudinal design to explore the effect of physical inactivity on these markers.

RESEARCH DESIGN AND METHODS—The data are part of a larger study on the influence of physical inactivity in healthy and prediabetic subjects as initiated and funded within the framework program of the European Union EXGENESIS (Health Benefits of Exercise: Identification of Genes and Signalling Pathways Involved in Effects of Exercise on Insulin Resistance, Obesity and the Metabolic Syndrome) consortium.
Inactivity deteriorates low-grade inflammation

Subjects
The study participants were 33 young healthy men and included 13 FDRs of patients with type 2 diabetes and 20 CON subjects without any family history of diabetes. The groups were matched with respect to age, BMI, and cardiorespiratory fitness. The purpose and potential risk of the study were explained to subjects before they gave written informed consent. The study was approved by the ethical committee of Copenhagen and Frederiksberg, Denmark (protocol no. [01]-2625±46). Inclusion criteria were male, white, age 20–30 years, fasting plasma glucose <6.1 mmol/L, VO_{2}max 35–55 mL/kg/min, and BMI 18.5–24.9 kg/m².

Pre-and post-testing
Fasting plasma glucose was determined in capillary blood using an ABL 625 (Radiometer, Copenhagen, Denmark). Body composition was determined by dual-energy X-ray absorptiometry full-body scanning (DPX-IQ 4.7e, Lunar Radiation Corporation, Madison, WI). VO_{2}max was measured using a bicycle ergometer exercise protocol by means of an Oxycon Pro System (Jaeger, Hochberg, Germany).

Study design
All subjects participated in one experimental day approximately 3 weeks before 10 days of strict bed rest (BR). On day 10 of the BR period, subjects participated in a second and identical experimental day. Four days before the first experimental day and during the BR period, subjects were provided a standardized isocaloric diet (55 E% carbohydrates, 15 E% protein, 30 E% fat) and wore an Actiheart, a combined accelerometer and heart rate sensor (Cambridge Neurotechnology, Cambridge, U.K.). Subjects were instructed to continue their usual activities of daily living during the 4 days and in the 3 weeks before the BR period and to refrain from vigorous physical activity 24 h before the first experimental day. During the BR period, subjects remained in bed all day under surveillance.

Experimental day protocol
The experimental day consisted of a 210-min baseline period, followed by a 180-min hyperinsulinemic (40 mU/min/m², Actrapid, Novo Nordisk, Copenhagen, Denmark) euglycemic clamp, as described previously (9). Microdialysis catheters were inserted and microdialysate was sampled during the last 60 min of baseline and the last 60 min of the clamp period. Subcutaneous adipose tissue blood flow was measured continuously, as previously described (10). An arterial catheter was inserted in the brachial artery for blood sampling. A venous catheter was inserted in the medial antecubital vein for infusion of insulin and glucose.

Microdialysis
Large-pore microdialysis probes were manufactured in the laboratory from semipermeable hollow fibers (Plasmalloy OP-05, Asahi Medical Co., Tokyo, Japan) with a molecular mass cutoff >950 kDa (11). An 18-gauge cannula was used to insert four microdialysis probes into the subcutaneous abdominal adipose tissue (SCAAT) and four probes into subcutaneous femoral adipose tissue (SCFAT), as described previously (11). The probes were perfused with Ringer acetate containing glucose (2 mmol/L) using a high-precision CMA100 syringe pump (CMA Microdialysis AB, Solna, Sweden) at a rate of 1 μL/min.

Biochemical analysis
Blood samples for analysis of adipokines and CRP were distributed in iced tubes containing 1.5 mg EDTA, and for analysis of insulin, the tubes contained 500 Kallikrein inhibitor units TrasyloL and 15 mg of EDTA per mL of blood.

Plasma and microdialysate adiponec- tin were measured by a human radioimunoassay kit (Linco Diagnostics Inc., St. Charles, MO). The intra- and interassay coefficients of variation were 9.3 and 1.8%. Plasma and microdialysate IL-10, IL-6, tumor necrosis factor-α (TNF-α), monocyte chemoattractant protein-1 (MCP-1), and leptin were analyzed by solid-phase protein immunonochemical assays (LumineX 100S, Ramcon A/S, Birkerød, Denmark). Microdialysate IL-10 was analyzed using a LINCoplex kit (Human Cardiovascular Disease, Panel 3, HCVD3–67CK, Linco Research, St. Charles, MO). The intra- and interassay coefficients of variation were 8.3 and 11.2%. Microdialysate IL-6 and TNF-α as well as microdialysate and plasma leptin and MCP-1 were analyzed using a MILLIPLEX MAP kit (Human Serum Adipokine, Panel B, HADK2–61K–B, Millipore Corp., St. Charles, MO). The intra- and interassay coefficients of variation were 7.8 and 18.0% for IL-6, 7.9 and 15.0% for leptin, 7.8 and 16.0% for TNF-α, and 7.9 and 18.0% for MCP-1. Plasma TNF-α, IL-6, and IL-10 were analyzed using a MILLIPLEX MAP kit (High Sensitive Human Cytokine Kit, HSCYTO–60SPMX13, Millipore Corp.). The intra- and interassay coefficients of variation were 3.5 and 3.8% for TNF-α, 3.5 and 4.5% for IL-6, and 3.3 and 11.8% for IL-10. Plasma insulin was analyzed by ELISA technique (DAKO Diagnostics, Cambridge, U.K.). Plasma CRP was measured with a CRP (Latex) HS Kit (Roche, Mannheim, Germany).

Adipose tissue biopsies
SCAAT biopsy specimens were collected in the basal state and at the end of a 180-min hyperinsulinemic (80 mU/min/m²) euglycemic clamp before BR and on day 9 of the BR intervention using the Bergstrom biopsy needle technique. Specimens were frozen in liquid nitrogen and stored at −80°C.

Determination of mRNA levels
Total RNA was isolated using Trizol reagent (Gibco BRL, Life Technologies, Roskilde, Denmark), and cDNA was made with random hexamer primers using the GeneAmp PCR kit (Applied Biosystems, Carlsbad, CA). GAPDH was used as a housekeeping gene. Quantification was performed with a SYBR Green real-time PCR assay, as previously described (12).

Statistical analysis
Data were analyzed using a linear mixed model where results are adjusted for variation within individuals. The model estimates differences between mean values. SAS 9.1 software (SAS Institute, Inc., Cary, NC) was used for statistical analysis.

Figures 1 and 2 show absolute means ± SE, and the differences and 95% CI described in the results are from the linear mixed model. If data were not normally distributed or homogeneous, as assessed by residual plots of each dependent variable, log-transformed data were used in the linear mixed model and significant effects described as relative (%) differences.

We evaluated the effect of groups (CON and FDR), BR (before vs. after), and time (baseline or insulin stimulated), and tested for differential effects of BR between the FDR and the CON groups. We also evaluated regional differences in microdialysate fluid proteins (SCAAT vs. SCFAT) at baseline and after BR. Threshold for significance was P ≤ 0.05. The Bonferroni corrected P value that is equivalent to an uncorrected P = 0.05 in the current study is P = 0.0028, although
Plasma concentrations of adipokines in the basal (no pattern) and the insulin-stimulated state (patterned) before (gray) and after (black) BR in CON and FDR subjects. Before BR: CON (n = 22) and FDR (n = 13). After BR: CON (n = 20) and FDR (n = 13). A: Adiponectin: *insulin-stimulated state before vs. after BR in CON (P = 0.04); **basal (P = 0.04) and insulin-stimulated state (P = 0.04) before vs. after BR in FDR. B: IL-6: no significant differences. C: TNF-α: *basal state after BR in CON vs. FDR (P = 0.05); *basal state before vs. after BR in FDR (P = 0.02). D: Leptin: *basal (P = 0.02) and **insulin-stimulated state (P = 0.03) before BR in CON vs. FDR; *basal (P = 0.02) and **insulin-stimulated state (P = 0.04) after BR in CON vs. FDR. E: MCP-1: *basal (P = 0.006) and **insulin-stimulated state (P = 0.03) before BR in CON vs. FDR; *basal (P = 0.0004) and **insulin-stimulated state (P = 0.003) after BR in CON vs. FDR. F: IL-10: *basal state before vs. after BR in FDR (P = 0.01). Data were log-transformed before statistical test. Mean data are shown with the SE.
Figure 2—Adipokine mRNA expression relative to GAPDH in the basal (no pattern) and the insulin-stimulated state (patterned) before (gray) and after (black) BR in CON and FDR subjects. A: Adiponectin mRNA expression: *basal ($P = 0.001$) and **insulin-stimulated state ($P = 0.002$) before BR in CON vs. FDR; *basal ($P = 0.02$) and **insulin-stimulated state ($P = 0.02$) after BR in CON vs. FDR; “basal state before vs. after BR in CON ($P = 0.04$). Data were log-transformed before statistical test. Before BR: CON (basal: $n = 16$, insulin: $n = 13$) and FDR (basal: $n = 10$, insulin: $n = 11$). After BR: CON (basal: $n = 15$, insulin: $n = 15$) and FDR (basal: $n = 10$, insulin: $n = 11$). B: IL-6 mRNA expression: *basal ($P = 0.002$) and **insulin-stimulated state ($P = 0.03$) before BR in CON vs. FDR; *basal ($P = 0.002$) and **insulin-stimulated state ($P = 0.03$) after BR in CON vs. FDR. Data were log-transformed before statistical test. Before BR: CON (basal: $n = 16$, insulin: $n = 14$) and FDR (basal: $n = 10$, insulin: $n = 11$). After BR: CON (basal: $n = 16$, insulin: $n = 14$) and FDR (basal: $n = 10$, insulin: $n = 11$). C: TNF-α mRNA expression: no significant differences. Data were log-transformed before statistical test. Before BR: CON (basal: $n = 15$, insulin: $n = 14$) and FDR (basal: $n = 10$, insulin: $n = 11$). After BR: CON (basal: $n = 16$, insulin: $n = 16$) and FDR (basal: $n = 10$, insulin: $n = 11$). D: Leptin mRNA expression: *basal ($P = 0.006$) and **insulin-stimulated state ($P = 0.01$) before BR in CON vs. FDR; *basal ($P = 0.02$) and **insulin-stimulated state ($P = 0.04$) after BR in CON vs. FDR; 1, basal vs. insulin-stimulated state.
this correction is likely overly conservative.

**RESULTS**

**Anthropometrics and physical activity**

The FDR group was characterized by increased body fat percentage compared with the CON group (23.0 ± 2.3% vs. 17.4 ± 1.7%, P < 0.05) and increased abdominal adiposity (trunk/total fat mass: 0.58 ± 0.001 vs. 0.48 ± 0.1, P < 0.05) but similar BMI (24.9 ± 0.9 vs. 24.1 ± 0.5 kg/m², P > 0.05). In response to BR, no changes in anthropometrics were observed. Total, resting, and activity-related energy expenditure, as well as the physical activity score on Actiheart recordings, did not differ between groups during daily living and decreased in both groups during BR, as described previously (10). VO_{2max} did not differ between FDR and CON groups before BR (39.1 ± 1.4 vs. 43.5 ± 1.3 mL O₂/kg/min, P > 0.05) and did not change in response to BR.

**Whole-body insulin sensitivity**

Before BR, whole-body insulin sensitivity (M value) was lower in the FDR compared with the CON group (4.3 ± 0.5 vs. 6.8 ± 0.5 mg/min/kg, P < 0.05), and BR decreased the M value in both FDR (P = 0.007) and CON subjects (P = 0.0001), as described previously (10).

**Subcutaneous adipose tissue blood flow**

SCFAT blood flow did not differ between groups and did not change in response to BR or insulin stimulation. SCFAT blood flow was lower before BR in FDR subjects compared with CON subjects during insulin stimulation (data not shown). SCFAT blood flow did not change in response to BR or insulin stimulation.

**Arterial plasma adipokines, CRP, and insulin.**

Levels of basal plasma leptin (Fig. 1D), MCP-1 (Fig. 1E), CRP, and insulin were higher in FDR than in CON subjects (difference between groups: leptin: 5.369 pg/mL [95% CI 1.031–9.708], P = 0.02; MCP-1: 29.3 [9.0–49.6], P = 0.006; CRP: 0.68 mg/dL [0.26–1.10], P = 0.003; and insulin: 15.6 pmol/L [2.1–29.0], P = 0.02).

Plasma adiponectin decreased in FDR subjects in response to BR (decrease: 1,060 pg/mL [95% CI 81–2,038], P = 0.04 [basal]; 692 pg/mL [20–1,365], P = 0.04 [insulin-stimulated]) and increased in CON (increase: 825 pg/mL [32–1,619], P = 0.04 [insulin-stimulated]). Basal plasma TNF-α and IL-10 increased in response to BR only in FDR subjects (increase: 2.4 pg/mL [0.52–4.32], P = 0.02; 54% [12–113], P = 0.01, respectively).

**Microdialysate adipokines in subcutaneous abdominal and femoral adipose tissue.**

SCFAT microdialysate IL-6 was lower in the FDR compared with the CON group (difference between groups: 399.8 pg/mL [95% CI 32–768], P = 0.03 [basal, before BR]), whereas SCAAT microdialysate IL-10 was lower in the FDR compared with the CON group (difference between groups: 17.6 pg/mL [0.52–34.6], P = 0.04 [insulin-stimulated, before BR]; Table 1).

In response to BR, basal SCAAT microdialysate leptin decreased in CON subjects (decrease: 64% [95% CI 20–84], P = 0.01). In CON subjects, but not in FDR subjects, SCAAT microdialysate IL-10 increased during insulin stimulation (increase: 14.9 pg/mL [5.5–24.3], P = 0.004 [before BR]; 18.9 pg/mL [9.7–28.2], P = 0.0004 [after BR]).

In CON subjects, microdialysate leptin was higher in SCAFAT than in SCAAT (difference: 314 pg/mL [95% CI 84–543], P = 0.01 [before BR]; 214 pg/mL [28–399], P = 0.03 [after BR]; Table 1). In FDR subjects, basal microdialysate IL-6 was higher in SCAFAT than in SCAAT before BR (difference: 636 pg/mL [257–1,015], P = 0.003).

**mRNA expression of adipokines in subcutaneous, abdominal adipose tissue**

Adiponectin (Fig. 2A) and leptin (Fig. 2D) expressions were lower in the FDR compared with the CON group (difference between groups: adiponectin: 93% [95% CI 31–99], P = 0.001 [basal]; 86% [53–96], P = 0.002 [insulin-stimulated]; leptin: 86% [47–96], P = 0.006 [basal]; and 84% [33–96], P = 0.01 [insulin-stimulated]). IL-6 (Fig. 2B) and MCP-1 (Fig. 2E) expressions were higher in the FDR compared with the CON group (difference between groups: IL-6: 75% [42–89], P = 0.002 [basal]; 56% [7–79], P = 0.03 [insulin-stimulated]; and MCP-1: 0.0009 [0.0002–0.0016], P = 0.02 [basal]).

In CON subjects, basal adiponectin expression increased in response to BR (increase: 45% [95% CI 2–69], P = 0.04). In the FDR group, basal IL-10 expression decreased in response to BR (decrease: 77% [24–93], P = 0.02) and adiponectin and IL-10 expressions increased upon insulin stimulation after BR (increase: adiponectin: 97% [80–99.5], P = 0.0009; IL-10: 75%, [13–93], P = 0.03). In CON subjects, leptin and MCP-1 expression increased in response to insulin stimulation before BR (increase: leptin: 49% [14–70], P = 0.02; MCP-1: 0.0025 [0.0002–0.0048], P = 0.04).

**CONCLUSIONS**—The key finding is that nonobese, insulin-resistant individuals with a family predisposition for type 2 diabetes exhibit low-grade inflammation and, importantly, as little as 10 days of physical inactivity negatively affected the condition. The FDR and CON groups both exhibited decreased whole-body insulin sensitivity in response to BR.

The anti-inflammatory, antidiabetic, and antiatherogenic properties of adiponectin are mediated through a reciprocal association between adiponectin and CRP (13). A low adiponectin expression, as in our FDR subjects, may play a pathogenic role in the development of insulin resistance and is probably the result of an increased level of CRP and proinflammatory cytokines. Indeed, we found higher plasma CRP and IL-6 gene expression in adipose tissue in FDR subjects than in CON subjects. TNF-α is a potent stimulator of IL-6 expression and secretion (1) and a potent inhibitor of adiponectin (14). The higher plasma TNF-α, as demonstrated...
in our FDR subjects, may partly explain the higher gene expression of SCAAT IL-6 and the lower gene expression of adiponectin. Because TNF-α and IL-6 are both known to reduce the expression of insulin receptor substrate-1, GLUT-4, and peroxisome proliferator–activated receptor-γ in adipocytes as well as decrease insulin-stimulated glucose transport (1,15), these factors may hold important functions for the insulin resistance found in FDRs.

Failure of adipocytes to adapt to energy storage is associated with reduced production of adiponectin and increased secretion of cytokines such as TNF-α (16,17), thus linking metabolic homeostasis and inflammation and suggesting that adipogenesis is pivotal for modulation of inflammation, which was also previously demonstrated by Menghini et al. (18). Increased TNF-α and decreased adiponectin, as in our FDR subjects, suggests that adipogenesis in these individuals is affected and plays a central role for the inflammatory condition.

Higher plasma concentrations of leptin have been found in insulin-resistant FDR subjects, and a positive correlation between serum leptin and body fat percentage has been found in both FDR and CON subjects (19); hence, the higher plasma leptin in our FDR subjects could simply be explained by their ~50% higher fat mass. Confirming previous findings (11), we found higher microdialysate leptin in SCFAT compared with SCAAT in CON subjects.

MCP-1 recruits monocytes, inducing macrophage infiltration in adipose tissue, and even hypophysiological levels of MCP-1 induced robust insulin resistance in human skeletal muscle cells (20). Interestingly, we found higher circulating MCP-1 and higher SCAAT expression of MCP-1 in FDR subjects than in CON subjects, suggesting an involvement of this adipokine in insulin resistance in FDRs.
The effect of physical inactivity on plasma TNF-α was pronounced in FDR subjects. Adipose tissue macrophages are a major source of TNF-α, which could indicate that macrophages infiltrate adipose tissue and secrete TNF-α in response to physical inactivity. Adipose tissue from obese individuals contains a higher number of macrophages than from lean subjects, and we previously demonstrated that a 15-week lifestyle intervention reduced the expression of macrophages and inflammatory proteins in adipose tissue of severely obese subjects (12).

Participants of the current study did not gain fat mass during the BR period; hence, the increase in plasma TNF-α must be ascribed to physical inactivity per se. Plasma TNF-α is the soluble fraction generated from membrane TNF-α caused by TNF-α converting enzyme (TACE) activity. TACE activity in the current study was measured indirectly by its substrates soluble intracellular adhesion molecule 1 and soluble vascular cell adhesion molecule 1 (data not shown), and both were increased by BR only in FDR subjects, supporting previous findings of a linkage between TACE activity and TNF-α (21).

A BR-induced decrease in plasma adiponectin, as found in the FDR subjects, could impair adipocyte differentiation (22) and induce enlargement of adipocytes and development of obesity during prolonged periods of physical inactivity. However, SCAAT expression of adiponectin and plasma adiponectin were upregulated in CON individuals in response to BR, indicating a compensatory action to the BR-induced reduction in whole-body insulin sensitivity. Interestingly, plasma IL-10 was upregulated in FDR subjects in response to BR. IL-10 modulates intramuscular fatty acid–derived metabolites and inhibits proinflammatory cytokine secretion and action (23,24). Thus, elevation of plasma IL-10 could be a compensatory mechanism in FDR subjects in response to the attenuated low-grade inflammation after BR. SCAAT microdialysate leptin was downregulated in CON subjects in response to BR, which could be explained by a decrease in adipose tissue lipid turnover (25). To maintain homeostasis, these adaptations are rational, but whether the adaptations persist if the period of physical inactivity is prolonged is unknown.

In conclusion, these data demonstrate that nonobese, insulin-resistant individuals with a family disposition to type 2 diabetes exhibit low-grade inflammation indicating dysregulation of adipose tissue. An equally important finding was that as little as 10 days of physical inactivity severely deteriorated the condition of low-grade inflammation in FDR subjects. The findings emphasize a particular importance of avoiding even short periods of physical inactivity in people at increased risk of type 2 diabetes.

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