

addition, SENP2 overexpression selectively enhanced the expression of the PPAR- $\gamma$  target genes FABP3 (fatty-acid-binding protein 3) and CD36 (fatty acid translocase), in the presence and absence of rosiglitazone, but had no effect on ADRP (adipose differentiation-related protein) [Chung SS et al. *Biochem J* 2011].

Prof. Park emphasized the important role that GPx3 plays in regulating oxidative stress, and its potential as a therapeutic target for both insulin resistance and T2DM. In addition, he also noted the potential for SENP2 as a potential therapeutic target to deal with excess fatty acids in skeletal muscle.

## Thermogenesis-Based Obesity Interventions

Written by Nicola Parry

Yangha Kim, PhD, Ewha Woman's University, Seoul, South Korea, reviewed the role of thermogenic agents in the management of cardiometabolic risk. The global obesity pandemic represents a major public health problem, in particular since overweight and obesity are well-known risk factors that predispose patients to cardiovascular disease (CVD) and type 2 diabetes [Seale P, Lazar MA. *Diabetes* 2009]. Indicators of abdominal adiposity, specifically waist circumference and waist-to-hip ratio have been shown to be associated with coronary heart disease (CHD) risk in middle-aged women [Rexrode KM et al. *JAMA* 1998].

The search for strategies to stimulate thermogenesis in obesity management represents a current focus of significant attention. Brown adipose tissue is important in thermogenesis and contributes to energy expenditure, and studies have shown its activity significantly affects body weight in mice [Seale P, Lazar MA. *Diabetes* 2009].

Cells in brown adipose tissue contain large numbers of mitochondria, the organelles where respiration and thermogenesis occur. Mitochondria also contain uncoupling proteins (UCPs) that function as transporters to control the coupling between cell respiration and phosphorylation of ADP. UCP1 is expressed predominantly in brown adipose tissue, UCP2 is expressed in various body tissues, and UCP3 is expressed in high levels mainly in skeletal muscle and brown adipose tissue. Although UCP2 and UCP3 do not play direct roles in thermogenesis, they can contribute when fully stimulated by certain environmental factors, and skeletal muscle plays an important role in energy expenditure by activation of uncoupling proteins. In one study, long-term high-fat feeding resulted in increased fat storage in mice lacking UCP3 [Costford SR. *Am J Physiol Endocrinol Metab* 2008], suggesting it protects against fat gain on high-fat diets. Skeletal muscle UCP3 gene expression was also increased by dietary fish oil and docosahexaenoic acid.

Research is ongoing to identify agents to exploit thermogenesis, specifically in the areas of increasing lipolysis, uncoupling protein expression, and body temperature:

- Various compounds have been shown to stimulate lipolysis, including green tea epigallocatechin-3-gallate [Lee MS et al. *Phytother Res* 2009], polyunsaturated acid (eicosapentaenoic acid; EPA) [Lee MS et al. *Genes Nutr* 2008], capsaicin [Lee MS et al. *Phytother Res* 2011], and L-carnitine [Lee MS et al. *J Med Food* 2006].
- Upregulation of UCP2 has also been described in studies in which rodents were fed capsaicin [Ann JY et al. *J Food Sci Nutr* 2011]. Prof. Kim reviewed recently published data from an *in vitro* study, demonstrating that EPA and DHA directly control UCP3 gene expression in muscle cells [Lee MS et al. *Nutrients* 2013].
- Increased body temperature, reduced body weight, and white adipose tissue weight were reported in high-fat diet-induced obese mice supplemented with epigallocatechin-3-gallate [Lee MS et al. *Ann Nutr Metab* 2009]. Increased energy expenditure has also been demonstrated in people following capsinoid ingestion.

It is suggested that these agents target the AMP-activated protein kinase pathway. This pathway is important in cellular energy homeostasis, in particular through inhibition of fat synthesis and promotion of thermogenesis [Lee MS et al. *Nutrients* 2013]. Manipulating these mechanisms may therefore provide novel ways to harness the body's thermogenic potential for the development of new therapies for millions of obese or diabetic patients.

## Management of Cardiovascular Risk Factors in Asymptomatic Patients With Hypertension

Written by Brian Hoyle

Hyuk-Jae Chang, MD, PhD, Severance Cardiovascular Hospital, Seoul, South Korea, presented the results of the Cardiovascular Risk factors management in Asymptomatic hypertensive Subjects (CREATIVES) study. CREATIVES was a prospective, observational study conducted between January 2010 and May 2011.

National Cholesterol Education Program-Adult Treatment Panel III (NCEP-ATP III) risk stratification that is based largely on the low-density lipoprotein cholesterol (LDL-C) level can overlook many patients with acute



myocardial infarction (AMI) who would benefit from lifestyle modifications or statin therapy [Yoon YE et al. *Prev Cardiol* 2009].

Noninvasive imaging may improve risk prediction and primary prevention of coronary artery disease (CAD). However, existing guidelines on the imaging of asymptomatic CAD patients differ regarding the need for additional imaging studies in patients without established CAD [Ferket BS et al. *J Am Coll Cardiol* 2011].

Evidence supporting the use of noninvasive imaging includes a 3-year follow-up study, in which computed tomography (CT) imaging of coronary calcium increased compliance with statin use [Kalia NK, Budoff M. *J Am Coll Cardiol* 2012]. The EISNER trial also showed the ability and cost-effectiveness of imaging in spurring improvements in management of risk factors [Rozanski A et al. *J Am Coll Cardiol* 2011]. However, other studies have had different results [McEvoy JW et al. *Arch Intern Med* 2011].

Defining whether imaging studies have a role in guiding lipid therapy is important in light of the proven benefits of statins in the prevention of and treatment following AMI [Penning-van Beest FJ et al. *Eur Heart J* 2007; Chapman RH et al. *Patient Prefer Adherence* 2009]. The CREATIVES study assessed whether use of ultrasound scanning of carotid intima media thickness (CIMT) or plaque to classify asymptomatic hypertensive patients for their cardiovascular disease (CVD) risk encouraged beneficial behavioral changes.

Patients (n=347) were enrolled from 22 hospitals in South Korea. Patients included in the study had hypertension (defined as systolic blood pressure [SBP]  $\geq$ 140 mm Hg or use of antihypertensive medication) and were aged 45 to 75 years (men) and 55 to 75 years (women). Patients with previously documented CAD, cerebrovascular, or peripheral arterial disease, and those with symptomatic heart failure were excluded.

Patients were considered to be high risk for CVD if they had a carotid plaque or CIMT  $>$ 0.9 mm on ultrasound. Patients were surveyed with a questionnaire and scored based upon the health-related behaviors such as smoking, exercise, consumption of salty foods and vegetables, and medication compliance. The high- and non-high risk groups comprised 182 and 165 patients, respectively. Significant differences at baseline were present in average age ( $62\pm 7$  and  $60\pm 8$  years, respectively;  $p<0.001$ ), duration of hypertension ( $5.3\pm 6.0$  and  $4.0\pm 4.3$  years;  $p=0.024$ ), triglyceride level ( $138\pm 71$  and  $156\pm 96$  mg/dL;  $p=0.040$ ), use of antiplatelet agents (72% and 47%;  $p=0.030$ ), and higher Framingham scores for high-risk patients (Table 1;  $p=0.005$ ).

After carotid ultrasound examination, SBP and LDL-C were lowered in 26% and 52% of the high-risk patients, respectively, versus 6% and 24% of the non-high-risk

patients, respectively. The findings persisted in patients classified as low- and moderate-risk by NCEP-ATP III criteria. Smoking, salty food intake, and medication compliance were improved in all patients after 6 months.

**Table 1. Framingham Risk Scores**

	High-Risk	Non-High-Risk
FRS $<$ 10%	73 (46.5)	84 (65.6)
FRS 10-20%	71 (45.2)	33 (26.4)
FRS $>$ 20%	13 (8.3)	8 (6.4)

FRS=Framingham Risk Score.

Multivariate analysis of the improvements in SBP and LDL-C revealed that classification as high-risk by carotid ultrasound was the sole independent factor associated with improved cholesterol level.

These findings that carotid ultrasound screening is associated with improved management of hyperlipidemia add support for the value of noninvasive imaging to screen for CVD risk in asymptomatic hypertensive patients. The benefits included improved physician behavior to reach target levels for SBP and LDL-C and improved health behaviors in both patient groups.

## Exercise and Healthy Diet for Management of Abdominal Obesity

Written by Toni Rizzo

### PHYSICAL ACTIVITY IN THE MANAGEMENT OF ABDOMINAL OBESITY

Robert Ross, PhD, Queen's University, Kingston, Ontario, Canada, studied the effects of diet or exercise with or without weight loss on abdominal obesity and insulin resistance [Ross R et al. *Ann Intern Med* 2000; Ross R et al. *Obes Res* 2004]. Obese men and women who exercised and lost weight had the greatest reductions in abdominal and visceral fat. There was no difference in fat reduction between those who dieted with weight loss or exercised without weight loss; however, both groups had significant fat reduction compared with controls. More recently, modest reductions in waist circumference in abdominally obese men, but not in women, were observed in a randomized trial on behavioral, lifestyle-based intervention in clinical settings [Ross R et al. *Arch Intern Med* 2012].

Several studies provided insight into the comparative benefits of various types of exercise. A recent study showed that individuals who exercise without weight loss have decreased abdominal and visceral fat and waist circumference, increased skeletal muscle mass and cardiorespiratory fitness, and decreased blood pressure [Ross R, Bradshaw AJ. *Nature Rev Endocrinol* 2009]. In a study comparing exercise modalities, aerobic exercise and