

Increased Subcutaneous and Epicardial Adipose Tissue Production of Proinflammatory Cytokines in Cardiac Surgery Patients: Possible Role in Postoperative Insulin Resistance

Jaromir Kremen, Marketa Dolinkova, Jana Krajickova, Jan Blaha, Katerina Anderlova, Zdena Lacinova, Denisa Haluzikova, Lenka Bosanska, Martin Vokurka, Stepan Svacina, and Martin Haluzik

Third Department of Medicine (J.Kre., M.D., J.Kra., K.A., Z.L., D.H., L.B., S.S., M.H.) and Departments of Anesthesia, Resuscitation, and Intensive Medicine (J.B.), Sports Medicine (D.H.), and Pathophysiology (M.V.), First Faculty of Medicine, Charles University and General University Hospital, Prague 2, Czech Republic

Context: Hyperglycemia and insulin resistance frequently occur in critically ill patients even without a history of diabetes.

Objective: Our objective was to study the role of adipose tissue hormonal production in the development of insulin resistance in cardiac surgery patients.

Participants, Interventions, and Settings: Fifteen patients with elective cardiac surgery underwent blood sampling before, at the end, and 6, 12, 24, 48, and 120 h after the end of their operation. Epicardial and sc adipose tissue sampling was done at the beginning and at the end of surgery in the Department of Cardiac Surgery.

Main Outcome Measures: We measured serum concentrations and sc and epicardial adipose tissue mRNA expression of IL-6, monocyte chemoattractant protein-1 (MCP-1), TNF- α , leptin, resistin, and adiponectin and sc and epicardial adipose tissue mRNA expression of CD14, CD45, and CD68.

Results: The rate of insulin infusion required to maintain euglycemia increased up to 7-fold 12 h after the operation, suggesting the development of insulin resistance. Serum IL-6 levels increased 43-fold 12 h after surgery. MCP-1 peaked 6-fold at the end of surgery. Smaller peaks of TNF- α and leptin appeared 6 and 12 h after surgery, respectively. Resistin levels peaked 4-fold 24 h after surgery, but adiponectin levels were not significantly affected. TNF- α and CD45 mRNA expression increased markedly during the operation in sc adipose tissue. IL-6, resistin, and MCP-1 mRNA expression increased in both sc and epicardial adipose tissue. Leptin, adiponectin, CD14, and CD68 mRNA expression did not change significantly.

Conclusions: Both sc and epicardial adipose tissue is a source of proinflammatory cytokines in cardiac surgery patients and may contribute to the development of postoperative insulin resistance. (*J Clin Endocrinol Metab* 91: 4620–4627, 2006)

INCREASED INCIDENCE OF obesity and type 2 diabetes worldwide stimulated intensive research focusing on the detailed etiopathogenesis of its relationship. During the last decade, a lot of new knowledge has been gained in this field, including the discovery of endocrine function of adipose tissue (1, 2). It is now generally accepted that adipose tissue secretes numerous hormones and cytokines that can have both insulin resistance-inducing and insulin-sensitizing effects (3, 4). Endocrine dysfunction of adipose tissue together with an excessive ectopic lipid storage in nonadipose tissues such as liver and muscle is now considered the major player in the etiopathogenesis of obesity-related insulin resistance (5, 6).

Increased blood glucose levels and decreased sensitivity to insulin effects frequently occur also in critically ill patients even without previous history of diabetes mellitus (7). Numerous studies have documented that increased blood glucose levels worsen morbidity and mortality in critically ill

patients (8, 9) and that intensive insulin therapy aimed at maintaining euglycemia markedly improves the outcome of these patients (10, 11).

The etiopathogenesis of insulin resistance in critically ill patients is still only partially understood and likely includes some of the mechanisms analogical or similar to that of obesity-induced insulin resistance and other processes. Major pathophysiological conditions underlying hyperglycemia in critical illness include enhanced hepatic gluconeogenesis, impaired insulin secretion, and decreased insulin sensitivity due to anti-insulin effects of stress hormones and proinflammatory cytokines (7, 9, 12). The exact mechanisms at the molecular level still remain to be elucidated.

Although the involvement of adipose tissue hormones in the obesity-induced insulin resistance has been studied extensively (3, 4), there is scarce information about its changes in critically ill patients. Recently, epicardial adipose tissue has been identified as a source of several proinflammatory cytokines and has been implicated as a possible player in the development of coronary artery disease (13, 14). Here we studied the dynamic changes of several proinflammatory and antiinflammatory adipose-tissue-derived hormones both on the systemic and local level as measured by changes of its mRNA expression in sc and epicardial adipose tissue.

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Abbreviations: ICU, Intensive care unit; MCP-1, monocyte chemoattractant protein-1.

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We demonstrate that both epicardial and sc adipose tissue becomes a significant source of proinflammatory factors after major elective cardiac surgery operation and thus may contribute to the development of insulin resistance in these patients.

Subjects and Methods

Study subjects

Fifteen patients (five men and 10 women; mean age, 68 ± 3 yr; mean body mass index, 26.6 ± 1.2 kg/m²) who had major elective cardiac surgery (10 patients with aorto-coronary bypass, five with valvular plastic) were included in the study. Three of the patients had type 2 diabetes and were on insulin therapy, and eight of the patients had arterial hypertension. None of the patients had malignant tumor, thyroid disease, or acute infectious disease. All patients on the intensive care unit (ICU) were treated by continuous iv insulin infusion (Actrapid HM; Novo Nordisk, Baegsvard, Denmark) using an internal glucose control protocol to maintain normoglycemia (4.4–6.1 mmol/liter). Written informed consent was signed by all participants before being enrolled in the study. The study was approved by the Human Ethical Review Committee, First Faculty of Medicine, and General University Hospital, Prague, Czech Republic, and was performed in accordance with the guidelines proposed in the Declaration of Helsinki.

Anthropometric examination and sampling

Anthropometric examination of the patients was performed at basal state 1 d before surgery. All subjects were measured and weighed, and body mass index was calculated.

Blood samples for hormonal measurement were taken at basal state (before the start of anesthesia), at the end of surgery, and 6, 12, 24, 48, and 120 h after the end of surgery. Serum was obtained by centrifugation, and the samples were subsequently stored in aliquots at -70 C until further analysis.

Samples of the sc and epicardial adipose tissue for mRNA expression analysis were taken at the beginning and before the end of surgery. sc samples were from the thoracic region. All of the samples (both at the beginning and at the end of operation) were taken from approximately same location in all of the patients. The samples were obtained from the tissue that had not been previously traumatized mechanically or by cauterization to avoid the influence of local damage on tissue parameters. Tissue samples were collected to RNAlater reagent (QIAGEN, Hilden, Germany) and stored at -70 C until further analysis. The average time between the withdrawal of the sample at the beginning and at the end of surgery was 252 ± 27 min.

Blood glucose was monitored in hourly intervals during first 48 h of stay on ICU and in 1- to 4-h intervals based on the actual glucose levels afterward. Insulin infusion was started at the time of admission to ICU (within 5 min after the end of surgery). The insulin infusion rate was adjusted according to an internal glucose control protocol aiming to maintain blood glucose within euglycemic limits (4.4–6.1 mmol/liter).

Hormonal and biochemical assays

Blood glucose was measured on an ABL 700 analyzer (Radiometer Medical A/S, Copenhagen, Denmark). Serum concentrations of insulin, IL-6, TNF- α , leptin, and monocyte chemoattractant protein-1 (MCP-1) were measured using human serum adipokine LINCOPlex Kit (panel B) on a Luminex200 instrument (Linco Research, St. Charles, MO). Sensitivity was 1.6 pg/ml for IL-6, 85.4 pg/ml for leptin, 0.14 pg/ml for TNF- α , 0.14 pg/ml for MCP-1, and 50.9 pg/ml for insulin. Intra- and interassay variability of the kit was 1.4–7.9 and less than 21%, respectively.

Serum adiponectin concentrations were measured by commercial RIA kit (Linco Research). Sensitivity was 1.0 ng/ml, and the intra- and interassay variability was 1.8 and 9.3%, respectively. Serum resistin concentrations were measured by commercial ELISA kit (BioVendor, Brno, Czech Republic, Czech Republic). Sensitivity was 0.2 ng/ml, and the intra- and interassay variability was 3.1 and 6.5%, respectively. Serum cortisol concentrations were measured using a cortisol RIA kit

(Immunotech, Prague, Czech Republic). Sensitivity was 10 nmol/liter, and the intra- and interassay variability was 5.8 and 9.2%, respectively.

Determination of mRNA expression

Approximately 100 mg of tissue was collected and added to 1 ml RNA stabilization reagent (RNAlater; QIAGEN) and stored at -80 C until further analysis. Total RNA was extracted from sc and epicardial adipose tissue by homogenization with an ULTRA-TURRAX T 18 basic (IKA Werke GmbH, Staufen, Germany) using the RNeasy lipid tissue mini kit (QIAGEN). The RNA concentration was determined from absorbance at 260 nm (BioPhotometer; Eppendorf AG, Hamburg, Germany). All samples had a 260/280-nm absorbance ratio of 1.89 ± 0.1 . The integrity of the RNA was checked by visualization of 18S and 28S ribosomal bands on 1% agarose gel with ethidium bromide. Total RNA (0.1–1 μ g) was used for RT to synthesize the first-strand cDNA using the oligo(dT)₁₈ primers following the instructions of the RevertAid First Strand cDNA synthesis kit (Fermentas Life Science, Vilnius, Lithuania). Measurements of adiponectin and leptin gene expression were performed on a LightCycler 2.0 instrument (Roche Diagnostics GmbH, Mannheim, Germany), using LightCycler FastStart DNA Master SYBR Green I kit (Roche Diagnostics) and specific DNA primers. Measurements of resistin, IL-6, MCP-1, TNF- α , CD14, CD45, and CD68 gene expression were performed on an ABI PRISM 7500 instrument (Applied Biosystems, Foster City, CA) using TaqMan Universal PCR Master Mix, NO AmpErase UNG, and specific TaqMan gene expression assays (Applied Biosystems).

All PCRs for each gene were amplified separately. Controls with no template cDNA were performed with each assay, and all samples were run at least in duplicate. The increase in fluorescence was measured in real time, and data were obtained as threshold cycle (C_T) values. To compensate for variations in input RNA amounts and efficiency of RT, β_2 -microglobulin (B2M) was used as an endogenous reference and results were normalized to these values. Relative gene expression of genes was calculated using the formula $2^{-\Delta\Delta(CT_{\text{cytokine}} - CT_{\text{B2M}})}$.

Statistical analysis

The statistical analysis was performed on SigmaStat software (SPSS Inc., Chicago, IL). The results are expressed as means \pm SEM. Changes of hormonal levels and gene expression during perioperative and postoperative state, respectively, were evaluated using repeated-measures ANOVA or paired *t* test as appropriate.

Results

Blood glucose levels and insulin requirements

The mean blood glucose level during the first 48 h of stay on the ICU was 6.5 ± 0.13 mmol/liter, and mean 48-h insulin consumption was 204 ± 37.6 IU (Table 1). The average insulin infusion rate was 4.01 ± 0.77 IU/h (Table 1). Glucose concentrations, insulin infusion rate, and serum insulin levels during first 48 h of the ICU stay are shown in Fig. 1.

Serum hormonal and cytokine concentrations

Serum concentrations of insulin, resistin, IL-6, MCP-1, TNF- α , adiponectin, leptin, and cortisol at the basal state and

TABLE 1. Clinical and biochemical characteristics of the cardiac surgery patients

	n or mean \pm SD
No. of subjects (male/female)	15 (5/10)
Body mass index (kg/m ²)	26.2 ± 2.54
Age (yr)	68 ± 10
Baseline blood glucose (mmol/liter)	6.61 ± 2.31
Mean blood glucose (mmol/liter)	6.58 ± 0.40
Insulin dose (IU/24 h)	102.5 ± 58.2
Insulin infusion rate (IU/h)	4.02 ± 2.35

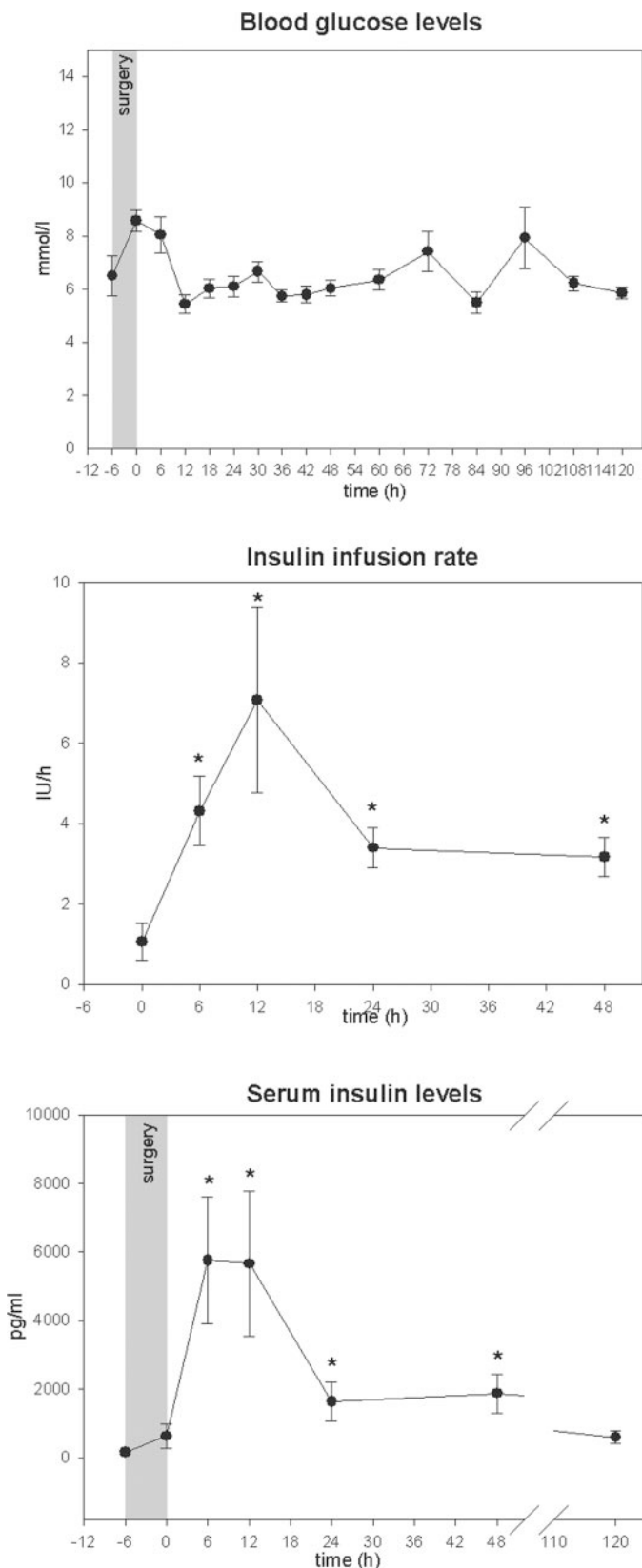


FIG. 1. Blood glucose levels, insulin infusion rate, and serum insulin levels in cardiac surgery patients. Samples for insulin measurements were taken at baseline (before the start of anesthesia, marked as -6 h), immediately after the end of surgery (time 0), and 6, 12, 24, 48, and

during the postoperative period up to 120 h after surgery are shown in Figs. 1 and 2, respectively. All of the serum hormonal concentrations with the exception of adiponectin were significantly affected by the operation. The time pattern of changes of insulin and IL-6 was very similar. Both insulin and IL-6 levels increased moderately after the operation, peaked 6 and 12 h after surgery, respectively, and remained two to three times elevated even 120 h after surgery (Figs. 1 and 2). Serum TNF- α showed a two-peak pattern, with increments at 6 and 20 h after the end of surgery (Fig. 2). Leptin levels doubled 6 h after the end of surgery, peaked 12 and 24 h after surgery, respectively, and normalized until 120 h after surgery (Fig. 2). MCP-1 levels peaked at the end of surgery (3-fold increase over the baseline) and returned to basal levels 48 h after the operation (Fig. 2). Resistin levels showed the slowest pattern of increase with peaks 24 and 48 h after surgery, respectively, remaining still 2-fold elevated 120 h after the end of the operation (Fig. 2). In contrast, serum adiponectin concentrations tended to decrease only during the operation and returned to preoperative levels 120 h after the end of surgery (Fig. 2). None of the changes of adiponectin levels reached statistical significance. Serum cortisol levels increased after the end of surgery, peaked 12 h after the end of surgery, and normalized 120 h after the end of surgery (Fig. 2).

Changes of mRNA expression of selected adipose tissue-derived hormones and cytokines

At baseline, TNF- α mRNA expression was significantly higher in epicardial relative to sc adipose tissue, whereas no significant differences between the two adipose tissue depots were found for leptin, adiponectin, resistin, MCP-1, and IL-6 expression (Fig. 3). In contrast, surgery induced major increases in IL-6 and MCP-1 mRNA in both sc and epicardial adipose tissue (Fig. 3). Resistin mRNA expression also significantly increased postoperatively in both sc and epicardial adipose tissue, although this increase was quantitatively less significant relative to IL-6 and MCP-1. TNF- α mRNA expression increased in sc but did not significantly change in epicardial adipose tissue (Fig. 3). No significant changes in sc or epicardial adipose tissue expression of leptin or adiponectin mRNA were detected (Fig. 3).

Changes of mRNA expression of immunocompetent cell markers

mRNA expression of CD14 (macrophage and monocyte marker), CD45 (monocyte, T lymphocyte, B-lymphocyte, and granulocyte marker), and CD68 (macrophage, monocyte, and polymorphonuclear cell marker) was measured in both sc and epicardial adipose tissue at the beginning and at the end of surgery. All three markers were detectable in both sc

120 h after the end of surgery. Samples for blood glucose measurements were taken at baseline (before the start of anesthesia, marked as -6 h) and then hourly for first 48 h after the end of surgery and 1–4 hourly for the next 72 h. For clarity, the graph shows only 4-hourly values for the first 48 h and 12-hourly values for the next 72 h. Values are mean \pm SE with $n = 15$ per group. Statistical significance is from repeated-measures ANOVA; *, $P < 0.05$ vs. baseline value.

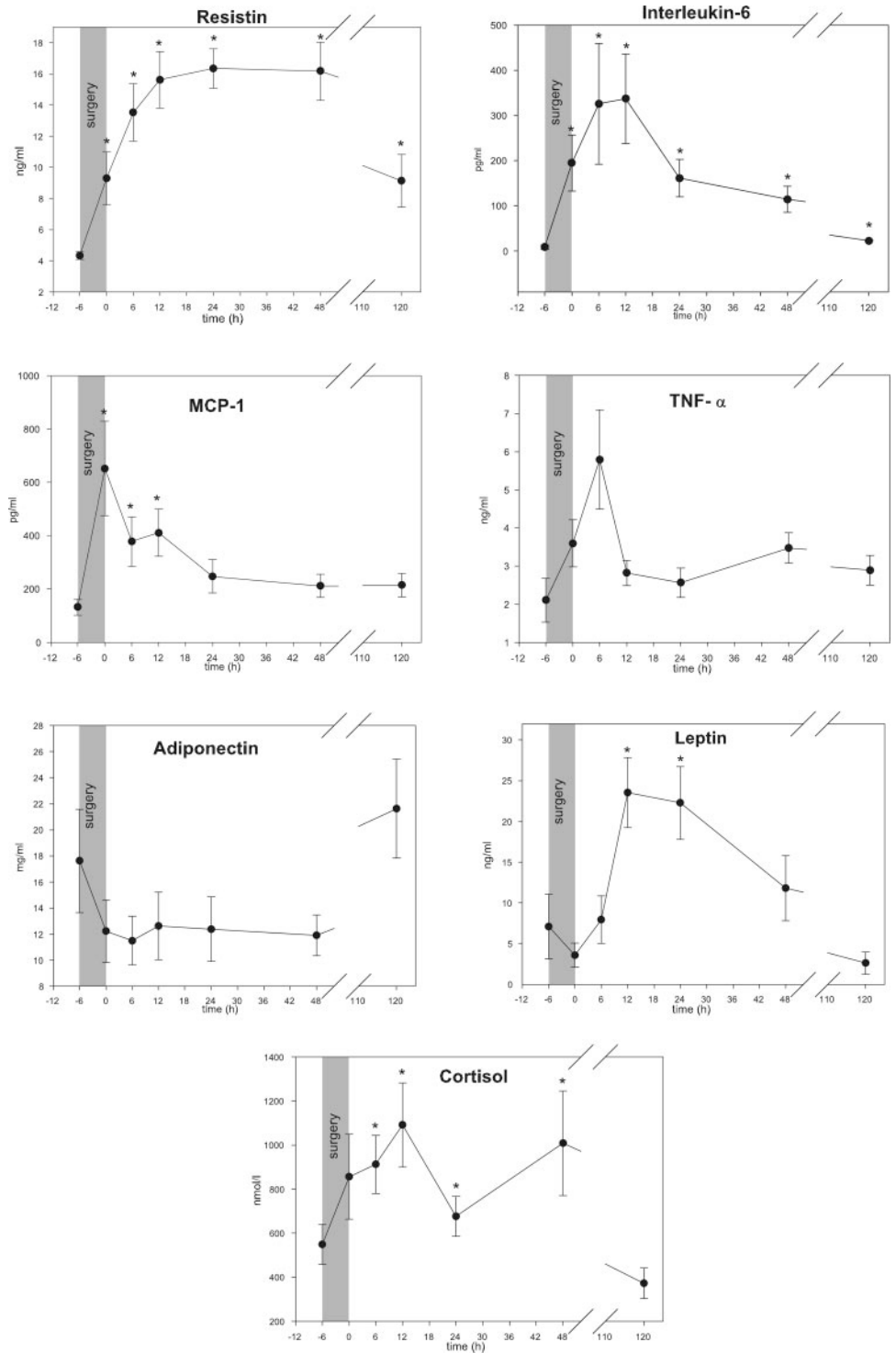


FIG. 2. Serum concentrations of resistin, IL-6, MCP-1, TNF- α , adiponectin, leptin, and cortisol in cardiac surgery patients. Samples were taken at baseline (before the start of anesthesia, marked as -6 h), immediately after the end of surgery (time 0), and 6, 12, 24, 48, and 120 h after the end of surgery. Values are mean \pm SE with n = 15 per group. Statistical significance is from repeated-measures ANOVA; *, $P < 0.05$ vs. baseline value.

and epicardial adipose tissue, indicating the presence of immunocompetent cells in both adipose tissue depots (Fig. 4). The presence of CD68-positive cells was further confirmed by immunohistochemistry with anti-CD68/KP1 antibody (data not shown).

At baseline, CD45 and CD68 mRNA expression was higher in epicardial vs. sc depot (Fig. 4). Operation increased CD45 expression in sc adipose tissue relative to baseline

values but did not affect its mRNA expression in epicardial adipose tissue or CD14 and CD68 mRNA in any adipose tissue depot (Fig. 4).

Discussion

The most important finding of this study is that both epicardial and sc adipose tissue can produce significant

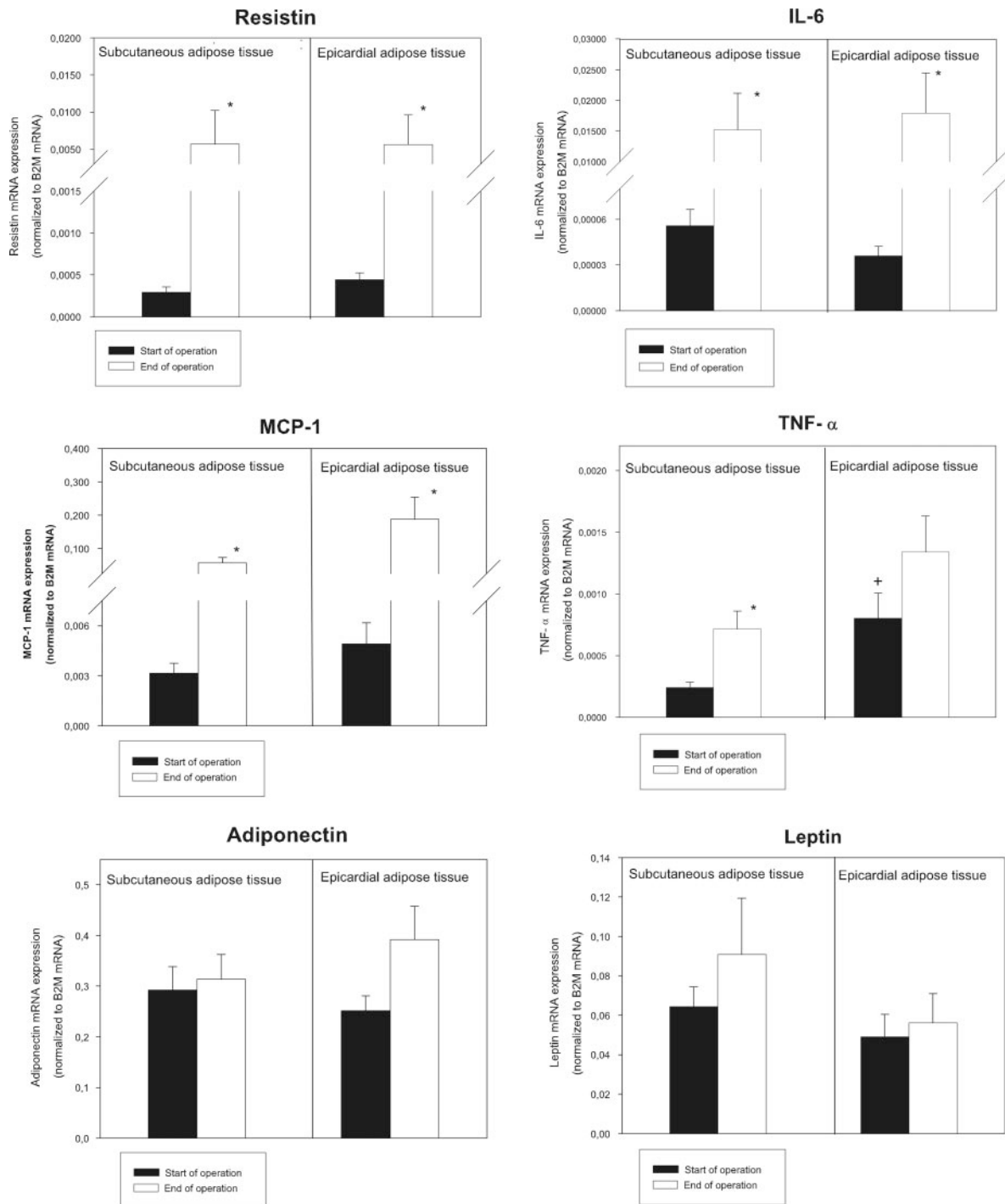


FIG. 3. mRNA expression of resistin, IL-6, MCP-1, TNF- α , adiponectin, and leptin in sc and epicardial adipose tissue samples taken at the beginning (*black bars*) and at the end (*white bars*) of surgery. Values are mean \pm SE with $n = 15$ per group. Statistical significance is from paired or unpaired *t* test; *, $P < 0.05$ vs. baseline expression in the same adipose tissue depot; +, $P < 0.05$ for sc vs. epicardial adipose tissue taken at the beginning of surgery.

amounts of proinflammatory factors after activation of the immune system and stress axis by major cardiac surgery. Epicardial adipose tissue as a source of inflammatory mediators under basal conditions has been identified previously (13, 14), although it has not yet been described how adipose tissue responds to a major stressor such as cardiac surgery.

Here we measured classical proinflammatory cytokines

such as TNF- α , more recently discovered substances such as resistin and MCP-1, and the only known adipose tissue-derived factor with major insulin-sensitizing and antiinflammatory properties, adiponectin, together with circulating insulin and cortisol levels. Surgery markedly increased the amount of exogenous insulin necessary to maintain euglycemia as well as circulating insulin levels, suggesting the

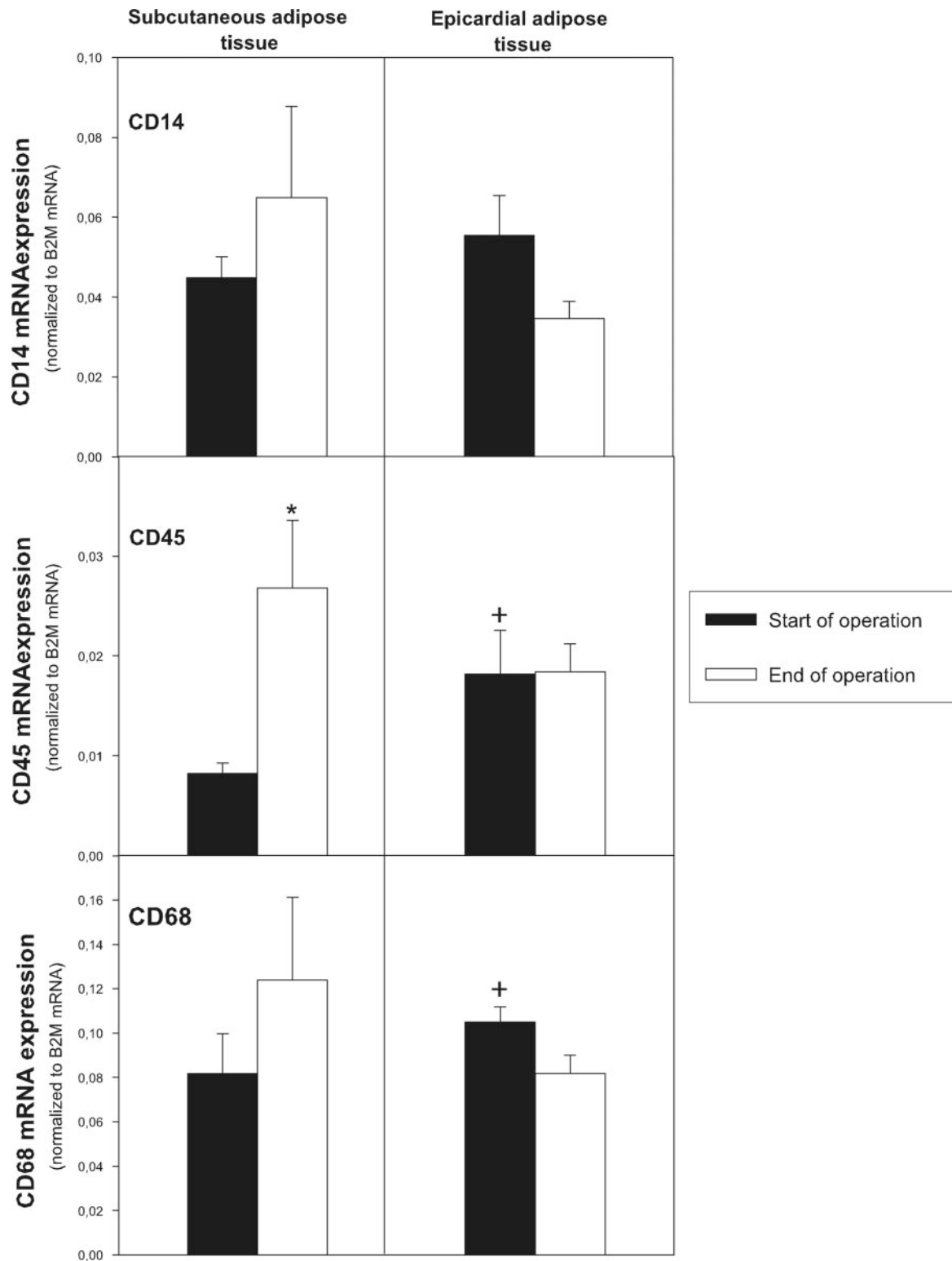


FIG. 4. mRNA expression of CD14, CD45, and CD68 in sc and epicardial adipose tissue samples taken at the beginning (*black bars*) and at the end (*white bars*) of surgery. Values are mean \pm SE with $n = 15$ per group. Statistical significance is from paired or unpaired *t* test; *, $P < 0.05$ vs. baseline expression in the same adipose tissue depot; +, $P < 0.05$ for epicardial vs. sc adipose tissue taken at the beginning of surgery.

development of insulin resistance. It has to be noted that the level of insulin resistance has not been directly measured in this study, but its presence in the postoperative period in

surgical patients has been documented by others previously (15, 16). Circulating concentrations of all proinflammatory factors increased markedly during the postoperative period.

Even more interestingly, the increase of the above-mentioned hormones appeared not only on the systemic level but also on the level of mRNA expression in adipose tissue as early as 4 h after surgery.

Another important finding of this study is the time pattern of the changes of proinflammatory cytokines levels. MCP-1 concentrations peaked as early as after the end of the operation followed by later peaks of TNF- α , IL-6, and resistin, respectively. These findings are in agreement with the concept of infiltration of adipose by macrophages that is initiated by the adipose tissue production of MCP-1 (17, 18). Activated macrophages that migrate to the adipose tissue produce proinflammatory cytokines and thus markedly contribute to the overall immune system activation. Excessive infiltration of adipose tissue by activated macrophages in obesity is considered one of the reasons for increased production of proinflammatory adipokines seen in obesity and type 2 diabetes (17–19). Here we measured mRNA expression of three immunocompetent cell markers, CD14, CD45, and CD68, to assess the role of this process in the production of proinflammatory cytokines. We found that mRNA expression of CD45, the marker of the presence of monocytes, T- and B-lymphocytes, and granulocytes, increased in sc but not epicardial adipose tissue at the end of surgery. In contrast, the other two markers, CD14 and CD68, were not affected by the operation. This suggests that even in relatively lean subjects participating in our study, a significant amount of immunocompetent cells is present in both sc and epicardial adipose tissue at the beginning of surgery. The lack of an acute increase of two of three immunocompetent cell markers at the end of surgery may indicate that both immunocompetent cells chronically residing in adipose tissue and those migrating there as a result of surgery are involved in the increased production of proinflammatory cytokines by adipose tissue. Taken together, our data suggest that adipose tissue may represent an important source of immunocompetent cells used to respond to different forms of stressors including metabolic stress in obesity and surgical stress in cardiac surgery patients as demonstrated here.

Although the possible involvement of epicardial adipose tissue in the production of IL-6, TNF- α , and MCP-1 has been described previously (13, 20), its role in the production of resistin has not been extensively studied so far. In the only report available, Baker *et al.* (14) found resistin expression in epicardial adipose tissue comparable to that in abdominal sc and visceral adipose tissue and higher than in gluteal sc adipose tissue. Here we did not see significant differences in resistin mRNA expression between epicardial and sc adipose tissue from the thoracic region and found a postsurgical increase in its expression in both sc and epicardial adipose tissue.

Resistin was originally discovered as an adipocyte-derived hormone increased in obesity and was suggested to link obesity to insulin resistance (21). Additional studies revealed that its major role in humans may lie in its proinflammatory rather than insulin resistance-inducing action and that in humans it is produced by activated immunocompetent cells rather than adipocytes (22–25). Here we show for the first time that resistin behaves similarly to other proinflammatory cytokines, being increased by operational

stress. Thus at least in cardiac surgery patients, it may in concert with other proinflammatory factors contribute to the development of insulin resistance. The exact source of resistin and other proinflammatory cytokines within the adipose tissue (adipocytes *vs.* immunocompetent cells in the stroma-vascular fraction) has not been addressed in this study. However, our preliminary data on another group of cardiac surgery patients indicate that resistin is produced almost exclusively by the stroma-vascular fraction (our unpublished data), which is in agreement with previously published data in visceral adipose tissue of lean humans (25). Taken together, the finding of increased adipose tissue mRNA expression of proinflammatory cytokines underlines its possible contribution in the development of insulin resistance of critically ill patients.

In addition to proinflammatory mediators, adipose tissue also produces adiponectin, a protein hormone with significant insulin-sensitizing, antiinflammatory, and antiatherosclerotic properties (4, 26, 27). In contrast to proinflammatory factors such as resistin, IL-6, TNF- α , and MCP-1 markedly affected by the cardiac surgery, no significant changes were detected in serum adiponectin levels or its adipose tissue mRNA expression. This suggests that in contrast to resistin, IL-6, TNF- α , and MCP-1, the changes in circulating adiponectin levels are probably not involved in the etiopathogenesis of insulin resistance in critically ill patients. However, it has to be noted that by measuring total adiponectin levels we may have missed the changes of its circulating fractions that can also modulate insulin sensitivity as was demonstrated previously (28).

Despite an attractive hypothesis of a significant role for adipose tissue-derived factors as important players in the insulin resistance of critically ill patients, it is important to interpret our findings cautiously. First, mRNA expression of adipose tissue-derived factors was measured only in sc adipose tissue in the thoracic region and epicardial adipose tissue in our study, and it is unknown whether such changes also appear in other fat deposits. Second, circulating monocytes and macrophages activated by the operation can also significantly contribute to the circulating pool of proinflammatory cytokines. It is also important to note that many other factors in addition to proinflammatory cytokines such as cortisol, catecholamines, GH, and other stress-related factors can significantly contribute to the development of insulin resistance in critically ill patients (29). For example, cortisol has been found to induce insulin resistance in both muscle (30) and liver (31), and its decrease by adrenalectomy under experimental conditions markedly decreased hyperglycemia and improved insulin sensitivity in different rodent models of insulin resistance (32, 33). Conversely, increased cortisol levels in patients with endogenous hypercortisolism such as Cushing syndrome induce insulin resistance that disappears after normalization of cortisol levels by appropriate treatment (33, 34). Cortisol levels were significantly elevated in the postoperative period in our study and therefore very likely contributed to the development of insulin resistance together with other stress-induced hormones (29).

In summary, we have demonstrated that both sc and epicardial adipose tissue becomes an important source of proinflammatory factors in patients with major cardiac surgery.

These factors together with other hormonal and metabolic changes contribute to the development of insulin resistance in these patients. Our finding suggests that therapeutic approaches suppressing proinflammatory factor production in adipose tissue may represent a new modality of prevention and/or treatment of insulin resistance in critically ill patients.

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Address all correspondence and requests for reprints to: Martin Haluzik, M.D., Ph.D., Third Department of Medicine, First Faculty of Medicine, Charles University, U Nemocnice 1, 128 08, Prague 2, Czech Republic. E-mail: mhalu@lf1.cuni.cz.

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References

- Hotamisligil GS, Shargill NS, Spiegelman BM 1993 Adipose expression of tumor necrosis factor- α : direct role in obesity-linked insulin resistance. *Science* 259:87–91
- Zhang Y, Proenca R, Maffei M, Barone M, Leopold L, Friedman JM 1994 Positional cloning of the mouse obese gene and its human homologue. *Nature* 372:425–432
- Havel PJ 2002 Control of energy homeostasis and insulin action by adipocyte hormones: leptin, acylation stimulating protein, and adiponectin. *Curr Opin Lipidol* 13:51–59
- Haluzik M, Parizkova J, Haluzik MM 2004 Adiponectin and its role in the obesity-induced insulin resistance and related complications. *Physiol Res* 53: 123–129
- Ravussin E, Smith SR 2002 Increased fat intake, impaired fat oxidation, and failure of fat cell proliferation result in ectopic fat storage, insulin resistance, and type 2 diabetes mellitus. *Ann NY Acad Sci* 967:363–378
- Shulman GI 2000 Cellular mechanisms of insulin resistance. *J Clin Invest* 106:171–176
- Van den Berghe G 2004 How does blood glucose control with insulin save lives in intensive care? *J Clin Invest* 114:1187–1195
- Butler SO, Btaiche IF, Alaniz C 2005 Relationship between hyperglycemia and infection in critically ill patients. *Pharmacotherapy* 25:963–976
- Vanhorebeek I, Langouche L, Van den Berghe G 2005 Glycemic and nonglycemic effects of insulin: how do they contribute to a better outcome of critical illness? *Curr Opin Crit Care* 11:304–311
- van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, Vlasselaers D, Ferdinande P, Lauwers P, Bouillon R 2001 Intensive insulin therapy in the critically ill patients. *N Engl J Med* 345:1359–1367
- Van den Berghe G, Wilmer A, Hermans G, Meersseman W, Wouters PJ, Milants I, Van Wijngaerden E, Bobbaers H, Bouillon R 2006 Intensive insulin therapy in the medical ICU. *N Engl J Med* 354:449–461
- Langouche L, Vanhorebeek I, Vlasselaers D, Vander Perre S, Wouters PJ, Skogstrand K, Hansen TK, Van den Berghe G 2005 Intensive insulin therapy protects the endothelium of critically ill patients. *J Clin Invest* 115:2277–2286
- Mazurek T, Zhang L, Zalewski A, Mannion JD, Diehl JT, Arafat H, Sarov-Blat L, O'Brien S, Keiper EA, Johnson AG, Martin J, Goldstein BJ, Shi Y 2003 Human epicardial adipose tissue is a source of inflammatory mediators. *Circulation* 108:2460–2466
- Baker AR, Silva NF, Quinn DW, Harte AL, Pagano D, Bonser RS, Kumar S, McTernan PG 2006 Human epicardial adipose tissue expresses a pathogenic profile of adipocytokines in patients with cardiovascular disease. *Cardiovasc Diabetol* 5:1
- Nygren J, Thorell A, Efendic S, Nair KS, Ljungqvist O 1997 Site of insulin resistance after surgery: the contribution of hypocaloric nutrition and bed rest. *Clin Sci (Lond)* 93:137–146
- Svanfeldt M, Thorell A, Nygren J, Ljungqvist O 2006 Postoperative parenteral nutrition while proactively minimizing insulin resistance. *Nutrition* 22: 457–464
- Xu H, Barnes GT, Yang Q, Tan G, Yang D, Chou CJ, Sole J, Nichols A, Ross JS, Tartaglia LA, Chen H 2003 Chronic inflammation in fat plays a crucial role in the development of obesity-related insulin resistance. *J Clin Invest* 112: 1821–1830
- Weisberg SP, McCann D, Desai M, Rosenbaum M, Leibel RL, Ferrante Jr AW 2003 Obesity is associated with macrophage accumulation in adipose tissue. *J Clin Invest* 112:1796–1808
- Neels JG, Olefsky JM 2006 Inflamed fat: what starts the fire? *J Clin Invest* 116:33–35
- Hotamisligil GS, Arner P, Caro JF, Atkinson RL, Spiegelman BM 1995 Increased adipose tissue expression of tumor necrosis factor- α in human obesity and insulin resistance. *J Clin Invest* 95:2409–2415
- Steppan CM, Bailey ST, Bhat S, Brown EJ, Banerjee RR, Wright CM, Patel HR, Ahima RS, Lazar MA 2001 The hormone resistin links obesity to diabetes. *Nature* 409:307–312
- Haluzik M, Colombo C, Gavrilova O, Chua S, Wolf N, Chen M, Stannard B, Dietz KR, Le Roith D, Reitman ML 2004 Genetic background (C57BL/6J versus FVB/N) strongly influences the severity of diabetes and insulin resistance in ob/ob mice. *Endocrinology* 145:3258–3264
- Lehrke M, Reilly MP, Millington SC, Iqbal N, Rader DJ, Lazar MA 2004 An inflammatory cascade leading to hyperresistinemia in humans. *PLoS Med* 1:e45
- Reilly MP, Lehrke M, Wolfe ML, Rohatgi A, Lazar MA, Rader DJ 2005 Resistin is an inflammatory marker of atherosclerosis in humans. *Circulation* 111:932–939
- Curat CA, Wegner V, Sengenès C, Miranville A, Tonus C, Busse R, Bouloumie A 2006 Macrophages in human visceral adipose tissue: increased accumulation in obesity and a source of resistin and visfatin. *Diabetologia* 49:744–747
- Pajvani UB, Scherer PE 2003 Adiponectin: systemic contributor to insulin sensitivity. *Curr Diab Rep* 3:207–213
- Matsuda M, Shimomura I, Sata M, Arita Y, Nishida M, Maeda N, Kumada M, Okamoto Y, Nagaretani H, Nishizawa H, Kishida K, Komuro R, Ouchi N, Kihara S, Nagai R, Funahashi T, Matsuzawa Y 2002 Role of adiponectin in preventing vascular stenosis. The missing link of adipo-vascular axis. *J Biol Chem* 277:37487–37491
- Pajvani UB, Hawkins M, Combs TP, Rajala MW, Doebber T, Berger JP, Wagner JA, Wu M, Knopps A, Xiang AH, Utzschneider KM, Kahn SE, Olefsky JM, Buchanan TA, Scherer PE 2004 Complex distribution, not absolute amount of adiponectin, correlates with thiazolidinedione-mediated improvement in insulin sensitivity. *J Biol Chem* 279:12152–12162
- Van den Berghe G 2002 Neuroendocrine pathobiology of chronic critical illness. *Crit Care Clin* 18:509–528
- Horner HC, Munck A, Lienhard GE 1987 Dexamethasone causes translocation of glucose transporters from the plasma membrane to an intracellular site in human fibroblasts. *J Biol Chem* 262:17696–17702
- Pilkis SJ, Granner DK 1992 Molecular physiology of the regulation of hepatic gluconeogenesis and glycolysis. *Annu Rev Physiol* 54:885–909
- Haluzik M, Dietz KR, Kim JK, Marcus-Samuels B, Shulman GI, Gavrilova O, Reitman ML 2002 Adrenalectomy improves diabetes in A-ZIP/F-1 lipotrophic mice by increasing both liver and muscle insulin sensitivity. *Diabetes* 51:2113–2118
- Solomon J, Mayer J 1973 The effect of adrenalectomy on the development of the obese-hyperglycemic syndrome in ob-ob mice. *Endocrinology* 93:510–512
- Newell-Price J, Bertagna X, Grossman AB, Nieman LK 2006 Cushing's syndrome. *Lancet* 367:1605–1617

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