Weight Loss through Nutrigenomics

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When it comes to health and wellness, there are few universal truths except this one: it's all in the genes. How else do we explain dietary approaches that work for some people, but not others? Or research findings that seem to contradict each other? The simple fact is, everyone is different and the way their body responds to a specific diet or exercise program can be quite variable. This is the idea behind a burgeoning field of science called "Nutrigenomics". Put simply, Nutrigenomics is the scientific study of the interaction between genes, food, and health. As stated by Trujillo[1] the concept of Nutrigenomics is based on the following four premises[2]:

1. diet and dietary components can alter the risk of disease development by modulating multiple processes involved with onset, incidence, progression, and/or severity;
2. food components can act on the human genome, either directly or indirectly, to alter the expression of genes and gene products;
3. diet could potentially compensate for or accentuate effects of genetic polymorphisms; and
4. the consequences of a diet are dependent on the balance of health and disease states and on an individual's genetic background

Admittedly, scientists are years away from being able to provide personalized diet and exercise programs that are uniquely suited to an individual's genetic profile. That said, there have been a number of studies published that offer a starting point. For example, it is known that diets high in fruits and vegetables are associated with a lower risk of obesity and chronic disease. This is likely due to the effects of specific ingredients within fruits and vegetables (along with red wine and cocoa – both of which are well documented to improve biomarkers of health) on the expression of genes responsible for insulin action, blood vessel health, control of blood sugar, and the storage and metabolism of fats. The problem is, recent estimates are that only 17% and 28% of all U.S. adults consume the recommended amount and types of fruits and vegetables, respectively, necessary to promote good health[3] Do you eat 5-8 servings of fruits and vegetables a day, emphasizing a variety of colors?

The Dietary Insurance Policy

Just as dietary variety is critical to good health, and because everyone's nutrigenomic profile is different, it seems logical to assume that to be effective, dietary supplements designed to aid weight loss need to address a number of different mechanisms:

- reducing fat storage (by ameliorating adipocyte function, and via stimulating uncoupling proteins, UCPs)
- burning extra calories (thermogenic and fat oxidation effects)
- breaking down stored fat (via stimulating UCPs)
- fat metabolism (via stimulation of specific sirtuins, such as *Sirt 1*)
- appetite suppression (via modulation of leptin)

Anthocyanins & Adipocyte Function

Anthocyanins are the largest group of water-soluble pigments in the plant kingdom. They are widely distributed in the human diet through crops, beans, fruits (especially berries), vegetables, and red wine[4], and are also a candidate for activating a gene involved in weight loss.

New research[5] from Japan suggests that anthocyanins have significant potency against adipocytes (aka, fat cells), and could be used for the prevention of weight gain.

The research shows that anthocyanins have significant anti-obesity activity and help ameliorate

adipocyte function in human cell lines and in mice; and they have important implications for preventing the "metabolic syndrome".

Metabolic syndrome is a condition characterized by central obesity, hypertension, and disturbed glucose and insulin metabolism. The syndrome has been linked to increased risks of both type 2 diabetes and cardiovascular disease. About 24% of adult Americans are estimated to be affected by metabolic syndrome[6]; and obesity is established to be the main risk factor for this disorder.

In one of the Japanese studies[7], mice were fed a high fat diet for 12 weeks; and some were also feed a purple corn extract, rich in anthocyanins. Feeding the high fat diet caused the fat cells and adipose tissue of mice to increase substantially in size. In addition, the high fat diet caused high blood sugar levels, high insulin levels and high levels of leptin. These increases, however did not occur in those mice feed the purple corn extract. Purple corn also suppressed the mRNA levels of enzymes involved in fatty acid and triglyceride production, and lowered the sterol regulatory element binding protein-1 mRNA level in white adipose tissue. The authors of the study suggested that their findings provide a basis for the possible use of purple corn extract in the prevention of obesity and diabetes.

In another study[8], human preadipocytes (cells that can be stimulated to develop into fully-fledged fat cells, adipocytes) were incubated with anthocyanins for 24 hours. A down-regulation of plasminogen activator inhibitor-1 (PAI-1), said to be associated with both obesity and type 2 diabetes, was observed after incubation. This suggested that regulation of PAI-1 expression is one of the important therapeutic targets for metabolic syndrome.

The primary author of these studies concluded, "These studies indicate anthocyanins have a unique therapeutic advantage responsible for the regulation of the adipocyte function. These findings provide a biochemical basis for the use of anthocyanins, which can also have important implications for preventing metabolic syndrome."[9]

Cocoa & Fatty Acid/Adipose Tissue Genes

Although it seems counter-intuitive that cocoa (the mother of chocolate) could possibly be involved in activating a gene involved in weight loss, it is nonetheless true. In one study[10], rats were fed either of two high-fat diets for three weeks, differing only in supplementation with real or imitation cocoa. The results were that body weights and mesenteric white adipose tissue weights were significantly lower in rats fed the real cocoa diet than in those fed the imitation cocoa diet, and triglyceride levels also tended to be lower in rats fed the real cocoa diet. Furthermore, cocoa ingestion suppressed the activations of genes involved in the production of fatty acids and white adipose tissues; and also decreased the activation of genes involved in facilitating the transport of fatty acids. Finally, cocoa activated genes for uncoupling protein-2 (UCP-2), which enhanced part of the thermogenesis (i.e., fat-burning) mechanism in liver and white adipose tissue.

Green tea & Fat Burning

Green tea (*Camellia sinensis*) contains valuable, naturally-occurring phytochemicals, including caffeine and epigallocatechin gallate (EGCG). Although green tea is often used for its immune-enhancing and cardiovascular-promoting benefits, other research has found that it may also be a weight-reducing agent, capable of stimulating thermogenesis and promoting fat oxidation; in other words, it helps burn body fat.

In one three-day study[11], subjects given green tea providing 270 mg catechins and 150 mg caffeine daily experienced a significant increase calorie expenditure (i.e., caused more fat calories to be burned than would ordinarily be the case). The research found that green tea has thermogenic properties and promotes fat oxidation beyond that explained by its caffeine content. Apparently, the EGCG also played a role in the process. The researchers concluded that "green tea extract may play a role in the control of body composition via sympathetic activation of thermogenesis, fat oxidation, or both."

In a three-month study[12], subjects given the same dose of green tea decreased their body weight by 4.6% and their waist circumference by 4.48%. In another three-month study[13], subjects given the same dose of green tea found that after their initial weight loss, they were able to maintain their weight loss and continue losing weight.

Undaria pinnatifida & Uncoupling protein 1

The actual burning of the fat takes place in the cellular furnace called the mitochondria. In the mitochondria, genes express a protein called mitochondrial uncoupling protein 1 (UCP1). Simply stated, UCP1 helps to "uncouple" or break down fat so that is can be burned rather than stored.[14] In *in-vivo* research it has been shown that a deficiency of UCP increases susceptibility to obesity.[15] As you can see, in a very real way fat burning is a function of UCP1 being in the right place at the right time. The problem is that adult humans do not have large amounts of BAT, but they do have plenty of white adipose tissue (WAT). Therefore, if there was a natural agent that helped increase UCP in WAT, that may provide a much more practical fat burning effect. Undaria pinnatifida may be just such an agent.

Undaria pinnatifida is an edible brown seaweed,

commonly referred to as Wakame. In *in-vivo* research[16], clear signals of UCP1 were detected in WAT of mice supplemented with Undaria pinnatifida. Even more exciting, those mice experienced a significant reduction of abdominal white adipose tissue (WAT) weights. The research shows that it was the naturally occurring fucoxanthin in the Undaria pinnatifida that had the effect. As promising as this animal research is, it is the human clinical research which really provides validation for weight loss benefits of Undaria pinnatifida for weight loss.

One hundred forty obese pre-menopausal female subjects took part in a 16-week, double-blind, placebo-controlled, randomized clinical trial.[17] Obese subjects diagnosed with nonalcoholic fatty liver disease (NAFLD) and with apparently healthy liver (HL) were matched in pairs based on age, body weight and body fat mass and were randomly divided into one of four groups: Undaria pinnatifida-HL, Placebo-HL, Undaria pinnatifida-NAFLD, and Placebo-NAFLD. All subjects followed a daily diet of 1800 calories, and were directed to take Undaria pinnatifida and/or Placebo, three times a day before meals. Results of this clinical study indicated that the supplementation of Undaria pinnatifida stimulated daily energy expenditure (i.e., burning of calories) in obese subjects with apparently healthy liver. Furthermore, Undaria pinnatifida supplemented subjects with healthy livers lost almost 14 lbs, while those supplemented with a placebo lost about 3 lbs. Likewise, those with NAFLD who were supplemented with Undaria pinnatifida lost almost 11 lbs, while the placebo subjects lost about 3 lbs. A statistically significant increase in the energy expenditure was observed only after 4-5th week of supplementation, while in obese subjects with NAFLD such increase was observed only after 6th week of clinical trial.

Resveratrol & Sirt 1

The mammalian gene *SIR2* produces the protein sirtuin 1 or *Sirt 1*. *Sirt 1* promotes fat mobilization in white adipose tissue.[18] Resveratrol is a natural substance produced by several plants, such as the skin of red grapes, peanuts and Giant Knotweed (*Polygonum sachalinense*), and has demonstrated potent antioxidant activity.[19] Resveratrol is also known activator of *Sirt 1*, and was shown in research to protect mice against diet-induced-obesity and insulin resistance.[20] By means of stimulating *Sirt 1* in mice, resveratrol was further shown to improve glucose homeostasis.[21]

One might think that protection against insulin resistance and improvements in glucose homeostasis could mean a reduction in metabolic syndrome; a condition associated with obesity. In fact, some researchers have suggested that sirtuins (such as *Sirt 1*) and other important metabolic pathways that affect calorie restriction may serve as entry points for drugs to treat metabolic syndrome. We think resveratrol might be a candidate.

Finally, consider that obesity is biologically characterized at the cellular level by an increase in the number and size of adipocytes (fat cells) differentiated from pre-adipocytes in adipose tissue. Resveratrol has been shown to inhibit pre-adipocytes[22], which may translate into reducing the production of new fat cells.

Admittedly, more research, particularly in humans, needs to be conducted on the effects of resveratrol on Sirt 1 on fat metabolism. Nonetheless, resveratrol remains an intriguing natural substance with potential to promote weight loss.

Calcium-potassium salt of (−)-hydroxycitric acid & Leptin

The dried fruit rind of *Garcinia cambogia*, also known as Malabar tamarind, is a unique source of (−)-hydroxycitric acid (HCA), and has been safely used for centuries in Southeastern Asia to make meals more filling.[23] A novel derivative of HCA, a calcium-potassium salt of (−)-hydroxycitric acid or HCA-SX (aka, Super Citrimax). In rats, HCA-SX was found to reduce leptin levels from abdominal fat, as well as reduce body weight gain.[24] The same results were found in similar research.[25]

Research in humans has also suggested that HCA-SX helps reduce leptin levels.[26] Furthermore, in a 6-week randomized placebo-controlled single-blinded cross-over trial[27], 2 weeks of daily administration of HCA-SX (300 mg, 3 times daily) on food intake and satiety in overweight men and women were assessed. The results were that food intake was decreased by 15 –30% with HCA-SX treatment compared to placebo, and body weight tended to decrease.

In another randomized, double-blind, placebo-controlled human study[28], HCA-SX alone (4667 mg daily) and in combination with niacin-bound chromium (4 mg daily) and a standardized Gymnema sylvestre extract (400 mg daily) was evaluated on weight loss in moderately obese subjects who received a 2000 calorie per day diet and participated in supervised walking. Results indicated that body weight and body mass index or BMI (a gross measure of obesity) decreased by 5–6% in both the HCA-SX alone and combination groups; and food intake, total cholesterol, low-density lipoproteins (the "bad" cholesterol), triglycerides and serum leptin levels were also significantly reduced in both groups. Likewise high-density lipoprotein (the "good" cholesterol) levels and excretion of urinary fat metabolites increased in both groups. A marginal or non-significant effect was observed on all parameters

in the placebo group.

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