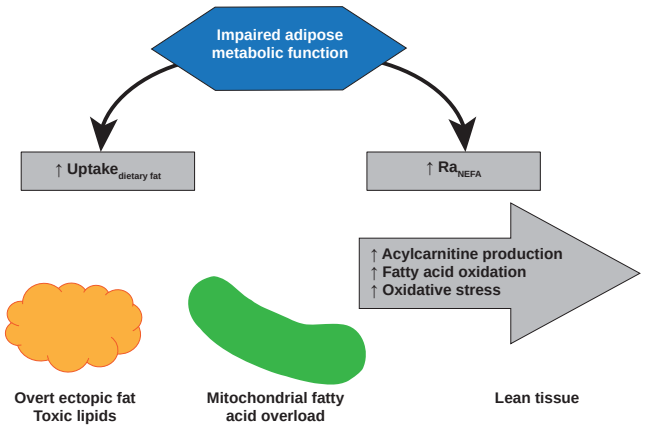
greatest uptake per tissue mass was found (in order) in the liver, heart, kidneys, visceral adipose tissue, white adipose tissue, and resting skeletal muscles [Labbe SM. *Am J Physiol Endocrinol Metab* 2011].

Figure 1. Mechanisms for Ectopic Fat Deposition



Reproduced with permission from AC Carpentier, MD.

Of the 9 subjects included in this study, those with impaired glucose tolerance (IGT), compared with those without IGT, were older (p<0.001), had higher body mass index (BMI; p<0.02) and waist circumference (p=0.008), more insulin resistance (p<0.001), fatty liver (p=0.10), and high triglycerides (TG; not significant). Postprandial metabolism was abnormal in patients with IGT. Persons with IGT had significantly less dietary fatty acid uptake in the anterior abdominal subcutaneous tissue (p=0.05). Predictors of less dietary fatty acid uptake were waist circumference, fasting TG, postprandial glucose area under the curve (AUC), and nonesterified fatty acid AUC (likely related to nonesterified fatty acid spillover associated with impaired white adipose tissue and dietary fatty acid uptake). In subjects with prediabetes, dietary fatty acid uptake was reduced in visceral and white adipose tissue. Dietary fatty acid spillover was clearly associated with impaired dietary fatty acid uptake by visceral adipose tissue.

A striking and consistent finding was a significant increase in dietary fatty acids. Uptake of dietary fatty acid by the myocardium appeared to be maintained over time in persons with IGT. However, there was no difference in liver uptake of dietary fatty acids in persons with and without IGT. Thus, Prof. Carpentier concluded, it does not appear that dietary fat is distributed to a greater degree in the liver in diabetes and does not seem to contribute to its ectopic fat deposition. The best predictors of increased dietary fatty acid uptake by the myocardium were IGT and insulin resistance, whereas there was an inverse relation between fasting TG and liver dietary fatty acid uptake.

To determine the effect of weight loss on organ-specific dietary fatty acid storage, persons with IGT in the imaging study were enrolled in a 1-year lifestyle intervention. Modest reductions were achieved in weight (-3.7 kg), BMI (-1.1 kg/m^2), and waist circumference (-5.0 cm). These reductions were associated with reductions in insulin resistance and postprandial insulin excursion, but IGT was not altered.

Subsequent imaging with FTHA showed that nonesterified fatty acids were significantly altered and TG were slightly reduced. Notably, dietary fatty acid uptake was decreased in the myocardium and increased in visceral adipose after weight loss. Prof. Carpentier hypothesized that weight loss is associated with at least partial normalization of impaired fat partitioning seen in IGT. In contrast, a 7-day hypocaloric diet (-500 kcal, saturated fats <7% of total calories) increased dietary fatty acid partitioning to the myocardium, but did not alter partitioning to the liver, white adipose tissue, or visceral adipose tissue.

Although there is clear evidence that impaired dietary fatty acid storage in adipose tissue is associated with risk of developing cardiometabolic disorders (high TG and increased waist circumference), it is less clear whether this association is mechanistically related to impaired dietary fatty acid storage in other organs. Thus, the local factors regulating cardiac metabolism of dietary fat require further investigation.

Inflammation, Adipose Tissue, and Cardiometabolic Risk

Written by **Mary Mosley**

Inflammation that develops in obese persons is thought to play an important role in the development of type 2 diabetes. Epidemiological and clinical data have shown that low levels of omega-3 polyunsaturated fat (PUFA) consumption is related to cardiovascular disease, and that a higher ratio of omega-6 PUFA to omega-3 PUFA consumption increases this risk. André Marette, PhD, Université Laval, Québec City, Québec, Canada, reviewed research from his group that explored whether omega-3 is a link between obesity and inflammation.

A mouse model (Fat-1) was developed in which inflammatory markers were significantly reduced, resulting in improvements in fasting insulin and insulin resistance (IR), and partial improvement in glucose tolerance [Kang JX et al. *Nature* 2004]. In addition, there was greater production of PD1, a molecule that decreases levels of inflammation in muscle, liver, and adipose tissue, and an improvement in IR when Fat-1 mice were fed a diet high in omega-3. This increase in PD1, 1 of several anti-inflammatory mediators, is thought to be an important mechanism by which omega-3

exerts its anti-inflammatory effects. Experiments using typical transcriptomic strategies in Fat-1 mice revealed changes in the regulation of cholesterol biosynthesis pathways, and prostaglandin synthesis and regulation, when omega-6 was increased and omega-3 was decreased in adipose tissue.

The lack of weight gain, despite adipogenesis, led to experiments that confirmed peroxisome proliferator activated receptor-gamma (PPAR-γ) was upregulated in adipose tissue in Fat-1 mice. PPAR-γ is known to contribute to regulation of adipogenesis. Remodeling of adipose tissue was also found in the Fat-1 mice. These mice had no increase in the overall amount of fat; however, they did have an increase in the number of adipocytes but these adipocytes were small. Because an increase in adipocyte size attracts macrophages and other immune cells in adipose tissue, this finding is considered to be important, said Prof. Marette.

Changes in the endocannabinoid signaling pathway were found in the Fat-1 mice with increased levels of omega-3 [Ge Q et al. *Int J Obes* (London) 2013]. This pathway comprises neuromodulatory lipids and receptors involved in appetite, among other processes. The cannabinoid CMR1 and CMR2 receptors were overexpressed, but interestingly the catabolic enzyme FAAH known to metabolize lipid molecules activating cannabinoid receptors, was reduced in adipose tissue. Increasing concentration of omega-3 in adipose tissue is thought to compete with omega-6 fatty acids, such as arachidonic acid, which are precursors of cannabinoid receptors, thus adipose tissue tries to increase the number of receptors and downregulates catabolic enzymes.

This reduction in endocannabinoid tone would explain improvements in inflammation and metabolic profiles in obese persons, perhaps through adiponectin production, he said. Further, their studies in Fat-1 mice have provided some understanding of the mechanisms through which omega-3 fatty acids control inflammation in the metabolic syndrome. Omega-3 fatty acids can activate resolution mediators to block inflammation, reduce endocannabinoid tone by competing with omega-6 fatty acids, and increase PPAR-γ. Together, these impact adipogenesis, insulin signaling, cholesterol biosynthesis, prostaglandin synthesis and regulation, and small ligand G-protein coupled receptors.

Obesity, Adiponectin, and Cardiometabolic Risk

Written by **Mary Mosley**

Visceral fat area, abnormal waist circumference, and metabolic abnormalities are closely related. Mitsuyoshi Takahara, MD, Osaka University, Osaka, Japan, explained that the Japanese diagnostic criteria for metabolic syndrome are unique. In Japan, metabolic syndrome is defined by an increased visceral fat area (as measured by a waist circumference ≥85 cm for men, ≥90 cm for women), plus 2 or more of the usual metabolic abnormalities. The waist circumference criterion is based on data from 12,443 Japanese subjects in the general population showing men and women have 1 or more metabolic abnormalities when their visceral fat area, as measured by CT scan, exceeds 100 cm^2, corresponding to the diagnostic waist circumference cut-offs [Hiuge-Shimizu A et al. *Ann Med* 2012]. A direct association between waist circumference and the number of metabolic abnormalities in men and women was shown by Takahara and colleagues [Takahara M et al. *J Atheroscler Thromb* 2012].

A reduction in visceral fat at 1 year has been associated with improvements in a number of metabolic abnormalities [Okauchi Y et al. *Diabetes Care* 2007]. Furthermore, reduction in visceral fat area was associated with a significant reduction in cardiovascular (CV) events [Okauchi Y et al. *Atherosclerosis* 2010].

Levels of adiponectin, an adipose-derived plasma protein with antiatherogenic and insulin-sensitizing activity, are substantially modulated by obesity and by genetic polymorphisms. A study by Ryo and colleagues found an inverse relation between visceral fat area and adiponectin levels, and a relationship between low adiponectin levels and the increased number of metabolic abnormalities [Ryo M et al. *Circ J* 2004]. A reduction in visceral fat area led to an increase in adiponectin levels at 1 year in men ($p<0.001$) and women ($p=0.015$) [Okauchi Y et al. *Diabetes Care* 2009].

The APN I164T gene polymorphism was associated with lower adiponectin levels (about two-thirds less than in persons without the polymorphism). Persons with this polymorphism had a significantly higher risk for type 2 diabetes (OR, 10; $p<0.01$) [Kondo H et al. *Diabetes* 2002], and for coronary artery disease (about 3%; $p<0.05$) [Ohashi K et al. *J Am Coll Cardiol* 2004]. The G276T gene polymorphism was associated with decreased circulating adiponectin levels, which decreased as weight increased [Hara K et al. *Diabetes* 2002], and increased cardiovascular risk in patients with type 2 diabetes [Katakami N et al. *Atherosclerosis 2012*].

Prof. Takahara stated that adiponectin has a significant and independent relationship with cardiometabolic risk, independent of abdominal obesity.