distribution. However, the fact that fat cell size reaches a plateau in individuals with severe obesity suggests it may not predict metabolic complications in this population. This conclusion coincides with reports from Lemieux et al. [*Diabetes Care* 2006] and Drapeau et al. [*Obes Surg* 2007] that cast doubt on the utility of waist circumference to predict metabolic abnormalities and complications in severely obese men and women.

Prof. Tchernof concluded the following:

- Visceral adipose tissue expands mostly through adipocyte hypertrophy and quickly becomes inefficient in storing excess lipids.
- Limited adipose tissue lipid storage capacity has emerged as a critical determinant of cardiometabolic alterations.
- Lipolytic responsiveness of visceral adipocytes to positive stimuli is increased in visceral obesity, but most studies support a reduced inhibitory response to insulin in visceral adipocytes compared with subcutaneous adipocytes.
- Visceral obesity and high lipolytic rates are closely related to macrophage infiltration and inflammation.
- The pathophysiology of metabolic disorders in severe obesity may no longer be related solely to excess visceral fat and/or visceral adipocyte hypertrophy.

Mechanisms and Consequences of Ectopic Fat Accumulation

Written by Rita Buckley

Ectopic fat is defined as storage of triglycerides in tissues other than adipose tissue, such as the liver, skeletal muscle, heart, and pancreas [Snel M et al. *Int J Endocrinol* 2012]. Marja-Riitta Taskinen, MD, University of Helsinki, Helsinki, Finland, discussed ectopic fat accumulation and cardiometabolic risk.

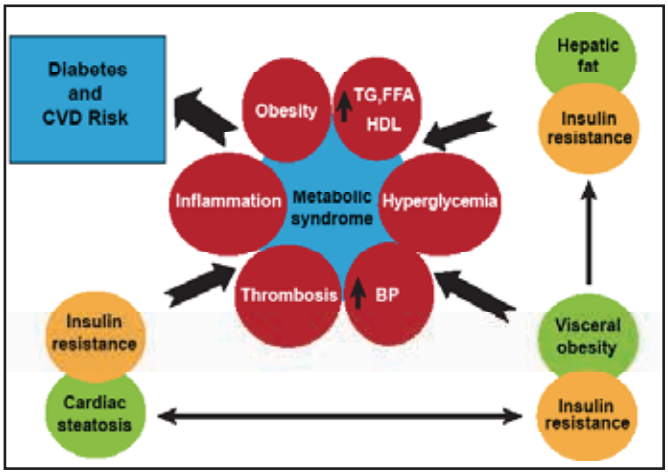
Excess body adiposity, especially abdominal obesity and ectopic fat accumulation, is a key risk factor in the development of a number of chronic diseases [Thomas EL et al. *Nutr Res Rev* 2012]. It can interfere with cellular functions, and, hence, organ functions, and is associated with insulin resistance [Snel M et al. *Int J Endocrinol* 2012].

Adipose tissue dysfunction is largely characterized by large adipocytes and secretion of adipokines with a proinflammatory profile, ultimately leading to ectopic fat deposition (among others) [Blüher M. *Exp Clin Endocrinol Diabetes* 2009].

Although visceral fat accounts for only 10% to 15% of ectopic fat accumulation, 82% to 97% is stored as subcutaneous fat. Other major sites of ectopic fat accumulation include the heart (0% to 3%), the liver (5% to 30%), and skeletal muscle fat (10% to 15%).

Ectopic fat is an important predictor of metabolic (in particular, insulin resistance) and cardiovascular disease (CVD), carrying more risk than general fat accumulation. Recent studies have shown a link between ectopic fat accumulation, as cardiac (epicardial or intramyocardial fat) and/or visceral and/or hepatic fat, and development of atherosclerosis, coronary heart disease, and hypertension (Figure 1) [Gastaldelli A, Basta G. *Nutr Metab Cardiovasc Dis* 2010].

Figure 1. Ectopic Fat and Cardiometabolic Risk.



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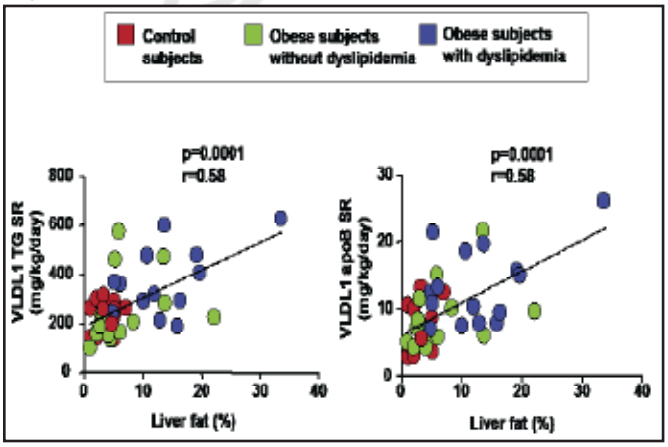
According to Dr. Taskinen, fatty liver produces a plethora of risk factors for CVD. The mediators that may link it and CVD include glucose, very low-density lipoprotein (VLDL), high-density lipoprotein (HDL), alanine aminotransferase and aspartate aminotransferase, fibrinogen, factor VII and plasminogen activator inhibitor-1, angiotensinogen, C-reactive protein and serum amyloid A, and tumor necrosis factor-α and interleukin-6. The atherogenic lipoprotein triad (increased large VLDL, increased small dense LDL, and decreased HDL-C) and hepatic steatosis lead to an increased risk of coronary artery disease.

Although obesity increases the risk of CVD and premature death, not all obese people (20% to 30%) develop the metabolic abnormalities associated with

obesity [Taskinen MR et al. *Arterioscler Thromb Vasc Biol* 2011]. In those who do, nonalcoholic fatty liver disease, especially in its more severe forms, is linked to an increased risk of CVD, independent of underlying cardiometabolic risk factors [Stefan N et al. *Endocr Rev* 2008; Gastaldelli A et al. *Hepatology* 2009; Speliotes EK et al. *Hepatology* 2010].

Taskinen and colleagues investigated if hypertriglyceridemia (HTG) in obese men with similar body mass indexes, waist circumferences, and levels of visceral adiposity is caused by increased hepatic secretion induced by increased liver fat. Results showed that dual metabolic defects are required to produce HTG in obese subjects with similar levels of visceral adiposity, ie, the combination of increased secretion driven by liver fat content and severely impaired clearance of triglyceride-rich $VLDL_1$ particles linked to the elevation of apolipoprotein CIII. Notably, there was an overproduction of large VLDL particles associated with small dense LDL and lowering of HDL as seen in the atherogenic lipid triad. The data suggest that overproduction of VLDL particles is a mechanism to export extra fat out of the liver (Figure 2) [Taskinen MR et al. *Arterioscler Thromb Vasc Biol* 2011]. The data highlights the clinical importance of assessing hypertriglyceridemic waist to indentify obese subjects at high cardiometabolic risk.

Figure 2. Liver Fat Drives Production of VLDL1.



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Strategies that decrease liver fat and improve insulin sensitivity may boost whole-body insulin sensitivity [Byrne CD. *Diabet Med* 2012] and reduce CVD risk factors and lipotoxicity related to contractile, mitochondrial, and endoplasmic reticulum dysfunction; steatosis; and apoptosis [Wende AR, Abel ED. *Biochim Biophys Acta* 2010].

Beyond Weight Loss: Rethinking Treatment Strategies for Obesity

Written by Rita Buckley

Can physical activity with little or no weight loss deliver health benefits? Robert Ross, PhD, Queen's University, Kingston, Ontario, Canada, answered this question and discussed the role of physical activity/exercise in the management of abdominal obesity.

The global prevalence of obesity (BMI≥30 kg/m^2) almost doubled between 1980 and 2008, bringing the number of obese people to half a billion [World Health Organization. *World Health Statistics: A Snapshot of Global Health* 2012]. This rapid growth indicates an urgent need to identify effective interventions that can reduce or eliminate the high personal, societal, and healthcare costs associated with obesity.

Anti-obesity programs to date have focused on weight loss through lifestyle interventions, ie, changes in diet and exercise. However, the emphasis on weight loss may be misleading, diverting efforts from other approaches that may also help to achieve public health objectives. According to Prof. Ross, it is time to rethink our lifestyle management targets. To manage obesity and related health risks, clinicians must look beyond weight loss as the only indicator of therapeutic/treatment success.

Data indicate that obesity and its associated health risks can be reduced by increased physical activity with or without weight loss [Ross R, Bradshaw AJ. *Nat Rev Endocrinol* 2009]. A study of premenopausal women with abdominal obesity showed that equivalent diet- or exercise-induced weight loss and exercise without weight loss produced similar decreases in visceral fat in all treatment groups ($p<0.008$) [Ross R et al. *Obes Res* 2004]. A study of obese men also found decreased abdominal and visceral fat in the weight-loss group ($p<0.001$) as well as in the exercise-without-weight-loss group ($p=0.001$) [Ross R et al. *Ann Intern Med* 2000].

Janiszewski and Ross [*Appl Physiol Nutr Metab* 2007] identified a dose-response relationship between minutes per week of exercise and decreases in subcutaneous and visceral adipose tissue (VAT). Similarly, Coker et al. [*Metab Syndr Relat Disord* 2009] reported significant reductions in the abdominal/visceral fat of elderly adults with high-intensity exercise (-39 cm^2) compared with the medium-intensity exercise group and the control group.