

MD+ Metabolic

Version III

Metabolic and Hormonal Optimizer

Formulated by Mauro Di Pasquale, M.D.

www.MetabolicDiet.com



Metabolic is formulated to help regulate and optimize metabolic and hormonal processes that can be disrupted by exercise, dieting, stress and aging.

By improving the metabolic and hormonal environment Metabolic improves body composition, helps get rid of body fat (especially cellulite) and increases energy levels and well being.

As well, Metabolic, because of its effects on optimizing the body's hormones, is effective in dealing with insulin, thyroid, growth hormone and sex hormone dysfunction that occurs secondary to weight loss and aging.

Ingredients in Metabolic that support weight and body fat loss and optimize body composition.

The ingredients in Metabolic are meant to help you lose weight, lose body fat, and improve your body composition, both directly and through their effects on the hormonal and central nervous systems.

Some of the ingredients are specifically included for their effects on weight and fat loss and body composition. Others are meant to deal with the body's counter productive response to a drop in calories, the mainstay of any effective diet. And still others are meant to adjust the body's hormonal responses to various stressors, whether due to chronic stress, dieting or aging, that can affect weight loss and body composition.

Some of the ingredients do double or triple duty in that they affect two or all three of the pathways I've described, and sometimes more.

For example, Metabolic contains **pyruvate**, a product of metabolism arising from carbohydrates and protein. Several studies have shown that pyruvate may aid weight and fat loss and improve body composition.^{1,2,3,4} As well, it increases insulin sensitivity, improves plasma lipids, has significant antioxidant effects, and may even inhibit the growth of certain cancers.^{5,6,7,8,9}

Another example is **hydroxycitric acid (HCA)**, which has been shown to block the enzyme that converts carbohydrates into body fat.¹⁰ Technically HCA competitively inhibits the extramitochondrial enzyme ATP-citrate-lyase, which catalyzes the cleavage of citrate to acetyl-CoA and oxaloacetate, a key step in lipogenesis. HCA also has thermogenic and appetite suppressant properties that are useful for weight and fat loss.

Laboratory research suggests that **garcinia cambogia** extract or **HCA** may be an effective compound for promoting weight loss. It is believed that HCA acts in several different ways. It is an effective appetite suppressant, and also limits the production of cholesterol and fatty acids in the body. It is also believed to raise body temperature to act in a thermogenic manner. HCA has also recently been shown to suppress weight regain.

HCA is not one of the new kids on the block. Over the last 30 years there has also been a lot of research on HCA, with even the early research looking at its effects on fat metabolism.¹¹

Theoretically, because HCA decreases the 2-carbon pool necessary for the formation of fat, and increases certain enzymes that promote fat oxidation, it should increase fat oxidation and decrease fat formation. In fact, several studies have shown that these effects do occur. For example, in one study, HCA and other tricarboxylic acids were shown to inhibit fatty acid synthesis from body glycogen without affecting protein synthesis.¹² Studies have also shown that HCA has appetite suppressant effects, especially if taken prior to meals.¹³

Even though its use in weight loss is supported by animal studies, where it appears to act (by a mechanism which is not yet clear, although some studies have implicated a serotonin connection) by reducing food intake, much of the research on the effects of HCA on appetite and body composition has been inconclusive and in some cases showed no effects, especially in humans. As well, there's been a lack of studies that show significant long lasting effects on weight loss and total fat formation and oxidation.

Over the past few years, however, this situation has changed. A recent study on humans has shown that 2 weeks of taking as little as 300 mg of HCA three times a day reduced 24 hour energy intake in obese humans with no increase in hunger.¹⁴

Another recent study has shown that HCA has sustained long-term effects in rats on various parameters of weight loss and hunger.¹⁵ An interesting finding in this study is that the fat content of the diet seemed to be important for the long-term suppressive effect of HCA on feeding. HCA had little effect on rats that were on a very low fat diet.

The bottom line is that HCA has the potential to decrease appetite and weight and fat loss and, along with a proper diet, exercise and other targeted nutritional supplements, should be part of any serious weight and fat loss regimen.

L-Carnitine

L-carnitine is essential for fatty acid transport and burning of fat for energy. As well, it's essential for proper muscle function and some studies have shown that carnitine supplementation improves exercise performance.¹⁶

L-carnitine also decreases the production of some of the pro-inflammatory cytokines and has anti-inflammatory and immunomodulating effects.^{17,18,19}

A recent pilot study showed that the use of **hydroxycitrate (HCA)**, **L-carnitine** and **pyruvate** (all in Metabolic) to obese subjects resulted in a remarkable rate of body-fat loss and thermogenesis,²⁰ which pointed to an uncoupling of fatty-acid oxidation – that is the energy from the burning of fat was thrown off mostly as heat, and thus took some fat out of the metabolic equation.

The increased flux, combined with the activation of fatty acid oxidation induced by the trio increases fat breakdown and the oxidation of fatty acids, along with an increase in uncoupling protein. The overall result is an increase in fat breakdown and an increase in heat production from the metabolism of fat.

Neurotransmitter Precursors

One of the problems with trying to lose weight is that the body tries to sabotage your efforts. That's because your body reacts to the imagined threat of starvation by instituting some ages old survival mechanisms, mainly slowing the metabolic rate so you can get by on fewer calories, and increasing hunger so you can take full advantage of any food that you find. Even though you're deliberately trying to lose weight to improve your looks and health, your body looks at the calorie reduction as a sign of impending starvation and adjusts accordingly.

One of the main ways your body does this is by decreasing neurotransmitter levels in the central nervous system resulting in lowered metabolic rate, decreased activity, hunger and fatigue.

Metabolic counters this by providing **tyrosine**, **DMAE**, **mucuna pruriens**, and **various choline compounds** including **CDP choline** and **phosphatidylcholine**, ingredients that increase neurotransmitter function and increase energy, activity and well being as well as decreasing appetite. Tyrosine, an amino acid, is also a precursor for thyroid hormone.

For example, CDP-choline serves as a choline donor in the metabolic pathways for biosynthesis of acetylcholine and neuronal membrane phospholipids, chiefly phosphatidylcholine.²¹ The principal components of CDP-choline, choline and cytidine, are readily absorbed in the GI tract and easily cross the blood-brain barrier. CDP-choline

supplementation has been researched in animal experiments and human clinical trials that provide evidence of its cholinergic and neuroprotective actions.

Vinpocetine and **bacopa monniera** also have neuroprotective effects, as well as effects on improving neurotransmitter levels.

Calcium, Magnesium, Potassium and Vitamin D

Calcium, while generally considered a key element for maintaining bone density and strength, also has other health benefits including reducing blood pressure,²² and more importantly for both men and women losing weight, the prevention of any adverse effects of dieting on bone mass and a preventative effect on osteoporosis.²³

For example, calcium can also help lower your cholesterol.²⁴ In a recent study it was found that people with cholesterol levels in the high range of 240 to 260 reduced their total cholesterol by 6 percent when they took in an extra 1,800 milligrams of calcium a day. And the best part is that LDL (low-density lipoprotein) cholesterol--the bad cholesterol that's implicated in coronary artery disease, dropped by 11 percent. As well, calcium has recently been inversely associated with the incidence of colorectal adenomas.²⁵

But there's more. Calcium has also been shown to modulate the inflammatory response²⁶ and to increase weight loss. A recent study found that an increase in dietary calcium intake, together with a normal protein intake, increased fecal fat and energy excretion by about 350 calories per day.²⁷ This observation may help explain why a high-calcium diet produces weight loss, and it suggests that an interaction with dietary protein level may be important.

Several studies have shown that calcium plays a key role in body weight regulation and especially on fat metabolism (with possible effects on lipolysis, fat oxidation, lipogenesis, energy expenditure and appetite suppression) and thus is a useful supplement for those looking to decrease weight and body fat.^{28,29,30,31,32,33,34,35,36,37}

For example, Zemel et al. (2002) looked at the effects of calcium supplements on obese adults who were dieting. They found that a high-calcium diet (1200-1300 mg/day) resulted in greater weight and fat loss in humans compared to a low-calcium diet (400-500 mg/day).

Another study published in November, 2004 found that a high intake of calcium may hinder weight and fat regain.³⁸ The study found that after putting mice on a low calorie diet and producing weight and body fat loss, that those on a low calcium diet regained their weight after 6 weeks. However, for those on a high calcium diet it was a different story. They found that the high calcium diets produced significant increases in lipolysis, decreases in fatty acid synthase expression and activity, and reduced fat regain. They also found that increasing calcium through the use of dairy products had significantly greater effects on fat regain.

The bottom line is that increasing calcium intake is a boon to those who want to not only lose weight, but to lose fat, improve body composition, and keep that fat and weight from coming back.

Magnesium, besides complementing the effects of calcium on obesity³⁹ and other functions, also has important effects on its own. Low levels of magnesium promote inflammation^{40,41} and impact on the body's ability to handle stress.⁴² These functions, modulated by the magnesium in Metabolic, are useful in alleviating the release of pro-inflammatory cytokines, and decreasing both insulin resistance and inappropriate cortisol secretion.

Vitamin D is important for augmenting calcium dynamics. However, it also has other important effects,⁴³ for example on insulin resistance⁴⁴, inflammation^{45,46} and obesity^{47,48} (for more on this see below). Although getting adequate amounts of vitamin D is crucial to health, vitamin D deficiency is relatively common.^{49,50,51} As such, supplementing with vitamin D is important to realize all the benefits that it has to offer.

Potassium helps correct the potassium loss often seen with dieting and in some people under some circumstances. Marginal potassium levels are often seen in women who lose it secondary to their menses and fluid retention.

Loss of potassium can lead to fatigue and lethargy, which can decrease well being and can be counterproductive to dieting.

Neurohormonal Effects of Metabolic

There are several ingredients in Metabolic that have multiple properties and that affect various hormonal and other pathways. These ingredients have beneficial effects not only on weight loss and body composition but on health and feelings of well-being.

For example, **ocimum sanctum** has been shown to have significant antioxidant properties, to regulate thyroid function and to increase insulin sensitivity.^{52,53}

CDP-choline increases growth hormone as well as noradrenaline and dopamine levels in the central nervous system.⁵⁴

Since most of the ingredients in Metabolic serve two or more purposes I'll discuss them under the various neurohormonal systems that are affected by them.

Hormonal Optimization

Hormonal support is a mainstay of Metabolic and involves not only the hormones themselves but their neuroendocrine regulatory systems. As such, it's much more than simply replacement therapy or a quick fix, it's a way to actually optimize hormonal functioning and regulation in both the short and long terms.

Adrenal Support

Metabolic contains ingredients that normalize adrenal functioning due to weight loss, stress and aging.

It is well known that plasma levels of dehydroepiandrosterone (DHEA), a steroid hormone secreted the adrenal cortex, reach the maximal values in the third decade of life and then gradually decline with age. On the other hand cortisol levels tend to increase at the same time. This also tends to occur with prolonged dieting and stress.

The decrease in DHEA and increase in cortisol leads to weight gain and increases in body fat especially around the midsection.

Metabolic thus contains **DHEA** to augment declines in DHEA secretion resulting in a variety of beneficial effects, and ingredients such as **vitamin A, zinc, magnesium,** and **phosphatidylserine** to decrease inappropriate increases in cortisol levels.⁵⁵

Phosphatidylserine has been shown to not only to reduce levels of inflammatory mediators,⁵⁶ but also to dampen the ACTH and cortisol response to physical stress and decrease the reaction of the body to stressors.⁵⁷

This combination of DHEA and ingredients to decrease cortisol results in a lower cortisol/DHEA ratio, which has been proposed as a mechanism that regulates body weight and body fat levels, as well as contributing to feelings of well being.

Other ingredients in Metabolic help to normalize your system and allow you to adapt to stress. For example bacopa monniera extract has adaptogenic properties and has been shown to decrease the effects of stress on the adrenals and on other systems in the body.^{58,59}

DHEA

DHEA has potent effects on improving body composition, weight loss and fat loss while at the same time maintaining muscle.^{60,61,62,63,64}

But DHEA does much more than help regulate body composition.

- Sex hormones are known to play an important role in mood and well-being in both sexes. Because levels of these hormones decline with aging, there is a parallel deterioration of mental function, and DHEA replacement is thought to be of potential benefit.
- Many disorders of aging, such as reduced immunocompetence, obesity, diabetes, and cancers, have been attributed to changes in DHEA based on animal studies and human epidemiological data.^{65,66,67}

- DHEA replacement seems to lead to an improvement in mood and cognition, and a decrease in depression.⁶⁸
- DHEA has antioxidant properties and can reduce this free radical-induced damage.⁶⁹
- DHEA lowers serum insulin levels and increases insulin sensitivity and has been shown to have a role in reducing age-related increases in insulin levels, insulin resistance, and blood glucose.^{70,71,72}

Maca Root

Lepidium meyenii (maca) is rich in amino acids, iodine, iron, and magnesium. Traditionally maca root has been used in the Andean region for its supposed aphrodisiac and/or fertility-enhancing properties. Modest empirical support exists for its ability to improve male sexual function.

Growth Hormone

Growth hormone has a potent effect on body composition both directly, by increasing fat loss and maintaining muscle, and through stimulating increased systemic and tissue levels of insulin-like growth factor I (IGF-I).

Various ingredients in Metabolic, including **cytidine 5'-diphosphocholine (CDP choline)**, **Velvet bean extract (L-dopa)**, **coleus forskohlii**, **L-tyrosine**, **arginine alpha-ketoglutarate** and **zinc** increase GH secretion and IGF-1 levels, either directly or through increases in dopamine, which together act to increase protein synthesis, decrease muscle breakdown and increase body fat loss.

For example, **CDP choline** has been shown in several studies to have an effect on dopamine metabolism and increase serum levels of GH in man.^{73,74,75}

Especially where a deficiency may be present, supplemental **zinc** has resulted in an increase the secretion of growth hormone and IGF-I.⁷⁶

Insulin

Insulin resistance is felt to be a causative factor in obesity, the metabolic syndrome, diabetes and a host of other diseases. As well, as insulin resistance increases it results in changes in other hormones that can be detrimental to health and well being.

Measures to increase insulin sensitivity are important in order to reverse the adverse effects of insulin resistance

For example, one of the most frustrating aspects of being overfat is that your body has become conditioned to converting excess calories, especially with high carbohydrate intake, into body fat. Part of the problem with this fat conditioning involves insulin.

The problem is that as you gain more body fat you become more insulin resistance so that you need more insulin to do the same job as when you had less body fat. This increase in insulin decreases your ability to use body fat as fuel, and stores more energy as body fat. The end result is a fatter you. Increasing insulin sensitivity allows fat to be mobilized and burned off.

There are several ingredients in Metabolic that will increase insulin sensitivity, including **chromium, zinc, manganese, vitamin A, vitamin D, gymnema sylvestre** and **banaba leaf extract**.

Chromium enhances insulin sensitivity and decreases insulin resistance, and helps you to lose body fat.

Many studies have shown the effects of chromium on insulin and diabetes. Chromium has been shown to decrease fasting glucose levels, improve glucose tolerance, lower insulin levels, and decrease total cholesterol and triglyceride levels while increasing HDL (good) cholesterol levels

Although most diets just barely provide the RDA for chromium, for many it's not enough to make up for daily losses, especially if they exercise. With Metabolic you get another 50 mcg per day (using two doses daily), so that you have all the chromium you need for fat loss purposes.

But not any kind of chromium is OK. For example the most commonly used form of chromium, chromium picolinate, has potential adverse effects associated with its use.⁷⁷ The amino acid chelate form of chromium used in Metabolic is a readily absorbable and biologically active form of chromium that enhances insulin sensitivity, without side effects.

Chromium also works synergistically with other ingredients in Metabolic, such as **banaba leaf extract, zinc, vitamin D,** and **gymnema sylvestre** and all the ingredients that decrease inflammation and the levels of some of the pro-inflammatory cytokines, to optimize insulin metabolism and function.

Gymnema sylvestre has been long used as a treatment for diabetes. As well there is some evidence that it may possibly regenerate or revitalize the insulin-producing beta cells of the pancreas.^{78,79,80,81}

Banaba leaf extract increases insulin sensitivity as well as promoting weight loss.^{82,83} The active ingredient in banaba extract, corosolic acid, has been shown to have some anti-obesity potential.

It's been shown that there is an improvement in insulin resistance with **zinc** supplementation and that zinc is involved in controlling some of the aspects of obesity.⁸⁴

Zinc also improves calcium metabolism and thus the beneficial effects that calcium has on fat metabolism (see below).

Vitamin A increases insulin sensitivity. Vitamin A intake is associated with enhanced insulin-mediated glucose disposal.

Manganese is necessary for the metabolism of proteins and fats. It's also vital for proper immune and central nervous systems functioning, increases insulin sensitivity, has antioxidant properties, and is involved in energy metabolism.

Manganese is a mineral that is required in small amounts to manufacture enzymes necessary for the metabolism of proteins and fats. It also supports the immune system, regulates blood sugar levels, and is involved in the production of cellular energy, reproduction, and bone growth.

Manganese works with vitamin K to support blood clotting, aids in digestion, and as antioxidant, is a vital component of Sodium Oxide Dismutase, a large molecule that is the body's main front-line defense against damaging free-radicals. Working with the B-complex vitamins, manganese help control the effects of stress while contributing to ones sense of well being.

A deficiency in intake of manganese can retard growth, cause seizures, lead to poor bone formation, impair fertility, and cause birth defects. Researchers are also looking at new links between manganese deficiency and skin cancers.

Like magnesium, **germanium** is also involved in the electron transport system and in improving immune function.

Thyroid

As we mentioned before, your body reacts to decreasing calorie intake, and what it believes is impending starvation, by putting in place various survival mechanisms.

One of these ways it to decrease your metabolic rate and energy output mainly by decreasing the amount and activity of thyroid hormone.

Metabolic keeps the metabolism from shutting down in response to fewer calories through the action of various ingredients. For example:

1. Phosphates help maintain a higher metabolic rate.
2. Guggulsterones stimulate the thyroid gland
3. L-Tyrosine acts as a precursor to some neurotransmitters and thyroid both acting to decrease the metabolic effects of dieting.

Several ingredients in Metabolic optimize and increase thyroid hormone activity and increase metabolic rate. For example, **phosphates, guggulsterones Z and E, ocimum**

sanctum, and kelp, promote thyroid function, increase the metabolic rate and support thermogenesis. All actions that promote fat breakdown and oxidation.

Studies have shown guggulsterones to have thyroid stimulating activity, and increases thyroid efficiency by increasing the conversion of the less active T-4 to the more active T-3.^{85,86} The use of guggulsterones has been shown to result in a decrease in body fat, and to also lower cholesterol levels.⁸⁷

Metabolic also contains substantial amounts of natural phosphates, in the form of calcium, magnesium and potassium phosphates, which have also been shown to prevent a decrease in T-3 and increase the BMR.

And there's more good news. The combination of guggulsterones and phosphates has been recently shown to optimize body composition in adults.⁸⁸

Bioperine, a patented preparation of the black pepper thermogen, piperine, has demonstrated the ability to improve the absorption of nutrients. This result in less degradation of the active compounds; thereby ensuring higher percentages get through to work their magic!

References

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- ¹ Kalman D, Colker CM, Willets I, Roufs JB, Antonio J. The effects of pyruvate supplementation on body composition in overweight individuals. *Nutrition*. 1999 May;15(5):337-40.
 - ² Ivy JL, Cortez MY, Chandler RM, et al. Effects of pyruvate on the metabolism and insulin resistance of obese Zucker rats. *Am J Clin Nutr* 1994;59:331-7.
 - ³ Stanko RT, Tietze DT, Arch JE. Body composition, energy utilization, and nitrogen metabolism with a severely restricted diet supplemented with dihydroxyacetone and pyruvate. *Am J Clin Nutr* 1992; 55: 771–776.
 - ⁴ Stanko RT, Tietze DL, and Arch JE. Body composition, energy utilization, and nitrogen metabolism with a 4.25-MJ/d low-energy diet supplemented with pyruvate. *Am J Clin Nutr* 1992;56(4):630-5.
 - ⁵ Cicalese L, Lee K, Schraut W, et al. Pyruvate prevents ischemia-reperfusion mucosal injury of rat small intestine. *Am J Surg* 1996;171:97-101.
 - ⁶ Cicalese L, Subbotin V, Rastellini C, et al. Acute rejection of small bowel allografts in rats: Protection afforded by pyruvate. *Trans Proc* 1996;28(5):2474.
 - ⁷ Deboer LWV, Bekx PA, Han L, et al. Pyruvate enhances recovery of rat hearts after ischemia and reperfusion by preventing free radical generation. *Am J Physiol* 1993;265:H1571-6.
 - ⁸ Stanko RT, Mullick P, Clarke MR, et al. Pyruvate inhibits growth of mammary adenocarcinoma 13762 in rats. *Can Res* 1994;54:1004-7.
 - ⁹ Stanko RT, Reynolds HR, Hoyson R, et al. Pyruvate supplementation of a low-cholesterol, low-fat diet: Effects on plasma lipid concentration and body composition in hyperlipidemic patients. *Am J Clin Nutr* 1994; 59:423–27.

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- ¹⁰ Nageswara RR, Sakariah KK.) Lipid-lowering and antiobesity effect of (-) hydroxycitric acid. *Nutr* 1988. Res. 8:209-212.
- ¹¹ Sullivan AC, Hamilton JG, Miller ON, Wheatley VR. Inhibition of lipogenesis in rat liver by (-)-hydroxycitrate. *Arch Biochem Biophys* 1972;150:183–90.
- ¹² McCune SA, Foe LG, Kemp RG, Jurin RR. Aurintricarboxylic acid is a potent inhibitor of phosphofructokinase. *Biochem J* 1989; 259(3):925-27.
- ¹³ Hellerstein MK, Xie Y. The indirect pathway of hepatic glycogen synthesis and reduction of food intake by metabolic inhibitors. *Life Sciences* 1993; 53(24):1833-45.
- ¹⁴ Westerterp-Plantenga MS, Kovacs EM. The effect of (-)-hydroxycitrate on energy intake and satiety in overweight humans. *Int J Obes Relat Metab Disord* 2002; 26(6):870-2.
- ¹⁵ Leonhardt M, Langhans W. Hydroxycitrate has long-term effects on feeding behavior, body weight regain and metabolism after body weight loss in male rats. *J Nutr* 2002; 132(7):1977-82.
- ¹⁶ Neumann, G. Effects of L-carnitine on athletic performance. Seim, H. Loster, H. eds. *Carnitine: Pathophysiological Basics and Clinical Applications* 1996:61-71 Ponte Press Bochum, Germany.
- ¹⁷ Manoli I, De Martino MU, Kino T, Alesci S. Modulatory effects of L-carnitine on glucocorticoid receptor activity. *Ann N Y Acad Sci.* 2004 Nov;1033:147-57.
- ¹⁸ Famularo G, De Simone C, Trinchieri V, Mosca L. Carnitines and its congeners: a metabolic pathway to the regulation of immune response and inflammation. *Ann N Y Acad Sci.* 2004 Nov;1033:132-8.
- ¹⁹ Pertosa G, Grandalano G, Simone S, Soccio M, Schena FP. Inflammation and carnitine in hemodialysis patients. *J Ren Nutr.* 2005 Jan;15(1):8-12.
- ²⁰ McCarty MF, Gustin JC. Pyruvate and hydroxycitrate/carnitine may synergize to promote reverse electron transport in hepatocyte mitochondria, effectively 'uncoupling' the oxidation of fatty acids. *Med Hypotheses* 1999; 52(5):407-16.
- ²¹ Weiss GB. Metabolism and actions of CDP-choline as an endogenous compound and administered exogenously as citicoline. *Life Sci* 1995;56(9):637-60.
- ²² McCarron DA, Reusser ME. Finding consensus in the dietary calcium-blood pressure debate. *J Am Coll Nutr* 1999; 18: 398S-405S.
- ²³ Bowen J, Noakes M, Clifton PM. A high dairy protein, high-calcium diet minimizes bone turnover in overweight adults during weight loss. *J Nutr* 2004; 134: 568-573.
- ²⁴ Denke MA, Fox MM, Schulte MC. Short-term dietary calcium fortification increases fecal saturated fat content and reduces serum lipids in men. *J Nutr* 1993; 123: 1047-1053.
- ²⁵ Hartman TJ, Albert PS, Snyder K, et al. The association of calcium and vitamin d with risk of colorectal adenomas. *J Nutr.* 2005 Feb;135(2):252-9.
- ²⁶ Febbraio MA. Signaling pathways for IL-6 within skeletal muscle. *Exerc Immunol Rev.* 2003;9:34-9.
- ²⁷ Jacobsen R, Lorenzen JK, Toubro S, Krog-Mikkelsen I, Astrup A. Effect of short-term high dietary calcium intake on 24-h energy expenditure, fat oxidation, and fecal fat excretion. *Int J Obes Relat Metab Disord.* 2005 Jan 18; [Epub ahead of print]
- ²⁸ Davies KM, Heaney RP, Recker RR, Lappe JM, Barger-Lux MJ, Rafferty K, Hinders S. Calcium intake and body weight. *J Clin Endocrinol Metab* 2000; 85: 4635-4638.
- ²⁹ Zemel MB, Shi H, Greer B, Dirienzo D, Zemel PC. Regulation of adiposity by dietary calcium. *FASEB J* 2000; 14: 1132-1138.
- ³⁰ Zemel MB. Effects of calcium-fortified breakfast cereal on adiposity in a transgenic mouse model of obesity. *FASEB J* 2001; 15: A598.

-
- ³¹ Shi H, Dirienzo D, Zemel MB. Effects of dietary calcium on adipocyte lipid metabolism and body weight regulation in energy-restricted aP2-agouti transgenic mice. *FASEB J* 2001; 15:291–293.
- ³² Zemel MB, Thompson W, Zemel P, Nocton AM, Morris K, Campbell P. Dietary calcium and dairy products accelerate weight and fat loss during energy restriction in obese adults. *Am J Clin Nutr* 2002; 75:342S
- ³³ Heaney RP. Normalizing calcium intake: projected population effects for body weight. *J Nutr* 2003; 133: 268S-270S.
- ³⁴ Melanson EL, Sharp TA, Schneider J, Donahoo WT, Grunwald GK, Hill JO. Relation between calcium intake and fat oxidation in adult humans. *Int J Obes Relat Metab Disord* 2003; 27:196-203
- ³⁵ Papakonstantinou E, Flatt WP, Huth PJ, Harris RBS. High dietary calcium reduces body fat content, digestibility of fat, and serum vitamin D in rats. *Obes Res* 2003; 11: 387-394.
- ³⁶ Shapses SA, Heshka S, Heymsfield SB. Effect of calcium supplementation on weight and fat loss in women. *J Clin Endocrinol Metab*. 2004 Feb;89(2):632-7.
- ³⁷ Zemel MB, Thompson W, Milstead A, Morris K, Campbell P. Calcium and dairy acceleration of weight and fat loss during energy restriction in obese adults. *Obes Res*. 2004 Apr;12(4):582-90.
- ³⁸ Sun X, Zemel MB. Calcium and dairy products inhibit weight and fat regain during ad libitum consumption following energy restriction in Ap2-agouti transgenic mice. *J Nutr*. 2004 Nov;134(11):3054-60.
- ³⁹ Lelovics Z. Relation between calcium and magnesium intake and obesity. *Asia Pac J Clin Nutr*. 2004;13(Suppl):S144.
- ⁴⁰ Rayssiguier Y, Mazur A. R [Magnesium and inflammation:lessons from animal models.] *Clin Calcium*. 2005;15(2):245-248.
- ⁴¹ Maier JA, Malpuech-Brugere C, Zimowska W, Rayssiguier Y, Mazur A. Low magnesium promotes endothelial cell dysfunction: implications for atherosclerosis, inflammation and thrombosis. *Biochim Biophys Acta*. 2004 May 24;1689(1):13-21.
- ⁴² Consequences of magnesium deficiency on the enhancement of stress reactions; preventive and therapeutic implications (a review). *J Am Coll Nutr*. 1994 Oct;13(5):429-46.
- ⁴³ Nagpal S, Na S, Rathnachalam R. Non-Calcemic Actions of Vitamin D Receptor Ligands. *Endocr Rev*. 2005 Mar 29;
- ⁴⁴ Chiu KC, Chu A, Go VL, Saad MF. Hypovitaminosis D is associated with insulin resistance and β cell dysfunction. *Am J Clin Nutr* 2004;79:820–5.
- ⁴⁵ Rutter MK, Meigs JB, Sullivan LM, D'Agostino RB Sr, Wilson PW. C-reactive protein, the metabolic syndrome, and prediction of cardiovascular events in the Framingham Offspring Study. *Circulation* 2004;110:380–5.
- ⁴⁶ Rutter MK, Meigs JB, Sullivan LM, D'Agostino RB Sr, Wilson PW. C-reactive protein, the metabolic syndrome, and prediction of cardiovascular events in the Framingham Offspring Study. *Circulation* 2004;110:380–5.
- ⁴⁷ Parikh SJ, Edelman M, Uwaifo GI, Freedman RJ, Semega-Janneh M, Reynolds J, Yanovski J 2004 The relationship between obesity and serum 1,25-dihydroxy vitamin D concentrations in healthy adults. *J Clin Endocrinol Metab* 89:1196–1199.
- ⁴⁸ Arunabh S, Pollack S, Yeh J, Aloia JF 2003 Body fat content and 25-hydroxyvitamin D levels in healthy women. *J Clin Endocrinol Metab* 88:157–161.

-
- ⁴⁹ Glerup H, Mikkelsen K, Poulsen L, et al. Commonly recommended daily intake of vitamin D is not sufficient if sunlight exposure is limited. *J Intern Med* 2000;247:260–8.
- ⁵⁰ Thomas MK, Lloyd-Jones DM, Thadhani RI, et al. Hypovitaminosis D in medical inpatients. *N Engl J Med* 1998;338:777–83
- ⁵¹ Weaver CM, Fleet JC. Vitamin D requirements: current and future. *Am J Clin Nutr.* 2004 Dec;80(6 Suppl):1735S-9S.
- ⁵² Chattopadhyay RR. Hypoglycemic effect of *Ocimum sanctum* leaf extract in normal and streptozotocin diabetic rats. *Indian J Exp Biol* 1993 Nov;31(11):891-3.
- ⁵³ Panda S, Kar A. *Ocimum sanctum* leaf extract in the regulation of thyroid function in the male mouse. *Pharmacol Res* 1998 Aug;38(2):107-10.
- ⁵⁴ Secades JJ, Frontera G. CDP-choline: pharmacological and clinical review. *Methods Find Exp Clin Pharmacol* 1995 Oct;17 Suppl B:1-54.
- ⁵⁵ Nerozzi D, Magnani A, Sforza V, et al. Early cortisol escape phenomenon reversed by phosphatidylserine in elderly normal subjects. *Clinical Trials J* 1989;26:33-38.
- ⁵⁶ Henson PM, Bratton DL, Fadok VA. The phosphatidylserine receptor: a crucial molecular switch? *Nat Rev Mol Cell Biol.* 2001 Aug;2(8):627-33.
- ⁵⁷ Hellhammer J, Fries E, Buss C, Engert V, Tuch A, Rutenberg D, Hellhammer D. Effects of soy lecithin phosphatidic acid and phosphatidylserine complex (PAS) on the endocrine and psychological responses to mental stress. *Stress.* 2004 Jun;7(2):119-26.
- ⁵⁸ Rai D, Bhatia G, Palit G, Pal R, Singh S, Singh HK. Adaptogenic effect of *Bacopa monniera* (Brahmi). *Pharmacol Biochem Behav.* 2003 Jul;75(4):823-30.
- ⁵⁹ Rohini G, Sabitha KE, Devi CS. *Bacopa monniera* Linn. extract modulates antioxidant and marker enzyme status in fibrosarcoma bearing rats. *Indian J Exp Biol.* 2004 Aug;42(8):776-80.
- ⁶⁰ Tagliaferro AR, Davis JR, Truchon S, Van Hamont N. Effects of dehydroepiandrosterone acetate on metabolism, body weight and composition of male and female rats. *J Nutr.* 1986;116:1977-1983.
- ⁶¹ Kurzman ID, MacEwen EG, Haffa AL. Reduction in body weight and cholesterol in spontaneously obese dogs by dehydroepiandrosterone. *Int J Obes.* 1990;14:95-104.
- ⁶² Morales AJ, Haubrich RH, Hwang JY, Asakura H, Yen SS. The effect of six months treatment with a 100 mg daily dose of dehydroepiandrosterone (DHEA) on circulating sex steroids, body composition and muscle strength in age-advanced men and women. *Clin Endocrinol (Oxf).* 1998;49:421-432.
- ⁶³ Herranz L, Megia A, Grande C, Gonzalez-Gancedo P, Pallardo F. Dehydroepiandrosterone sulphate, body fat distribution and insulin in obese men. *Int J Obes Relat Metab Disord.* 1995;19:57-60.
- ⁶⁴ Maccario M, Mazza E, Ramunni J, et al. Relationships between dehydroepiandrosterone-sulphate and anthropometric, metabolic and hormonal variables in a large cohort of obese women. *Clin Endocrinol (Oxf).* 1999;50:595-600.
- ⁶⁵ Schneider EL, Reed JD Jr. Life extension. *N Engl J Med.* 1985;312:1159-1168.
- ⁶⁶ Barrett-Connor E, Khaw KT, Yen SS. A prospective study of dehydroepiandrosterone sulfate, mortality, and cardiovascular disease. *N Engl J Med.* 1986;315:1519-1524.
- ⁶⁷ Thoman ML, Weigle WO. The cellular and subcellular bases of immunosenescence. *Adv Immunol.* 1989;46:221-261.
- ⁶⁸ Bloch M, Schmidt PJ, Danaceau MA, Adams LF, Rubinow DR. Dehydroepiandrosterone treatment of midlife dysthymia. *Biol Psychiatry.* 1999;45:1533-1541.

-
- ⁶⁹ Bastianetto S, Ramassamy C, Poirier J, Quirion R. Dehydroepiandrosterone (DHEA) protects hippocampal cells from oxidative stress-induced damage. *Brain Res Mol Brain Res.* 1999;66:35-41.
- ⁷⁰ ED, Buffington CK, Hubert GD, et al. Divergent correlations of circulating dehydroepiandrosterone sulfate and testosterone with insulin levels and insulin receptor binding. *J Clin Endocrinol Metab.* 1988;66:1329-1331.
- ⁷¹ Diamond P, Cusan L, Gomez JL, Belanger A, Labrie F. Metabolic effects of 12-month percutaneous dehydroepiandrosterone replacement therapy in postmenopausal women. *J Endocrinol.* 1996;150(suppl):S43-S50.
- ⁷² Jakubowicz D, Beer N, Rengifo R. Effect of dehydroepiandrosterone on cyclic-guanosine monophosphate in men of advancing age. *Ann N Y Acad Sci.* 1995;774:312-315.
- ⁷³ P. Fonlupt, M. Martinet and H. Pacheco, Effect of CDP-choline on dopamine metabolism in central nervous system. In: V. Zappia, E.P. Kennedy, B.I. Nilsson and P. Galetti, Editors, *Novel biochemical, pharmacological, and clinical aspects of CDP-choline*, Elsevier Science, New York (1985), p. 169.
- ⁷⁴ Matsuoka T, Kawanaka M, Nagai K. Effect of cytidine diphosphate choline on growth hormone and prolactin secretion in man. *Endocrinol Jpn* 1978 Feb;25(1):55-7.
- ⁷⁵ Salvadorini F, Saba P, Forli C, Tusini G, Galeone F. Effect of cytidine diphosphate choline on growth hormone secretion in patients with brain or pituitary lesions. *Endocrinol Jpn* 1980 Jun;27(3):265-71.
- ⁷⁶ Imamoglu S, Bereket A, Turan S, Taga Y, Haklar G. Effect of zinc supplementation on growth hormone secretion, IGF-I, IGFBP-3, somatomedin generation, alkaline phosphatase, osteocalcin and growth in prepubertal children with idiopathic short stature. *J Pediatr Endocrinol Metab.* 2005 Jan;18(1):69-74.
- ⁷⁷ Vincent JB. The potential value and toxicity of chromium picolinate as a nutritional supplement, weight loss agent and muscle development agent. *Sports Med.* 2003;33(3):213-30.
- ⁷⁸ Persaud SJ, Al-Majed H, Raman A, Jones PM. *Gymnema sylvestre* stimulates insulin release in vitro by increased membrane permeability. *J Endocrinol* 1999 Nov;163(2):207-12.
- ⁷⁹ Shanmugasundaram ER, Gopinath KL, Radha Shanmugasundaram K, Rajendran VM. Possible regeneration of the islets of Langerhans in streptozotocin-diabetic rats given *Gymnema sylvestre* leaf extracts. *J Ethnopharmacol.* 1990; 30(3):265-79.
- ⁸⁰ Sugihara Y, Nojima H, Matsuda H, Murakami T, Yoshikawa M, Kimura I. Antihyperglycemic effects of gymnemic acid IV, a compound derived from *Gymnema sylvestre* leaves in streptozotocin-diabetic mice. *J Asian Nat Prod Res.* 2000;2(4):321-7.
- ⁸¹ Basakaran, K.; Ahmath, B. K.; Shanmugasundaram, K. R.; Shanmugasundaram, E. R. B. Antidiabetic effect of a leaf extract from *Gymnema sylvestre* in non-insulin-dependent diabetes mellitus patients. *J. Ethnopharm.* 1990, 30, 295-305.
- ⁸² Kakuda T, Sakane I, Takihara T, Ozaki Y, Takeuchi H, Kuroyanagi M. Hypoglycemic effect of extracts from *Lagerstroemia speciosa* L. leaves in genetically diabetic KK-A_Y mice. *Biosci Biotechnol Biochem.* 1996 Feb;60(2):204-8.
- ⁸³ Suzuki Y, Unno T, Ushitani M, Hayashi K, Kakuda T. Antiobesity activity of extracts from *Lagerstroemia speciosa* L. leaves on female KK-A_Y mice. *J Nutr Sci Vitaminol (Tokyo).* 1999 Dec;45(6):791-5.

-
- ⁸⁴ Marreiro DN, Geloneze B, Tambascia MA, Lerario AC, Halpern A, Cozzolino SM. [Participation of zinc in insulin resistance] Arq Bras Endocrinol Metabol. 2004 Apr;48(2):234-9.
- ⁸⁵ Tripathi YB, Malhotra OP, Tripathi SN. Thyroid stimulating action of Z-guggulsterone obtained from Commiphora mukul. Planta Med 1984; 1:78-80.
- ⁸⁶ Tripathi YB, Tripathi P, Malhotra OP, Tripathi SN. Thyroid stimulatory action of (Z)-guggulsterone: mechanism of action. Planta Med 1988 Aug;54(4):271-7.
- ⁸⁷ Urizar NL, Moore DD. Gugulipid: A Natural Cholesterol-Lowering Agent. Annu Rev Nutr 2003; 26; 303-313.
- ⁸⁸ Antonio J, Colker CM, Torina GC, et al. Effects of a Standardized Guggulsterone Phosphate Supplement on Body Composition in Overweight Adults: A Pilot Study. Current Therapeutic Research 1999; 60(4):220-227.