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.