Orentreich Foundation for the Advancement of Science, Inc.

VitaLongevity™

Logo: Life's blood flows through the hourglass; the stopcock represents the alteration of aging and disease as biomedical research progresses.

March 2005

Calorie Restriction & Lifespan Extension

By now you've undoubtedly heard of the lifespan extension afforded by rather severe calorie restriction in a variety of animal species ranging from insects to mammals. Early results from long-term studies in non-human primates hint that such deprivation might also work in human beings. Already, numerous stalwart individuals practice various forms of calorie restriction in hopes of slowing the rate of aging and postponing the development of age-associated maladies (*e.g.,* dementia, cancer, and cardiovascular disease). Unfortunately, these motivated human 'guinea pigs' suffer from constant hunger and an abnormal focus on food 24/7 as well as loss of libido. Such a drastic reduction in food intake is out of the question for most of us. Incredibly, a more palatable solution might exist, one that is intimately related to the story of insulin resistance and the Metabolic Syndrome.

The Insulin Connection

Science cannot yet answer the question of how calorie restriction slows the rate of aging. Originally, scientists assumed that the absolute reduction in the amount of food metabolized, primarily via oxidation, results in fewer highly reactive and damaging molecules normally produced as by-products. These reactive oxygen species (ROS) wreak havoc by attacking proteins, lipids, and DNA; over time, cellular repair processes falter, and organs and tissues no longer function optimally. While calorie restriction might avert some of that wear and tear, newer evidence implicates benefits derived from improvements in the activity of the hormone insulin.

Insulin accomplishes its vital and myriad roles in metabolism and maintenance of blood glucose levels in an extraordinarily complex manner, interacting with many other molecules. Researchers in the aging field are busy sorting out where in the scheme of insulin signaling calorie restriction has its apparent effects; the answer, when it comes, could be totally unexpected.

Glycemic Index of Common Foods

Apple, 1 med	38
Banana, 1 med	55
Watermelon, 1 cup (5 oz)	72
Oatmeal, old-fashioned, 1/2 cup in water (4 oz)	49
Cornflakes, 1 cup (1 oz)	83
Yogurt, nonfat, unsweetened, 8 oz	14
Milk, whole, 1 cup	27
Tomato soup, canned, 1 cup	38
Orange juice, 1 cup	46
Cola, 1 can (12 oz)	63
Spaghetti, white, 1 cup cooked	37
Peas, canned, 1/2 cup	42
Potato, baked with skin, 1 med (4 oz)	85
Peanuts, 1/2 cup (2.5 oz)	14
Pretzels, 1 oz	83

The more insulin sensitive an animal is (the lower the insulin level needed to maintain optimum blood glucose levels), the better for long-term health and longevity. Insulin resistance, wherein ever higher levels of insulin production are needed just to maintain the status quo, lies at the opposite end of the spectrum. Abdominal obesity appears to be the main culprit in most cases of insulin resistance and, if left unchecked, frequently leads to the Metabolic Syndrome, which promotes early aging as well as cardiovascular disease and Type 2 diabetes. Thus we see a continuum of insulin's effects from retarded aging in sensitive animals to accelerated aging in resistant animals.

Calorie Restriction Mimetics

Calorie restriction mimetics can be either nutritional approaches or pharmaceutical compounds that mimic insulin's effects or reduce the need for insulin by making it more efficient. The goal, from an anti-aging viewpoint, is greater-than-normal insulin sensitivity without onerous calorie restriction—the "let them eat cake" approach. Can one expect to benefit from improvements in insulin signaling without starving, gain without pain so to speak? Our own work with methionine*-restricted (MR) rats leads us to suspect the answer is yes. MR rats actually eat more for their size than unrestricted rats, maintain insulin sensitivity into old age, and live 40% longer.

We discuss below the nutritional approaches and supplements with the most scientific validity to date. As to how to know whether you can benefit from implementing any of these suggestions, we strongly urge you to ask your physician for an Insulin Glucose Tolerance Test (IGTT).

Not all physicians can provide an IGTT; at the very least, insist upon a fasting insulin level. A result above 15 μU/mL for a non-diabetic means requiring more insulin than normal to maintain an ideal fasting blood glucose level of <110 mg/dL. The goal to shoot for: a fasting insulin under 10 μU/mL, optimally 7 μU/mL or less. Consider two time-tested methods for improving the insulin profile: losing as little as 5-7% of body weight and 30 minutes/day of aerobic exercise (*e.g.,* walking). Other suggestions:

*an essential amino acid

Nutritional Approaches

Pay attention to the **glycemic index** (GI) of the foods you eat (see table). The GI ranks foods based on how they affect blood glucose levels. The lower the GI, the more slowly the food is absorbed and the more slowly blood glucose levels rise, requiring less insulin production. For example, peanuts (GI 14) make a better snack than pretzels (GI 83). You can find a guide to GI at <www.prevention.com>.

Strive to keep your between-meal insulin level as low as possible. Frequent sweet snacks keep basal insulin levels moderately elevated throughout the day; this in turn primes the liver to overproduce triglycerides (TG) and VLDL (bad lipoprotein particles) after a large meal. Fructose, without causing much of an insulin rise, can also increase TG and VLDL output; therefore, avoid fructose and foods made with high-fructose corn syrup (HFCS), especially between meals.

Insulin-Sensitizing Supplement	Dose (mg/day)
Alpha-Lipoic Acid	250-500
Biotin	2.5-5
Magnesium	500
Resveratrol (grape seed extract)	200

Emphasize the **nut** in nutrition. Substitute nuts for refined sugar and HFCS-rich snacks. The Nurse's Health Study reported that eating just 5 ounces of nuts per week caused a 27% decline in diabetes development. Experts cannot yet say what component in nuts might be responsible for this effect. Walnuts, particularly rich in α-linolenic acid used by the body to make beneficial omega-3 fatty acids, afford the best results; but other nuts, as well as peanuts (a legume), provide benefits. One ounce of walnuts equals 12 walnut halves and 185 calories.

Add some spice to your diet in the form of **cinnamon.** Extracts from cinnamon mimic some of the effects of insulin and actually enhance its activity in a synergistic way. As little as one-half teaspoonful of cinnamon daily can prevent insulin 'spikes' and lower both glucose and TG levels. **Oat fiber** also helps control blood sugar and increases insulin sensitivity; this is in addition to its favorable cholesterol-lowering effects. All forms of oatmeal, including instant, show similar benefit and, conveniently, provide a place to sprinkle cinnamon.

A little **alcohol** goes a long way if no health-related conditions prohibit you from partaking. The amount of alcohol in a 5-ounce glass of wine or 12 ounces of beer daily lowers insulin levels and beneficially raises HDL-cholesterol. Red wine, because of its **resveratrol** content, is the best choice. Calorie restriction revs up the production of a protein called SIRT1 which spurs fat breakdown, a critical component of its lifespan extension effects in mammals. Resveratrol also increases the activity of SIRT1, earning it a place on the short-list of calorie restriction mimetics.

Supplements

Many supplements lay claim to improving insulin activity; no one can take them all nor should one. We have selected those most likely to help the majority of consumers, that provide other non-insulin-related benefits, and that are considered to be relatively safe.

Alpha-Lipoic Acid (αLA), a fatty acid that functions as an enzyme cofactor during oxidative glucose metabolism and cellular energy production, improves insulin sensitivity in a number of ways. Primarily, αLA counteracts oxidative stress that reduces effectiveness of insulin. It is both safe and well-tolerated. Look for extended-release formulations; 250-500 mg per day should be sufficient. αLA can compete with biotin at this dosage, so we suggest taking biotin for this reason as well as for its own ability to improve insulin action.

Biotin, or Vitamin H (see VitaLongevity June 2004), appears to regulate some of the same enzymes as insulin and substantially lowers fasting glucose levels in Type 2 diabetics. Since sub-optimum biotin status might be quite prevalent and as there are no known toxic effects of biotin, we suggest a supplement of 2.5-5 mg daily.

Magnesium is required for optimal activity of several of the enzymes responsible for glucose metabolism, and most of us simply do not get enough of it. Because magnesium deficiency is so widespread, it probably contributes to insulin resistance in over 50% of cases. Daily magnesium supplementation of 500 mg should be safe for all but those with kidney disease. An added bonus: magnesium safely lowers blood pressure. If you already take calcium, consider a product that also contains magnesium to counteract calcium's constipating effect.

Resveratrol, in the form of 100 mg capsules of grape seed-skin extract, can be taken in lieu of red wine or grape juice. Two capsules daily should suffice.