It's Getting Hot in Here

By Heather Granato, Group Editorial Director

Managing weight is a fact of life for most adults; the scale goes up and down, and we promise we'll cut back on those desserts or get back to the gym. At this point, the United States is facing an epidemic of overweight and obesity, with more than two-thirds of Americans weighing more than is considered optimal for their height.

Interestingly, while the federal government has increasingly touted exercise as one of the critical steps in losing and managing weight—even adding it to the federal dietary guidelines—a cover article in *Time* magazine at the height of the 2009 summer swimsuit season questioned the conventional wisdom. The theory put forth in "Why Exercise Won't Make You Thin" is exercise stimulates appetite instead of suppressing it and feeds into the mental idea of "earning" extra calorie intake. And while the author noted muscle does burn more calories than fat, he added the difference in calorie burning is negligible.

One reason for the inefficiency in fat burning? Humans generally lack great quantities of "brown fat," which is better at turning nutrients into energy. Researchers at Boston's Joslin Diabetes Center recently published an analysis of amount of brown adipose tissue (BAT) and its influence on thermogenesis, mediated by the expression of uncoupling protein 1 (UCP1), in almost 1,800 adults.[1] They found women generally had a greater mass of functionally active BAT, and reported an inverse correlation between BAT levels and body mass index (BMI).

The question may be how to stimulate BAT activity and thermogenesis in adults. Fortunately, studies are increasingly pointing to the ability of many nutritional ingredients, from macronutrients to botanicals, to upregulate the body's process of thermogenesis—increasing the metabolic rate to burn energy.

Every individual has a basal metabolic rate (BMR) linked to the amount of energy needed to maintain basic life functions; this generally slows as the body ages and muscle mass and activity level decline. Metabolic energy needs are also influenced by physical activity (basic and more strenuous activity, such as exercise) and digestion. In fact, the metabolic rate increases immediately after eating, as the body works to transport, metabolize and absorb nutrients.

Protein has been shown to significantly increase diet-induced thermogenesis. A review out of Maastricht University, Netherlands, noted sustaining protein intake can affect metabolic targets during weight loss, particularly during calorie restriction, helping to sustain energy expenditure and spare lean body mass.[2] Additionally, moderately elevated protein intake while reducing overall calories appears to increase thermogenesis, influencing satiety, while maintaining lean muscle mass, further improving the metabolic profile.[3] In one recent study, researchers out of Purdue University, West Lafayette, IN, reported women (n=38) consuming a high-protein, energy-deficit diet had greater satiety and fat oxidation compared to a normal protein diet.[4]

Some studies suggest **dairy protein** in particular may exert positive effects on thermogenesis and accelerated fat loss, supported by higher calcium levels inhibiting lipogenesis and bioavailable protein

affecting satiety and lipolysis.[5] In one double blind, randomized study at the Minnesota Applied Research Center, subjects (n=106) reduced their caloric intake by 500 calories per day and consumed a specialized whey fraction (as Prolibra™, from Glanbia) or an isocaloric ready-to-mix beverage 20 minutes before breakfast and dinner.[6] The Prolibra group lost significantly more body fat compared to control subject, with a greater preservation of lean muscle.

It may be the **amino acids** found in protein exert a particular effect on the body's thermogenic pathways. Italian researchers reported providing an amino acid-infused solution to adults increased protein synthesis and energy expenditure, with the thermic effect not dependent on the dosage of amino acids.[7] **L-leucine** specifically may stimulate protein synthesis in muscle cells and promote retention of lean muscle mass during calorie reduction.[8] It also appears to regulate the oxidative use of glucose by skeletal muscle, sparing protein during energy restriction.[9]

The amino acid **L-carnitine** may also exhibit some thermogenic properties. A recent French study found providing aged rats with 30 mg/kg body weight of L-carnitine (as L-Carnipure™, from Lonza) for 12 weeks restored L-carnitine levels in muscle cells and induced positive changes in body composition including a decrease in abdominal fat mass without any change in food intake.[10] A previous human trial examined the impact of L-carnitine supplementation on fat oxidation, body composition and weight development in 12 slightly overweight adults.[11] Supplementation with 3 g/d of L-carnitine (as L-Carnipure) for 10 days significantly increased dietary fat oxidation without impacting protein catabolism.

A host of biological active compounds also exert a thermogenic effect on the body, increasing the metabolic rate. Perhaps the best-known of the energy enhancers is **caffeine**. Studies suggest it not only upregulates UCP-1, -2 and -3 expression in BAT,[12] but also increases oxygen consumption in BAT mitochondria and resting metabolic rate (RMR).[13] A review from Maastricht University noted a combination of caffeine and ephedrine has been shown to be effective in enhancing release of catecholamines, although ephedrine's adverse effects have negated that tool for dietary supplement formulators.[14] They added, however, that **green tea**, which contains both caffeine and tea catechins, may contain in one extract synergistic compounds to exert a thermogenic and weight reducing effect. Scientific interest in green tea's effects on weight loss is high, not only to understand its mechanisms, but also the synergy between the active compounds. A review from the University of Fribourg, Switzerland, noted while green tea's thermogenic effects have been generally attributed to its caffeine content, studies show green tea extract stimulates BAT thermogenesis to a much greater degree than could be attributed to just the amount of caffeine; they suggest there could be interaction between the catechin polyphenols and caffeine in the body.[15] Researchers from DSM Nutritional Products, Basel, Switzerland, agreed in their review, adding green tea, green tea catechins and epigallocatechin gallate (**EGCG**) have been demonstrated to exert effects on lipogenesis, fat mass and thermogenesis, and that EGCG poses particular promise in the area.[16]

Researchers have been exploring the possibilities. In one trial involving 10 healthy men, those who received green tea extract (50 mg caffeine and 90 mg EGCG) had significant effects on fat oxidation and energy expenditure, while those taking just caffeine (50 mg) had no increase in energy expenditure (EE).[17] Similarly, a pilot study in Germany found providing overweight men with EGCG alone (300 mg/d) for only two days significantly increased fat oxidation.[18] Another trial out of Laval University, Quebec, provided adults (n=14) with capsules containing 200 mg of caffeine (from **guarana** extract) and varying doses of EGCG—90, 200, 300 or 400 mg—three times daily.[19] All

interventions increased 24-hour EE, with no great differences among the doses of EGCG.
Green tea **catechins** have also been studied in combination with other possible thermogenic agents beyond caffeine. A pair of studies out of The Royal Veterinary and Agricultural University, Frederiksberg, Denmark, explored the impact of a combination of green tea extract (catechins and caffeine), capsaicin, tyrosine and calcium, either as a simple combination or in an enteric-coated version. In the first trial, a three-way crossover, placebo-controlled, double blind intervention, 19 overweight to obese men consumed the supplements for one week.[20] The simple combination was found to increase 24-hour EE without raising the heart rate, while the enteric-coated version had no effect. The second trial involved 80 overweight/obese subjects who initially underwent a four-week hypocaloric diet, and were then randomized to receive a placebo or simple combination.[21] After eight weeks, subjects taking the supplement had a greater decrease in body fat mass compared to the placebo group and increased rates of thermogenesis.

In fact, research suggests spices such as capsaicin, black pepper and ginger may all exert a thermogenic effect, and even upregulate fat oxidation.[22] **Capsaicinoids** are the major pungent principles in red hot peppers, and commonly referred to collectively as capsaicin. Studies have shown when capsaicin is consumed, it stimulates the sensory neurons to enhance the release of adrenal hormones including epinephrine and norepinephrine.[23] A review out of the University of Memphis, TN, noted capsaicinoids have been shown to reduce ad libitum food intake, increase thermogenesis and increase lipolysis, with few adverse outcomes, generally limited to gastric discomfort associated with higher intake levels.[24]

Clinical trials are building a strong base of support. Japanese researchers investigated the effects of capsaicin (150 mg) on metabolism and thermogenic activity during exercise, reporting in the male subjects (n=10), intervention did not impact heart rate during exercise, but did increase markers of fat oxidation.[25] A larger double blind, placebo-controlled, 12-week study, conducted at the University of Maryland School of Medicine, Baltimore, involved 80 overweight adults randomly assigned to capsinoid (6 mg/d) or placebo groups.[26] At study's end, no significant differences appeared between the groups in total changes in adiposity, although the capsinoid group had greater decreases in abdominal adiposity; fat oxidation was also higher in the capsinoid group. Another trial, this time in overweight subjects who had lost 5 to 10 percent body weight, reported capsaicin (135 mg/d) could sustain fat oxidation during a three-month weight-maintenance period, although weight regain was almost similar between the groups.[27]

Another common spice is black pepper, which has a pungent effect on food and may support food-induced thermogenesis. Studies have shown the ability of **piperine**, an active constituent in black pepper, to stimulate the release of epinephrine, which activates the beta-receptors that initiate thermogenesis.[28] Sabinsa Corp. has supported research into the possible role of its patented black pepper extract (Bioperine®) as a thermonutrient, with the ability to enhance nutrient absorption and related thermogenesis. In one 28-day double blind, crossover study, subjects who received 5 mg of piperine along with a dose of beta-carotene had a 60-percent greater increase in serum beta-carotene levels, which was a result of piperine's non-specific thermogenic effects.[29] Similar results were reported in a study examining the effects of 5 mg piperine on bioavailability of 90 mg or 120 mg of coenzyme Q10 (CoQ10).[30] Supplementation of 120 mg CoQ10 with piperine for 21 days had a statistically significant increase in plasma CoQ10 levels, which was again linked to the thermonutrient effects of piperine.

Another crossover, double blind, placebo-controlled study examined the impact of a combination of piperine (as Bioperine), capsicum extract, niacin and caffeine (as Capsimax™ Plus Blend, from OmniActive Health Technologies) on metabolic and safety parameters. In the unpublished trial, when the healthy adults (n=25) took the combination blend one hour prior to exercising, they burned three times more calories before, 3 percent more calories during, and 12 times more calories for up to an hour after exercise compared to taking a placebo. The subjects also had a greater oxygen uptake and ventilation when taking the Capsimax Plus Blend.

Also from the botanical kingdom comes the extract many formulators turned to when ephedra (ma huang) was eliminated from the U.S. supplement market—**bitter orange** (*Citrus aurantium*). The extract of Citrus aurantium (CA) contains indirect adrenergic amines that stimulate metabolism, enhance amino acid uptake by muscle and increase lipolysis. It appears to have the ability to positively impact sympathetic nervous system (SNS) activity and responsiveness of the body to stimulation of thermogenic beta-adrenoreceptors, without stimulating other beta-adrenoreceptors that control systems such as blood pressure, avoiding the side effects associated with ephedra. Georgetown University researchers noted in a 2002 review that CA extract aids weight loss and increases thermogenesis, and is likely the most effective ephedra substitute.[31]

Studies have supported its efficacy and safety. In a Canadian trial, CA extract (as Advantra Z®, from Nutratech Inc.) increased the thermic effect of food when given with a meal, although the effect was more pronounced in men than in women.[32] Additionally, CA was found to increase epinephrine excretion by 2.4 times, without adversely affecting blood pressure. That margin of safety was also reported by University of California, San Francisco, researchers, who reported a multi-component supplement formulation with 5.5 mg synephrine (from CA) did affect blood pressure, whereas an eight-fold higher level (46.9 mg synephrine) from Advantra Z alone did not increase either diastolic or systolic measures.[33]

Recent trials on bitter orange have focused on its ability to work synergistically with exercise to increase fat oxidation. Researchers from the University of Chichester, West Sussex, England, examined the ability of a combination of CA (Advantra Z), green tea and guarana to influence metabolic rate and thermogenesis; two groups of 10 men received two 500 mg capsules of the active formula or placebo and tested either at rest or during treadmill walking.[34] The intervention positively influenced fat oxidation and ATP production, particularly at rest. In another trial, researchers out of the University of California, San Francisco, examined the effects of a combination of caffeine and Citrus aurantium (as AdvantraZ), as the Ripped Fuel Extreme Cut® supplement, on 10 healthy adults and found supplementation prior to moderately intense exercise modestly improved exercise tolerance.[35]

Another Asian botanical, *Garcinia cambogia*, yields an extract known as hydroxycitric acid (**HCA**), which influences several aspects of weight management. A recent review from InterHealth Nutraceuticals noted studies using cDNA microarrays found HCA supplementation can alter gene expression involved in lipolytic and adipogenic pathways in adipocytes, and also appears to upregulate the expression of serotonin receptor genes in abdominal fat.[36] Animal trials also found garcinia extract may modulate a number of genes associated with adipogenesis, fighting visceral fat accumulation.[37]

Ongoing studies support the efficacy of HCA in thermogenesis. An in vitro trial using subcutaneous preadipocytes from obese women found HCA-SX (as Super CitriMax®, from InterHealth) could markedly induce leptin expression and downregulate fat- and obesity-related genes.[38] A trial in mice further found garcinia extract could exert leptin-like activity to prevent body weight gain during sucrose loading.[39] A review out of Georgetown University, Washington, examined a range of studies on HCA-SX (as Super CitriMax).[40] It noted clinical studies on HCA-SX's safety and efficacy have found a dosage of 2,800 mg/d HCA could significantly reduce food intake and serum leptin levels, while increasing levels of serotonin and excretion of urinary fat metabolites, a biomarker of fat oxidation. No significant adverse effects were reported.

More recent studies in the botanical field have looked at the impact of **green coffee bean extract** (GCBE) on metabolism. A Japanese study found GCBE could reduce visceral fat content and body weight in mice given olive oil, possibly by inhibiting fat absorption and activating fat metabolism in the liver; further, the chlorogenic acid in GCBE may particularly aid in hepatic function.[41] Even as GCBE contains caffeine, which may increase blood pressure, studies on the extract suggest its chlorogenic acid may offset increases in blood pressure.[42]

Interestingly, studies have also shown **yerba maté** (*Ilex paraguariensis*), a natural source of xanthenes similar to caffeine, may exert a thermogenic effect, attenuating adiposity and upregulating UCP-1 and other genes linked to metabolism.[43,44] And like GCBE, yerba maté contains chlorogenic acid as well as caffeic acid, possibly exerting an anti-glycation effect.[45]

Other specialty compounds are also under investigation for their possible thermogenic effects. **Fucoxanthin**, a carotenoid found primarily in brown algae, has been high profile in the nutrition industry in the last two years. One review out of Japan noted feeding fucoxanthin to mice tended to reduce body weight, possibly by enhancing UCP-1 expression in white adipose tissue (WAT) leading to fat oxidation and mitochondrial energy production.[46] In another trial, the researchers, from Hokkaido University, noted providing fucoxanthin to mice along with medium-chain triacylglycerols (MCT) enhanced absorption of the carotenoid, and increased UCP-1 expression, significantly reducing abdominal fat weight in the animals.[47] They reported similar findings when using fish oil in place of MCTs.[48] The researchers noted that because fucoxanthin exerts its effects in WAT, rather than BAT, it may be more efficacious in human adults, who tend to have a higher percentage of WAT. Clinical trials are ongoing to assess fucoxanthin's influence on thermogenesis. However, one unpublished three-month clinical trial involved 19 overweight adults who received a placebo or 2 mg/d or 4 mg/d of a proprietary blend of fucoxanthin and other ingredients (as ThinOgen™ Plus, from Beijing Gingko Group). At study's end, 94.5 percent of the 2 mg group and 99 percent of the 4 mg group reported weight loss, with measurable losses in abdominal fat areas.

Another specialty compound with thermogenic effects is 3-acetyl-7-oxo-dehydroepiandrosterone, better known as **7-oxo-DHEA**, a natural substance produced by the adrenal glands. Studies have shown 7-oxo DHEA has the ability to enhance the activity of three thermogenic enzymes: glycerol-3-phosphate dehydrogenase, malic enzyme and fatty acyl CoA oxidase.[49,50] By doing so, 7-oxo-DHEA increase heat production and utilization of fat stores for energy. Safety studies have found 7-oxo-DHEA (as 7-Keto®, from Humanetics) is safe for human consumption at a dose of 200 mg/d.[51] Initial clinical trials found adults taking 7-oxo-DHEA (as 7-Keto) lost significantly more weight and body fat—up to three times as much—than subjects taking placebo.[52,53] Interestingly, supplementation also

increased RMR even while the subjects followed a calorie-restricted diet, which normally decreases RMR.

A follow-up investigation examined whether 7-oxo-DHEA (as 7-Keto) could increase RMR in overweight subjects on a calorie-restricted diet.[54] The randomized, double blind, placebo-controlled trial included 45 adults placed on a calorie-restricted diet and given 7-oxo-DHEA or placebo during 7-day treatment periods with washout between. RMR decreased 3.9 percent during placebo treatment, but increased by 1.4 percent while taking 7-oxo-DHEA.

While fats generally do not exert a thermogenic effect on the body, there are some studies suggesting certain nutritional fats may impact metabolic rate. **Conjugated linoleic acid** (CLA) has been studied for more than 25 years for its ability to reduce fat mass and retain lean body mass during weight loss. A study out of Norway reported healthy adults who exercised regularly and took 0.6 mg tid of CLA (as Tonalin®, from Cognis Nutrition & Health) for 12 weeks had a significant reduction in body fat, although not body weight.[55] Supplementing with 5 g/d of CLA (as Tonalin) for seven weeks during resistance weight training similarly resulted in decreases in fat mass and increases in lean tissue mass in healthy adults (n=76).[56] Long-term studies have shown overweight adults who consumed CLA (as Tonalin) for one year or two years showed a reduction in body fat mass, which was not related to diet and/or training.[57,58]

Evolving scientific research will likely provide even greater substantiation for the beneficial metabolic effects of nutrients to help consumers lose weight. Whether coupled with exercise, or used in combinations to offer thermogenic and appetite suppressant effects, these powerful compounds may hold the key to unlocking long-term sustainable weight management.

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