



# Abdominal Adipose Tissue Metabolism in Human Ectopic Fat and Cardiometabolic Risk

Written by Brian Hoyle

André Tchernof, PhD, Université Laval, Laval, Québec, Canada, discussed visceral adipose tissue metabolism and its association with cardiometabolic risk.

Visceral obesity is associated with a variety of conditions that increases the risk developing type 2 diabetes and cardiovascular disease [Kissebah AH, Krakower GR. *Physiol Rev* 1994; Després JP, Lemieux I. *Nature* 2006; Tchernof A, Després JP. *Physiol Rev* 2013]. These features include:

- Glucose intolerance
- Insulin resistance
- Hyperinsulinemia
- Dyslipidemia
- Hypertension
- Proinflammatory and prothrombotic state
- Hepatic stenosis

Regional differences in the average size and number of adipocytes found in subcutaneous and visceral adipose tissue have been described [Tchernof A. Sex differences in energy balance, body composition, and body fat distribution. In: Tsatsoulis A, Wyckoff J, Brown FM, eds. *Diabetes in Women*. USA: Springer; 2010: 1-24.]. Other mechanisms by which obesity may increase cardiometabolic risk include changes in lipoprotein lipase activity and in the release of free fatty acids, adiponectin, and interleukin-6 that occur in obese patients.

Increasing body fat mass is associated with increased adipocyte diameter. In addition, there is an increased number of larger diameter adipocytes in subcutaneous and visceral adipose tissue [Spalding KL et al. *Nature* 2008; Veilleux A et al. *Diabetes* 2011]. The enlargement of existing adipocytes—adipocyte hypertrophy—that occurs in visceral fat may be associated with an altered lipid profile independent of body composition and fat distribution in women [Veilleux A et al. *Diabetes* 2011].

Visceral adipocyte hypertrophy is associated with a hyperlipolytic response to beta-adrenergic and post-receptor agents in adipose cells as well as elevated expression of CCAAT enhancer-binding protein beta (C/EBPB), and reduced expression of glucose transporter type 4 in subcutaneous adipose tissue. In addition, visceral adipocyte hypertrophy is associated with elevated expression of CD31 and von Willebrand factor in subcutaneous and omental adipose, and elevated expression of CD68 in omental adipose.

In the metabolic syndrome, adipocyte hypertrophy plays a role in lipid uptake and lipolytic rate of adipocytes [Varlamov O et al. *Am J Physiol Endocrinol Metab* 2010; Tchernof A et al. *Diabetes* 2006], release of adiponectin and leptin [Drolet R et al. *Obesity* 2009; Lee MJ, Fried SK. *Am J Physiol Endocrinol Metab* 2009], macrophage infiltration [Michaud A et al. *Metabolism* 2012], insulin resistance [McLaughlin T et al. *Diabetologia* 2007], and dyslipidemia [Veilleux A et al. *Diabetes* 2011].

Adipocyte hyperplasia is associated with subcutaneous fat in men and women. Prof. Tchernof noted that in many instances visceral adipocyte hypertrophy is a stronger predictor of metabolic alterations than subcutaneous adipocyte hypertrophy. Visceral fat quickly becomes inefficient for lipid storage as its mass and the size of its adipocytes increase, perhaps because expansion is mostly through lipogenesis.

It is important to note that the previously described results have been obtained in lean-to-moderately obese subjects, in whom fat cell size tends to increase linearly with adiposity.

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The same relationship has not been described in more obese individuals where the predictive ability and pathophysiological importance of fat cell size may differ.

## Resistin Receptor Mediates Inflammatory Actions

Written by Brian Hoyle

Hyo-Soo Kim, MD, PhD, Seoul National University Hospital, Seoul, South Korea, reported on the cloning of the receptor for resistin, and its involvement in chronic inflammation and cardiometabolic disease.

Cardiometabolic disease is the collective term used to describe events that occur due to cardiovascular disease, diabetes, and obesity. Proinflammatory and proatherogenic pathways are also related to obesity and can contribute to insulin resistance and atherosclerosis. Chronic lipid loading and cellular stress may also lead to enlargement of adipocytes. The hypertrophic cells respond to inflammation by becoming insulin resistant, driving the metabolic syndrome.

One of the implicated molecules is resistin, a cytokine that is secreted from cells such as adipocytes in mice and human monocytes and macrophages. Resistin increases the level of low-density lipoprotein cholesterol leading to the development of atherosclerosis. Increased resistin production has also been linked with obesity in a mouse model [Steppan CM et al. *Nature* 2001]. In humans, elevated resistin is associated with chronic inflammation [Kaser S et al. *Biochem Biophys Res Commun* 2003; Silswal N et al. *Biochem Biophys Res Commun* 2005], vascular inflammation [Jung HS et al. *Cardiovasc Res* 2006] and arterial atherosclerosis. Yet, the cell receptor has remained unknown and has not been described.

In order to characterize the resistin receptor, a fusion protein was constructed that contained human resistin with mouse Fc, allowing expression of resistin in transfected HEK cells. Used as a ligand, the human resistin bound to a 55 kDa protein in human monocytes. The protein was identified as adenylyl cyclase-associated protein 1 (CAP1). Immunofluorescence staining showed the membrane localization of CAP1 in THP-1 human monocytes. Fluorescence-activated cell sorting revealed increased CAP1 in monocytes exposed to resistin. Finally, immunofluorescent antibodies to CAP1 and resistin were found to be co-localized in the monocyte membrane.

The physical association between CAP1 and resistin was determined conclusively using a variety of experimental approaches. The site of resistin binding in the 3 functional domains of CAP1 was determined using deletion mutants lacking the adenylyl cyclase-binding domain, proline-rich SH3 binding domain, and actin-binding domain. The proline-rich domain was implicated as the active site.

THP-1 monocytes treated with resistin displayed a time-dependent increase in the levels of cAMP, consistent with the known role of CAP1 in the yeast adenylyl cyclase complex. Resistin increased the production of protein kinase A (PKA) and nuclear factor-kappa B (NF- $\kappa$ B) in monocytes, and upregulated the protein level of integrin  $\beta$ 1 and the mRNA expression of the cytokines interleukin-6, -1 $\beta$ , and tumor necrosis factor-alpha. All responses could be abolished by a small interfering RNA that targeted CAP1.

These results support a scenario involving crosstalk between the monocyte cAMP, PKA signaling and NF- $\kappa$ B pathways, in which CAP1 acts as a receptor for resistin and regulates the resistin-induced activity of monocytes.

In support of this hypothesis, inhibition of PKA activity *in vitro* abolished resistin-induced activation of NF- $\kappa$ B and expression of inflammatory cytokines. *In vivo*, expression of human resistin in mice demonstrated that CAP1 overexpression significantly enhanced monocyte migration to resistin, macrophage infiltration, and expression of cytokines. All were abrogated by curtailed CAP1 expression. Further work is needed to define the cellular pathways associated with this receptor; however, CAP1 may become a novel target in the treatment of inflammatory diseases such as atherosclerosis.

## Storage of Dietary Fatty Acids in Type 2 Diabetes

Written by Mary Mosley

White adipose tissue is thought to be critical in controlling the amount of fat in lean tissue because it takes up excess dietary fat to prevent potentially toxic dietary fatty acids from being metabolized by lean tissue. Dietary fatty acid spillover drives, at least in part, regulation of ectopic fat, which plays a role in insulin resistance and metabolic abnormalities related to the metabolic syndrome. At least 4 different mechanisms are thought to contribute to the deposition of ectopic fat: increased dietary fat, increase uptake of nonesterified fatty acids from white adipose tissue lipolysis, impaired fatty acid oxidation, and increased lipogenesis (Figure 1).

André C. Carpentier, MD, Université de Sherbrooke, Sherbrooke, Québec, Canada, reviewed research to understand abnormal organ-specific postprandial storage of dietary fatty acids, and the impact of lifestyle intervention to reduce this storage.

Using a novel approach with whole body positron emission tomography (PET), computed tomography (CT), and a fatty acid tracer (18F fluoro-6-thia-heptadecanoic acid [FTHA]), Prof. Carpentier and colleagues showed most dietary fatty acid uptake occurred 4 to 6 hours after eating. Dietary fatty acids first appear in the thoracic duct, and the