# Insulin Resistance

## Pathophysiology and Natural Therapeutics for The Metabolic Syndrome

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Published by the North American Isntitute of Medical Herbalism, Inc
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# Insulin Resistance Syndrome Overview

## Normal insulin function

- After a meal, the increased glucose and/or amino acids in the blood cause the pancreas to secrete insulin
- Insulin binds to the cell membranes.
- The binding triggers the expression of glucose receptors through the cell membrane.
- Glucose, amino acids, and fats are then transported into the cell, along with magnesium and some other nutrients.
- The binding causes preferential use of glucose rather than fat as fuel
- The binding inhibits the burning of fat by the cells.
- Growth hormone is inhibited, and thyroid effects are slightly depressed during the insulin surge (conversion of T-4 to T-3 is blunted.
- Once the nutrients are cleared from the blood, the pancreas stops secreting insulin. Under normal conditions, this occurs within 3 hours.

## Abnormal function = Insulin Resistance.

- *Either* the circulating insulin does not bind to the insulin receptors on the cell
- *Or* it binds, but its effects are deficient, and the nutrients are not efficiently cleared from the blood.
- The pancreas then continues to secrete more insulin, leading to higher levels in the blood, and for a longer time period, before the nutrients are eventually cleared from the cell.

***Insulin resistance*** with compensatory ***hyperinsulinemia*** is called Syndrome X, The Metabolic Syndrome, or Insulin Resistance Syndrome

Pathological consequences may be due to:

- Deficient function in insulin resistant cells (liver, fat, untrained muscle)
- Excess anabolic effects and ***oxidation*** in cells that are not insulin resistant but which are now exposed to much higher levels of insulin than normal(epithelial cells, endothelium in the arteries, cancer cells)
- Systemic inflammation. Hypersinsulnemia with escess abdominal fat is strongly associated with elevated systemic inflammatory markers such as c-reactive protein.
- The pharmacological effects of excess insulin on the system(for example, hypertension, "thick" blood, water retention, suppressed fat burning)
- The adverse systemic effects of blunted growth hormone and thyroid hormone effects.

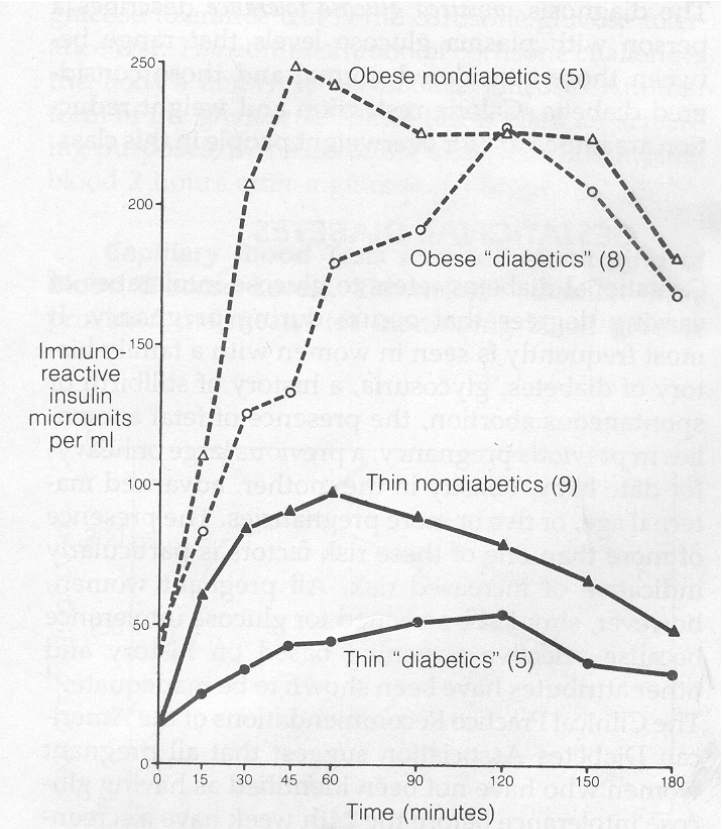



**FIG. 46-3.** Mean absolute insulin responses in both thin and obese patients with diabetes during a 3-hour (100-g) oral glucose tolerance curve. (Bagdade, J. D., Biermann, E. L., & Porter, D. [1967]. The significance of basal insulin levels in evaluation of the insulin response to glucose in diabetic and nondiabetic subjects. *Journal of Clinical Investigation (New York), 46*(10), 1553.)

## The possible manifestations of syndrome X

- Abdominal obesity.
- Hypertension
- Abnormal blood lipids, elevated Triglycerides and depressed HDL cholesterol. (Does not affect total cholesterol or LDL cholesterol levels, but promotes smaller and more atherogenic LDL particles
- Oxidative damage to arteries and other tissues may initiate or promote atherosclerosis and neoplasia
- The elevated insulin causes thick, sticky blood that tends to clot.
- Advanced Metabolic Syndrome may manifest as hypoglycemia, abnormal glucose tolerance, or Gestational or Type II diabetes. The majority of people with the Metabolic

Syndrome die of something else (heart attack, stroke) before they develop diabetes or glucose abnormalities.

- May be a primary factor in an initation and growth of breast, colon, prostate, and other cancers.
- Is a primary contributor to polycystic ovarian syndrome
- May be involved in neurological damage accompanying senility.

### How to diagnose.

- Elevated triglycerides (> 150) or depressed HDL cholesterol (< 40 male < 50 female)
- Waist:hip ratio > or equal to 1 in a male, or waist > 40 inches
- Waist:hip ratio > or equal to 0.8 in a female, or waist > 35 inches
- Abnormal glucose tolerance // Fasting glucose > 100

If these are present, then the rest of it is, especially the arterial damage and thick blood, and the risk of diabetes is greatly elevated.

## What causes insulin resistance?

- Genetic predisposition. About 25% of the North American population are highly genetically prone. Native Americans and Mexican Americans with native blood are very highly prone. African Americans may be more prone than whites. Another 40% are moderately prone. About a third of North Americans are only slightly prone. By age 60, 40% of Americans have at least 3 different markers for the Metabolic Syndrome, and 60-70% have at least one marker.
- Omega-3 fatty acid deficiency in the cell membrane. Specifically the essential fat doxohexaenoic acid (DHA).
- Elevated Omega 6: omega 3 fatty acid ratio in cell membrane.
- Trans fatty acids in cell membrane
- Deficiencies of chromium, magnesium, zinc, B-vitamins. Possibly also the trace elements boron and lithium. Chromium's only known physiological role is in a "docking molecule" that allows insulin to bind to its receptors on the cell. Magnesium repletion is necessary for complete response of the cell to insulin binding.
- Lack of resistance exercise, manual labor, and trained muscle mass.
- Diet with high glycemic index.
- Eating high glycemic snacks and sweet drinks.
- Stress may contribute through hypersortisolemia
- Insufficient protein in the diet

- Sleep deprivation
- Nicotine. Smoking, chewing tobacco, or nicotine gum all induce insulin resistance and its various manifestations. This effects accounts for many of the non-respiratory adverse effects of nicotine.

## The cure (or prevention).

- Aggressive supplementation with the nutrients known to be essential for normal insulin sensitivity, and increasing foods that contain them.
- A diet with a low glycemic index (lower carbohydrate, more protein, higher "good" fats)
- Regular resistance exercise to increase trained muscle mass.
- Proper rest, especially adequate sleep at night.

The above interventions, engaged in together, rapidly reverse insulin resistance. Typical results are seen within a week, and profound results within a month.

# Metabolic Dysregulation in the Insulin Resistance Syndrome

**The factors contributing to The Metabolic Syndrome are very recent in human history, and the organism does not have an effective response to correct it through homeostasis. In fact, the responses of the system to hyperinsulinemia are counter-productive, and tend to make it worse in a vicious-cycle pathology.**

## How hyperinsulinemia promotes hyperinsulinemia

- In response to chronic insulin elevation, many cells down-regulate their own insulin receptors, by reducing their number or their responsiveness to insulin. The cell establishes regulatory homeostasis at the new level of hyperinsulinemia. Afterwards, elevated insulin is necessary to elicit a normal response from the cell. This situation is the **organic phase** of carbohydrate addiction.
- Hyperinsulinemia inhibits growth hormone, in turn reducing trained lean muscle mass, further increasing total insulin resistance.
- Hyperinsulinemia inhibits fat burning, promoting increased fat mass, further increaisng insulin resistance. Fat cells are inherently insulin resistant compared to trained muscle mass.

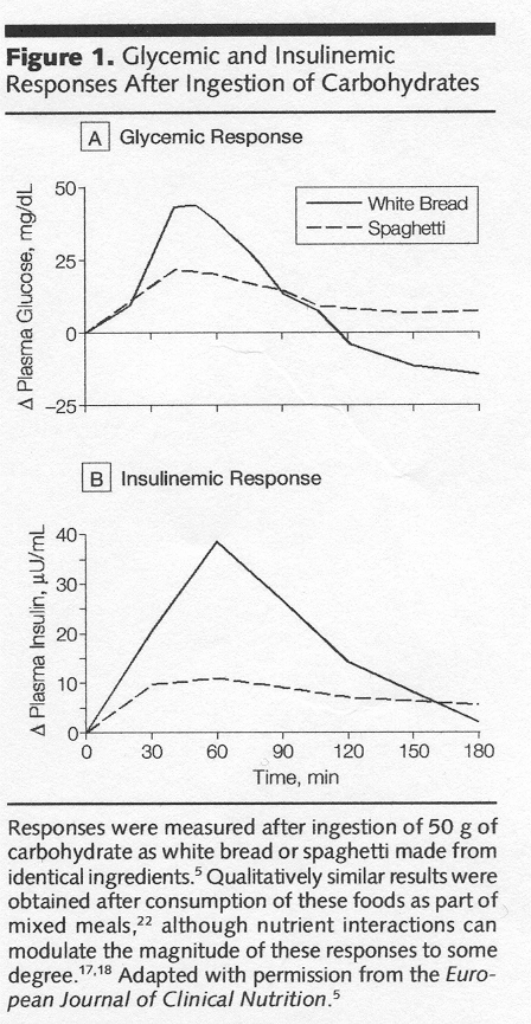
**Impaired chromium and magnesium**

- Chromium is normally stored away in the liver between meals. It is released in response to insulin secretion, and promotes the binding of insulin to the cells during the insulin excursion. During this period it may also be excreted. Elevated and prolonged insulin curves allow excessive excretion of chromium, "strip-mining" it from the system. One estimate of total body chromium stores found that some individuals have less than 10% of the chromium stores of some others. Hyperinsulinemia promotes chromium excretion, and chromium deficiency promotes hyperinsulinemia.
- Magnesium follows a similar pattern in that insulin is effectively a "magnesium diuretic" and promotes excessive loss. Magnesium is essential for the cellular response to insulin binding. Thus hyperisnulinemia causes magnesium deficit, and mangesium loss promotes insulin resistance.

**Therapeutic preview: Immediate supplementation with chromium and magnesium is necessary to break the vicious cycle of insulin resistance.**

## How High Glycemic Carbohydrate (HGC) promotes HGC addiction

- HGC promote an elevated insulin response, relative to anthropological norms. This promotes the homeostatic adaptation to hyperinsulinemia (see above). Now HGC effect are necessary for normal cell metabolism, and carbohydrate cravings replace true hunger.
- HGC promote acute hypoglycemia and counter-regulatory spikes of cortisol and/or adrenalin, which in turn promote HGC craving (See graph at top of next page).




Ludwig, DS. The glycemic index: physiological mechanisms relating to obesity, diabetes, and cardiovascular disease. JAMA 287(18):2414-2423

- HG diet completely inhibits ketosis. The brain and muscle lose adaptation to burn ketones as fuel, the normal function of ketones. The result is fatigue, depression, and cognitive disorientation in response to ketosis. Withdrawal and re-adaptation takes 2-3 weeks, with remittent binges on HGC a universal phenomenon to suppress the discomfort.

The lower graph at the left shows the insulin response to the same amount of calories consumed as low glycemic (bottom curve) vs high glycemic (uypper curve) carbohydrates in normal adults without indications of insulin resistance or diabetes. The insulin response to the HGC is approximately four times that to the LGC.

The upper graph shows the glycemic responses to the two foods. The initial glucose spike in response to the HGC is about twice as high as that of the LGC. However, the high insulin response seen in the lower graph causes a "crash" of the glucose to produce hypoglycemia. As the glucose approaches the point of hypoglycemia, the body secretes counterregulatory hormones (cortisol, adrenalin, and others) in order to drive the glucose up.

At this point, cortisol is demanding the release of glucose from the cells, lwhile insulin is blocking the release. The result is gnawing hunger and craving for carbohydrates, frequently seen in modern individuals at the two hour point after eating HGC.

**Therapeutic preview: Supplementing low glycemic snacks and drinks for high glycemic ones is a vritical first step in breaking the cycle.**

See also the chapter on Appetite Hormones for a deeper look at dysregulation of appetite and fat burning.

## How sedentary lifestyle promotes sedentary lifestyle

- Lack of moderate exercise promotes untrained muscle mass and increased obesity.

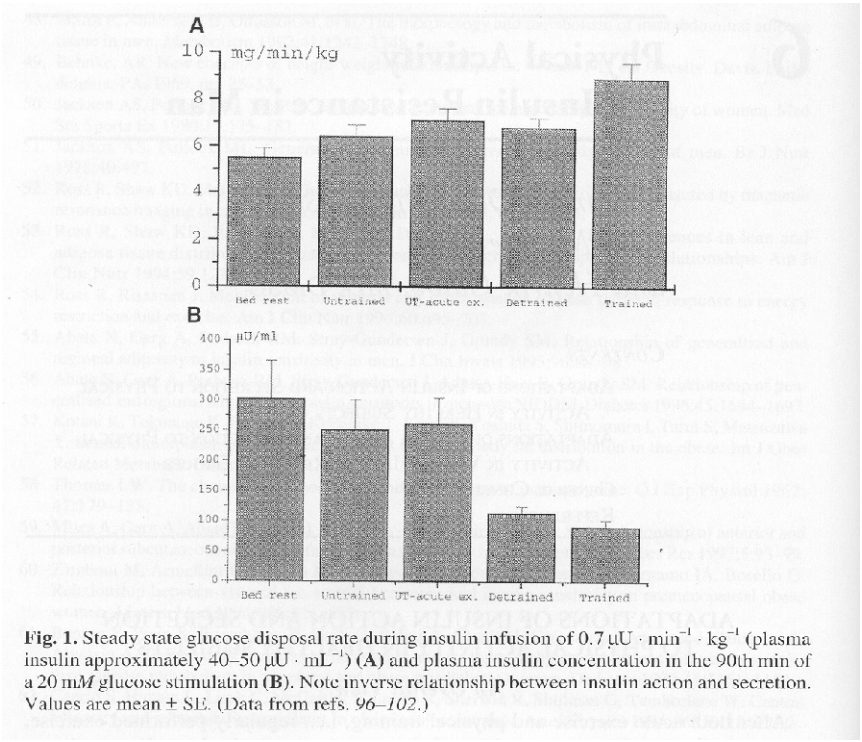



**Fig. 1.** Steady state glucose disposal rate during insulin infusion of 0.7 μU · $min^{-1}$ · $kg^{-1}$ (plasma insulin approximately 40–50 μU · $mL^{-1}$) **(A)** and plasma insulin concentration in the 90th min of a 20 m*M* glucose stimulation **(B)**. Note inverse relationship between insulin action and secretion. Values are mean ± SE. (Data from refs. *96–102*.)

**Graph A** above shows the ability of the muscles under different conditions to utilize glucose with the assistance of insulin. Trained muscle clears glucose more effectively that untrained muscle.

**Graph B** shows the amount of insulin remaining in the serum ninety minutes after administration of glucose under various conditions of the muscle. Trained muslce is more efficient at using glucose and reducing insulin than untrained.

Flemming D, Mikines K, Galbo H. Physical activity and insulin resistance in man. In: Reaven GM and Laws A Insulin Resistance: The Metabolic Syndrome X. Totowa, NJ, Humana Press, 1999

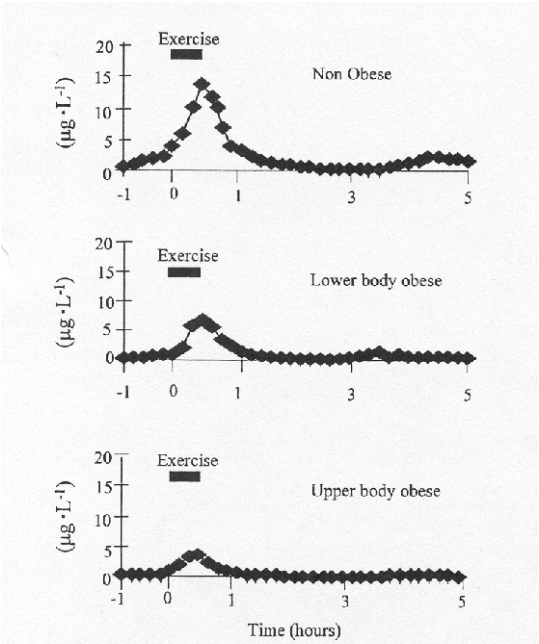



FIG. 1. Mean serum GH concentrations for each group over the 6-h period of blood sampling. Exercise began at time zero and continued for 30 min at an intensity of 70% $VO_2$ peak.

- Increased weight, weakened muscles, and blunted growth hormone response to exercise all frustrate attempts to exercise. (Sports drinks negate any beneficial effect of GH on fat burning and muscle deposition)

As obesity progresses, the GH response to exercise decreases. Exercise this does less and less to promote fat burning and build lean muscle mass the more obese an individual becomes.

Kanaley M, Weatherup-Dentes M, Jaynes EB, Hartman ML. Obesity attenuates the growth hormone response to exercise. *J Clin Endocrinol Metab.* 84(9): 3156-3161.

**Therapeutic preview: Cross training of as many muscle groups as possible can rapidly reduce insulin resistance.**

# Pathophysiology of Insulin Resistance

Pathological consequences may be due to:

- Deficient function in insulin resistant cells (liver, fat, untrained muscle)
- Excess anabolic effects and ***oxidation*** in cells that are not insulin resistant but which are now exposed to much higher levels of insulin than normal(epithelial cells, endothelium in the arteries, cancer cells)
- Systemic inflammation
- The pharmacological effects of excess insulin on the system(for example, hypertension, "thick" blood, water retention, suppressed fat burning)
- The adverse systemic effects of blunted growth hormone and thyroid hormone effects.

## Insulin-like growth factor (IGF-1)

Under conditions of hyperinsulinemia, the liver secretes large amounts of IGF-1 in an endocrine manner. IGF-1 in a growth factor. Through its *anabolic* and *oxidative* effects on non-insulin-resistant tissues, such as epithelial cells and some tumors, hypersinsulinemia may initiate cancers or atherosclerosis, and IGF-1 may then promote their growth.

**The "cocktail" of I and Igf-1 is at the root of several manifestations of Insulin Resistance Syndrome.**

PANCREAS ——-> Insulin ———> LIVER ——> IGF-1 ——> (inhibits) blood sugar

**Insulin** promotes oxidative effects, which may initiate cancer. **IGF-1** is a growth factor that may promote the growth of various tumors. It has a demonstrated connection in colon, breast, and prostate cancers. It may also promote hyperkeratinization in acne, elongation of the eyeball in juveline onset myopia, overgrowth of bones during youth and adolescence, the growth of uterine fibroids, and other conditions. Research in this area is very recent, but is proliferating rapidly due to strong positive results.

**More detail:**

Elevated insulin ———-> elevated IGF-1

———-> decreased IGF binding protein-3 ———-> decreased sensitivity to Retinoic acid, which normally INHIBITS cell growth

Injecting IGF-1 into test animals increased tumor growth

Injecting IGFBP3 decreases tumor growth.

**Effects on Growth Hormone Secretion**

Insulin ———-> Elevated IGF-1 ———-> Blocks pituitary secretion of Growth Hormone

## Insulin resistance and obesity

Insulin "switches" the cell from fat burning to storage mode. Prolonged insulin curves, or more frequent insulin spikes from snacking for greater total daily exposure to insulin promotes obesity.

Obesity, expressed as increased fat mas relative to trained muscle, increases net insulin resistance

## Insulin resistance and dyslipidemia

Hyperinsulinemia alters the lipid profile of the serum in ways detrimental to health. It affects three lipid parameters. Each of these is a separate risk factor for atherosclerosis and heart attack.

- **Increases triglycerides**. It has been known since the 1950s that elevated triglycerides present a greater risk for heart attack than elevated cholesterol, and this knowledge is responsible for the recent lowering of "normal" triglycerides to 150 from 200 mg/dl.
- **Decreases HDL cholesterol**. HDL cholesterol is the "good cholesterol."
- **Increases the "small dense" portion of LDL cholesterol** LDL is the "bad cholesterol" but the actual culprit has been a moving target in research. In about 1994 it emerged that *oxidized* LDL was much more dangerous than LDL itself. More recently, researchers found that ***small dense LDL particles*** were more susceptible to oxidation. The discovery that the liver began elevating the small dense portion of LDL when triglycerides went over 150 mg/dl resulted in the lowering of the upper normal level for TG from 200 to 150 in 2002.

## Insulin resistance and hypertension

- Insulin resistance and hypertension are linked, but everyone with hypertension is not insulin resistant, and everyone with insulin resistance is not hypertensive. About half of individual with hypertension have insulin resistance and hyperinsulinemia. People with hypertension as part of the presentation of Metabolic Syndrome are at the highest risk for a Metabolic Syndrome-induced heart attack.
- Insulin itself has a sympathetic effect.
- Hyperinsulinemia makes the kidneys retain salt and water and also promotes elevated stress hormones, both of which may be responsible for the hypertensive effect.

Reaven G,Strom TK, Fox B. Syndrome X: Overcoming the Silent Killer That Can Give you a Heart Attack. New York. Simon and Schuster. 2000

## Insulin resistance and thrombosis

Hyperinsulinemia causes an increase in fibronogen (which promotes clotting) and also a increase in PAI-1 (which inhibits clot breakdown). Both factors are associated with increased risk of heart attack.

Reaven G,Strom TK, Fox B. Syndrome X: Overcoming the Silent Killer That Can Give you a Heart Attack. New York. Simon and Schuster. 2000

## Insulin resistance and heart disease/atherosclerosis

The above factors are all related to the formation of atherosclerosis, instability of atherosclerotic plaque (promoting plaque rupture and thrombotic events), and heart attacks. The Syndrome X factors known to be associated with heart attacks are: elevated triglycerides, decreased HDL cholesterol, increases small dense LDL, increased thrombosis and "sticky" blood, and hypertension. In addition, IGF-1 is a growth factor for atherosclerosis.

**ABSTRACT: Insulin-like growth factors I and II (IGF-I and -II) and their regulatory proteins are secreted by cells of the cardiovascular system. They are growth promoters for arterial cells** and mediators of cardiovascular disease. IGFs are bound to IGF binding proteins (IGFBPs), which modulate IGF ligand-receptor interaction and consequently to IGF action. IGFBPs are in turn posttranslationally modulated by specific proteases. This dynamic balance (IGFs, IGFBPs, and IGFBP proteases) constitutes the IGF axis and ultimately determines the extent of IGF-dependent cellular effects. **Dysregulated actions of this axis influence coronary atherosclerosis through effects on vascular smooth muscle cell growth, migration, and extracellular matrix synthesis in the atherosclerotic plaque. IGF-I promotes macrophage chemotaxis, excess LDL cholesterol uptake, and release of proinflammatory cytokines. Endothelial cells also receive the effects of IGFs stimulating their migration and organization forming capillary networks. Neointimal hyperplasia of restenosis after coronary artery injury is also modulated by the IGF axis. IGFs stimulate vascular smooth muscle cell proliferation and migration to form the neointima and upregulate tropoelastin synthesis after disruption of the elastic layer. Understanding IGF axis regulation establishes a scientific basis for strategies directed to limit or reverse plaque growth and vulnerability in atherosclerosis and in the neointimal hyperplasia of restenosis.**

Bayes-Genis A, Conover CA, Schwartz RS.The insulin-like growth factor axis: A review of atherosclerosis and restenosis. Atherosclerosis Circ Res. 2000 Feb 4;86(2):125-30.

## Insulin, IGF-1 and Cancers

As described above, hyperinsulinemia may initiate cancers through oxidative damage, and may also promote the growth on non-insulin-resistant tumors. Its companion hormone IGF-1 is also a growth factor for tumors. The specific cancers which are not recognized to be related to insulin/igf-1 are:

- breast
- prostate
- colon
- endometrium

The insulin/IGF-1 combination may also promote:

- uterine fibroids (In conjunction with elevated estrogen)
- benign prostatic hypertrophy

A collection of recent scientific abstracts on this topic follows

## Cancer in general

Although an association between diabetes and cancer was found over 100 years ago, the issue underwent different interpretations over the subsequent decades, and only modern, prospective, epidemiological cohort and case-control studies conducted in several countries have provided reliable evidence of an increased cancer risk in diabetic patients, mainly in those with type 2 diabetes. This **risk varies according to the tumor site: it is the greatest for primary liver cancer, moderately elevated for pancreatic cancer, and relatively low for colorectal, endometrial, breast, and renal cancers.** The cause of the association is not clear and remains the subject of different hypotheses. **The most frequently cited reason is the potential effect of insulin. Found in high concentrations, due to insulin resistance in most patients with type 2 diabetes, this hormone is believed to express a mitogenic effect.** This hypothesis needs to be confirmed in appropriately programmed prospective studies, but it may already be helpful in choosing an adequate treatment for type 2 diabetes to achieve optimal metabolic control with a simultaneous reduction in hyperinsulinemia, such as diet, physical exercise, metformin, and acarbose.

**Czyzyk A, Szczepanik Z. Diabetes mellitus and cancer. *Eur. J. Intern. Med.* 2000 Oct;11(5):245-252**

### John Yudkin, University of London

Dietary sugar and insulinemic effects on cancer risk

**Correlation coefficient of dietary sugar and some cancers**

| | |
|---|---|
| Cancer of the rectum in men | .60 |
| Cancer of the rectum in women | .50 |
| Cancer of the breast | .63 |
| Leukemia | .53 |
| Leukemia in women | .51 |

Yudkin, J. *Sweet and Dangerous.* New York: Bantam, 1972

## Colorectal Cancer

Diet is clearly implicated in the origin of colorectal cancer, with risk factors for the disease including reduced consumption of vegetables, fiber, and starch and increased consumption of red meat and animal fat. Several hypotheses have been developed to explain these associations. Most recently, McKeown-Eyssen and Giovannucci noted the **similarity of the risk factors for colorectal cancer and those for insulin resistance and suggested that insulin resistance leads to colorectal cancer through the growth-promoting effect of elevated levels of insulin, glucose, or triglycerides.** We briefly review the evidence from observational, epidemiological, and experimental animal studies linking diet with insulin resistance and colorectal cancer. The evidence suggests that diets high in energy and saturated fat and with high glycemic index carbohydrate and low levels of fiber and n-3 fatty acids lead to insulin resistance with hyperinsulinemia, hyperglycemia, and hypertriglyceridemia. We then consider how **insulin, the related insulin-like growth factors, triglycerides, and nonesterified fatty acids could lead to increased growth of colon cancer precursor lesions and the development of colorectal cancer.** Finally, we

consider the implications of this scheme on possible future research directions, including studies of satiety and clinical tests of the importance of insulin resistance in the colon carcinogenesis process.

**Bruce WR, Wolever TM, Giacca A Mechanisms linking diet and colorectal cancer: the possible role of insulin resistance. Nutr Cancer 2000;37(1):19-26**

A sedentary lifestyle, obesity, and a Westernized diet have been implicated in the aetiology of both colorectal cancer and non-insulin dependent diabetes mellitus, leading to the hypothesis that hyperinsulinaemia may promotecolorectal cancer. We prospectively examined the association between colorectal cancer risk and factors related to insulin resistance and hyperinsulinaemia, including BMI, physical activity, diabetes mellitus, and blood glucose, in a cohort of 75 219 Norwegian men and women. Information on incident cases of colorectal cancer was made available from the Norwegian Cancer Registry. Reported P values are two-sided. During 12 years of follow up, 730 cases of colorectal cancer were registered. In men, but not in women, we found a negative association with leisure-time physical activity (P for trend = 0.002), with an age-adjusted RR for the highest versus the lowest category of activity of 0.54 (95% CI = 0.37-0.79). Women, but not men, with a history of diabetes were at increased risk of colorectal cancer (age-adjusted RR = 1.55; 95% CI = 1.04-2.31), as were women with non-fasting blood glucose > or = 8.0 mmol l(-1)(age-adjusted RR = 1.98; 95% CI = 1.31-2.98) compared with glucose <8.0 mmol l(-1). Overall, we found no association between BMI and risk of colorectal cancer. Additional adjustment including each of the main variables, marital status, and educational attainment did not materially change the results. We conclude that **the inverse association between leisure-time physical activity and colorectal cancer in men, and the positive association between diabetes, blood glucose, and colorectal cancer in women, at least in part, support the hypothesis that insulin may act as a tumour promoter in colorectal carcinogenesis**.

**Nilsen TI, Vatten LJ Prospective study of colorectal cancer risk and physical activity, diabetes, blood glucose and BMI: exploring the hyperinsulinaemia hypothesis. Br J Cancer 2001 Feb 2;84(3):417-22**

## Breast

**There is a hypothesis that hyperinsulinemia or insulin resistance may be a mediator for breast cancer risk factors. On the other hand, some, but not all, of the well-known risk factors of breast cancer have been associated with serum estrogen concentrations. We assessed the relationships of potential breast cancer risk factors to indicators of insulin resistance, fasting plasma insulin concentration and homeostasis model assessment insulin resistance (HOMA-R), in 88 postmenopausal Japanese women. We also examined whether insulin resistance would explain the association of breast cancer risk factors with serum estradiol and sex hormone-binding globulin (SHBG). Information on potential breast cancer risk factors, such as demographic characteristics, smoking and drinking habits, diet, exercise, menstrual and reproductive factors, was obtained by self-administered health questionnaire including a validated semiquantitative food frequency questionnaire. Body mass index (BMI) was significantly correlated with the ratio of estradiol to SHBG (Spearman r = 0.30, P = 0.0004), fasting plasma insulin (r = 0.45)** and HOMA-R (r = 0.43, P = 0.0001) after controlling for age. The correlations were still significant between BMI and estradiol / SHBG ratio (r = 0.21, P = 0.047) after controlling for fasting plasma insulin and between BMI and fasting plasma insulin (r = 0.40, P = 0. 0001) as well as HOMA-R (r = 0.38, P = 0.0003) after controlling for estradiol / SHBG ratio. **There is a possibility that effect of BMI on breast cancer risk is mediated by both insulin resistance and estrogen metabolism.**

Nagata C, Shimizu H, Takami R, Hayashi M, Takeda N, Yasuda K Relations of insulin resistance and serum concentrations of estradiol and sex hormone-binding globulin to potential breast cancer risk factors. Jpn J Cancer Res 2000 Sep;91(9):948-53

OBJECTIVE: The incidence of breast cancer in the Western world runs parallel to that of the major components of the insulin resistance syndrome—hyperinsulinaemia, dyslipidaemia, hypertension and atherosclerosis. Evidence is reviewed that the growth of breast cancer is favoured by specific dietary fatty acids, visceral fat accumulation and inadequate physical exercise, all of which are thought to interact in favouring the development of the insulin resistance syndrome. DESIGN: Clinical, epidemiological and experimental studies linking breast cancer risk with evidence of insulin resistance and its concomitants, were searched for in the MEDLINE database since 1985. RESULTS: Clinical and epidemiological evidence suggests that both breast cancer and the metabolic disorders comprising the insulin resistance syndrome are polygenic and multifactorial in origin. Experimental evidence suggests that hyperinsulinaemia and its concomitants can increase the promotion of mammary carcinogenesis and the mechanism is likely to involve increased bioactivity of insulin-like growth factor 1 (IGF-1). Case-control and cohort studies have shown that higher serum levels of IGF-1 are associated with increased breast cancer risk. Pharmacological agents which lower IGF-1 concentrations are under clinical trial for breast cancer prevention. CONCLUSIONS: **Nutritional and lifestyle modifications that improve insulin sensitivity may not only decrease a tendency to atherosclerosis but also reduce breast cancer risk in women.** In addition to a reduced fat intake, the dietary regimen might involve **a reduced n-6/n-3** ratio of polyunsaturated fatty acids and should be associated with avoidance of obesity and **regular physical exercise**. Interventions to decrease breast cancer risk in first-degree relatives of breast cancer patients need to begin at an early age.

**Stoll BA Western nutrition and the insulin resistance syndrome: a link to breast cancer. Eur J Clin Nutr 1999 Feb;53(2):83-7**

## Endometrial cancer

Angiogenesis is crucial for tumor growth and dissemination. Vascular endothelial growth factor (VEGF) is a potent angiogenic factor that promotes vascular growth and therefore tumoral growth and metastasis. Overweight, frequently associated with hyperinsulinemia, constitutes the major risk factor for endometrial carcinoma. Thus, **elevated insulin levels may partly explain the increased risk of endometrial cancer observed in obese postmenopausal women.** The aim of the present work was to test the role of insulin in the control of VEGF expression in endometrial carcinoma cells (HEC-1A). We have shown that insulin induced a biphasic expression of VEGF messenger ribonucleic acid, with an early, but low, induction (4 h of stimulation) and a delayed, but high, induction (24 h). The delayed effect of insulin on VEGF expression involved transcriptional and posttranscriptional regulation, as evidenced by the increased rate of VEGF transcription and the prolonged half-life of VEGF messenger ribonucleic acid. Simultaneously we observed higher levels of VEGF protein in the conditioned medium of stimulated cells compared with unstimulated ones. Therefore, **insulin could contribute to the increased risk of endometrial carcinoma due to its ability to induce VEGF expression and thus participate in the maintenance of an angiogenic phenotype.**

**Bermont L, Lamielle F, Lorchel F, Fauconnet S, Esumi H, Weisz A, Adessi GL Insulin up-regulates vascular endothelial growth factor and stabilizes its messengers in endometrial adenocarcinoma cells. J Clin Endocrinol Metab 2001 Jan;86(1):363-8**

## Prostate Cancer

**A possible relation may exist between higher insulinlike growth factor (IGF)-1 levels and the risk of premenopausal breast, prostate, or other cancers from recent prospective and case-control studies**. Separately, a large prospective study has shown a potential association between chronic depression and cancer risk, whereas other preliminary studies have suggested a link between increasing IGF levels with major depression. Other studies have found that certain standard cancer treatments reduce the effect and levels of IGF, and 1 small study has found that standard antidepressants may reduce IGF levels in some patients diagnosed with major depression. It is possible that IGF-1 (or other IGFs) may be a mediator between depression and cancer, because separately both have been implicated in the risk of various cancers. This hypothesis first and foremost relies on the unsettled notion that an actual relation already exists or may be found in the future. It requires more extensive investigation because several studies have not found an association between IGF or depression and cancer risk, and other limitations such as small sample sizes and other influential factors on IGF levels need to be elucidated. Whether or not a mind-body effect exists with cancer, as seems to be the case with other diseases, remains to be seen. Is depression a potential confounder of human studies that attempts to establish a relation between IGF and disease? All of the studies to date have attempted to at least determine the effect of a variety of factors on IGF levels-including age, sex, diet, family history, weight, smoking status-and then have adjusted their results accordingly. Depression has not been included in this list of potential factors that may need to be considered when analyzing IGF-1 data and cancer risks. The time seems ripe to at least define further the relation, if any, between IGF-1 and depression.

**Moyad MA, Pienta KJ. Mind-body effect: insulinlike growth factor-1; clinical depression; and breast, prostate, and other cancer risk-an unmeasured and masked mediator of potential significance? Urology 2002 Apr;59(4 Suppl 1):4-8**

We review the extensive body of data on the molecular aetiology of hormone refractory disease in metastatic prostate cancer patients. Particular emphasis is placed on the crucial role of the bone micro-environment, especially the intercellular interactions of metastatic prostate cancer cells and osteoblasts in promoting the establishment of hormone refractory disease. Resistance of tumour cells to anticancer therapies is generally viewed as a phenomenon almost exclusively determined by chromosomal defects and/or gene mutations. However, it is now well-documented that the local milieu of the bone metastases can also protect tumour cells from anticancer therapy- induced apoptosis, either independently or synergistically with resistance-related genetic alterations. A key determinant of this protection is the urokinase/plasmin cascade which modulates the local concentration of **survival factors, such as insulin-like growth factor (IGF-1). The molecular pathways whereby this major growth and survival factor for prostate cancer cells** exerts its anti-apoptotic effect on prostate cancer cells are discussed.

**Mitsiades CS, Koutsilieris M. Molecular biology and cellular physiology of refractoriness to androgen ablation therapy in advanced prostate cancer. Expert Opin Investig Drugs 2001 Jun;10(6):1099-115**

Prostate cancer is one of the most common malignant tumors in Western countries. The etiology of prostate cancer is currently unknown, but it has been suggested that growth factor abnormalities may be involved in initiation and progression of this disease. **Insulin-like growth factors (IGFs), including IGF-1 and IGF-2, are mitogenic peptides involved in**

**the regulation of cell proliferation, differentiation and apoptosis. Studies have shown that IGFs are potent mitogens for a variety of cancer cells including prostate cancer since they stimulate cancer cell growth and suppress programmed cell death.** This review outlines elements of IGF pathophysiology, reviews recent evidence that circulating IGF-1 levels are related to prostate cancer risk and discusses the clinical implications of these lines of research with respect to prevention and treatment.

Djavan B, Waldert M, Seitz C, Marberger M. Insulin-like growth factors and prostate cancer. World J Urol 2001 Aug;19(4):225-33

OBJECTIVES: To investigate whether dietary factors that appear to affect the risk of prostate cancer may be similarly associated with serum levels of insulin-like growth factor 1 (IGF-1). Patients and methods In the context of a case-control study, 112 men were admitted to three teaching hospitals in Athens, Greece, for disorders other than cancer. Sociodemographic data and detailed histories of smoking, alcohol and coffee consumption were recorded. A validated food-frequency questionnaire was administered by an interviewer and serological measurements of IGF-1 and its binding protein-3 conducted. RESULTS: IGF-1 declined significantly by almost 25% among men aged >75 years and there was a small reduction in IGF-1 levels with increased alcohol intake, with a mean (95% confidence interval, CI) change of -1.6 (- 2.2 to -0.9)% for an increment of one drink per day. There was no evidence for an effect of either smoking or coffee consumption on IGF-1 level. Among foods, the consumption of cooked tomatoes was substantially and significantly inversely associated with IGF-1 levels, with a mean (95% CI) change of -31.5 (- 49.1 to -7.9)% for an increment of one serving per day. CONCLUSIONS: The strongest known dietary risk factor for prostate cancer (lycopene deficit, as reflected in a reduced intake of cooked tomatoes) and an important endocrine factor in the aetiology of this disease (IGF-1) seem to be related in a way that suggests that at least one, and perhaps more, exogenous factors in the development of prostate cancer may be mediated through the IGF-1 system.

**Mucci LA, Tamimi R, Lagiou P, Trichopoulou A, Benetou V, Spanos E, Trichopoulos D Are dietary influences on the risk of prostate cancer mediated through the insulin-like growth factor system?. BJU Int 2001 Jun;87(9):814-20**

## Insulinemic foods and cancer risk

The proportion of colorectal cancer attributed to dietary habits is high, but several inconsistencies remain, especially with respect to the influence of some food groups. To further elucidate the role of dietary habits, 1,225 subjects with cancer of the colon, 728 with cancer of the rectum and 4,154 controls, hospitalized with acute non-neoplastic diseases, were interviewed between 1992 and 1996 in 6 different Italian areas. The validated food-frequency questionnaire included 79 questions on food items and recipes, categorised into 16 food groups. After allowance for non-dietary confounding factors and total energy intake, **significant trends of increasing risk of colorectal cancer with increasing intake emerged for bread and cereal dishes (odds ratio [OR] in highest vs. lowest quintile = 1.7), potatoes (OR = 1.2), cakes and desserts (OR = 1.1), and refined sugar (OR = 1.4). Intakes of fish (OR = 0.7), raw and cooked vegetables (OR = 0.6 for both) and fruit other than citrus fruit (OR = 0.7) showed a negative association with risk. Consumption of eggs and meat (white, red or processed meats) seemed uninfluential.** Most findings were similar for colon and rectum, but **some negative associations (i.e., coffee and tea, and fish) appeared stronger for colon cancer.** Our findings lead us to reconsider the role of starchy foods and refined sugar in light of recent knowledge on the digestive physiology of

carbohydrates and the insulin/colon cancer hypothesis. **The beneficial role of most vegetables is confirmed, with more than 20% reduction in risk of colorectal cancer from the addition of one daily serving.**

Franceschi S, Favero A, La Vecchia C, Negri E, Conti E, Montella M, Giacosa A,Nanni O, Decarli A. Food groups and risk of colorectal cancer in Italy. Int J Cancer 1997 Jul 3;72(1):56-61

It has been hypothesized that levels of triglycerides, glucose, and insulin are associated with risk of colon cancer and that diets high in simple sugars increase risk of colon cancer because of their impact on these factors. Limited epidemiological evidence supports the association between simple carbohydrates and risk of colon cancer. Using data from a population-based case-control study (n = 1993 cases and 2410 controls), we examined the associations between dietary sugars, foods containing high level of sugars, and dietary glycemic index (GI) and colon cancer. A dietary GI was developed to estimate metabolic response to a diet that may increase plasma glucose levels. Dietary data were obtained using a validated diet history questionnaire. **High levels of sucrose intake were associated with increased risk of colon cancer among younger men [odds ratio (OR) for highest quintile relative to lowest, 1.59; 95% confidence interval (CI), 1.07-2.37]. There was also a trend of increasing colon cancer risk associated with a higher sucrose:dietary ratio for proximal tumors in both men and women. Individuals with proximal tumors who consumed a diet ranked as having a high GI were at increased risk (for men, comparing highest quintile to lowest quintile: OR, 1.58; 95% CI, 1.06-2.36; P trend 0.04; for women: OR, 1.72; 95% CI, 1.11-2.67; P trend 0.04). Those at greatest risk from a high dietary GI were those who were sedentary (for men, relative to those who were most active and had a low-GI diet: OR, 3.46; 95% CI, 1.78-6.70; for women: OR, 2.00; 95% CI, 0.98-4.07). We also observed that people who had a high sucrose: dietary fiber ration and who also were sedentary and had a large body mass index were at increased risk (OR, 4.58; 95% CI, 2.33-8.98) relative to those who had a low sucrose:dietary fiber ratio, were active, and had low body mass indices**. These findings support previous reports that dietary sugars, especially diet high in simple carbohydrates relative to complex carbohydrates, increase risk of colon cancer, possibly through their impact on plasma glucose levels.

**Slattery ML, Benson J, Berry TD, Duncan D, Edwards SL, Caan BJ, Potter JD. Dietary sugar and colon cancer. Cancer Epidemiol Biomarkers Prev 1997 Sep;6(9):677-85**

In order to examine the relationship between dietary sucrose intake and colorectal cancer, a case-control study was conducted in Uruguay in the time period 1992-1996. In all, 289 cases and 564 controls, admitted for diagnosis or treatment in the 4 major hospitals in Montevideo, were considered eligible for the study. Total sucrose intake was associated with a monotonic positive gradient of risks and the **odds ratio (OR) for the uppermost quartile of intake was of 2.18 (95% confidence interval, CI, 1.35-3.51).** Glucose intake was associated with a small and non-significant increase in risk (OR 1.46, 95% CI 0.76-2.82). **Finally, an interaction between sucrose and protein intake was found, and the OR for high intakes of sucrose and protein was 6.07.**

Note: very high protein is insulinemic, and the most insulinemic food combination is HGC plus high protein.

**Int J Cancer 1998 Jan 5;75(1):40-4 Sucrose as a risk factor for cancer of the colon and rectum: a case-control study in Uruguay.**

A large case-control study (2,569 women with breast cancer and 2,588 control women) carried out in Italy between 1991 and 1994 permits elucidation of breast cancer risk in relation to dietary patterns in a southern European population. **Major findings include direct associations with the intake of bread and cereal dishes, sugar, and pork meat, and inverse associations with the intake of vegetable oils, raw vegetables, fish, beta-carotene, vitamin E, and calcium.**

**Favero A, Parpinel M, Franceschi S Diet and risk of breast cancer: major findings from an Italian case-control study. Biomed Pharmacother 1998;52(3):109-15**

To examine whether dietary sugar modifies lung cancer risk, a case-control study involving 463 cases with lung cancer and 465 hospitalized controls was conducted in Uruguay in the period 1993-1996. Dietary patterns were assessed in detail using a 64-item food-frequency questionnaire, which allowed the calculation of total energy intake. After adjustment for potential confounders through a model that included tobacco smoking and total energy, total fat, vitamin C, and alpha-carotene intakes, an increased risk for sugar-rich foods, total sucrose intake, sucrose to dietary fiber ratio, and glycemic index for lung cancer was observed (odds ratio for highest category of total sucrose intake = 1.55, 95% confidence interval = 0.99-2.44). When lung cancer was analyzed separately by cell type, odds ratios for small cell and large cell undifferentiated carcinoma were higher than those observed for squamous cell and adenocarcinoma of the lung. The joint effect of pack-years, total fat intake, and sucrose intake was associated with an increased risk of 28.3 (95% confidence interval = 13.4-59.7) for high values of the three variables. **The study suggests that high sucrose intake could be an important risk factor in lung carcinogenesis.** Further studies, both epidemiological and experimental, are needed to replicate the present findings and to clarify the mechanism(s) of sucrose intake in lung carcinogenesis.

**Nutr Cancer 1998;31(2):132-7 Dietary sugar and lung cancer: a case-control study in Uruguay.**

To investigate the relation of dietary intakes of sucrose, meat, and fat, and anthropometric, lifestyle, hormonal, and reproductive factors to colon cancer incidence, data were analyzed from a prospective cohort study of 35,215 Iowa (United States) women, aged 55-69 years and without a history of cancer, who completed mailed dietary and other questionnaires in 1986. Through 1990, 212 incident cases of colon cancer were documented. Proportional hazards regression was used to adjust for age and other risk factors. **Risk factors found to be associated significantly with colon cancer included: (i) sucrose-containing foods and beverages other than ice cream/milk; relative risks (RR) across the quintiles = 1.00, 1.73, 1.56, 1.54, and 2.00** (95% confidence intervals [CI] for quintiles two and five exclude 1.0); (ii) **sucrose; RR across the quintiles = 1.00, 1.70, 1.81, 1.82, and 1.45** (CI for quintiles two through four exclude 1.0); (iii) height; RR = 1.23 for highest to lowest quintile (P for trend = 0.02); (iv) body mass index; RR = 1.41 for highest to lowest quintile (P for trend = 0.03); and (v) number of livebirths, RR = 1.59 for having had one to two livebirths and 1.80 for having had three or more livebirths compared with having had none (P for trend = 0.04). **These data support hypotheses that sucrose intake or being tall or obese increases colon cancer risk; run contrary to the hypothesis that increased parity decreases risk; support previous findings of no association with demographic factors other than age, cigarette smoking, or use of oral contraceptives or estrogen replacement therapy; and raise questions regarding previous associations with meat, fat, protein, and physical activity.**

Cancer Causes Control 1994 Jan;5(1):38-52 Sugar, meat, and fat intake, and non-dietary risk factors for colon cancer incidence in Iowa women (United States). Bostick RM, Potter JD, Kushi LH, Sellers TA, Steinmetz KA, McKenzie DR, Gapstur SM, Folsom AR.

### Uterine Fibroids

To study roles of insulun-like growth factor 1(IGF-I) and estradiol(E2) in the growth of leiomyoma. Protein expressions of IGF-I receptor(IGF-I-R), estrogen receptor(ER), and cell proliferation associated nuclear antigen(ki-67) were analysed by streptavidin-peroxide method in 40 cases. Serum level and local concentration of IGF-I were determined by immunoradiometric assay(IRMA) in 20 cases. Serum level of estradiol was determined by radioimmunoassay in 20 cases. Twenty normal fertile women were studied as control. Protein expressions of IGF-I-R and ER in uterine leiomyoma were significantly higher than in myometrium(P < 0.05); and local concentration of IGF-I positively correlated with ki-67 (r = 0.6513, P < 0.05); and expression of estrogen receptor. The serum levels of IGF-I and E2 had no significant difference between leiomyoma patients and normal women. **IGF-I and E2 promote the growth of leiomyoma and IGF-I may act as a mediator of estrogen.**

Huang J, Zou J, Xu B, Zhang Y, Chen X, Liu D. Affect of insulin-like growth factor I and estradiol on the growth of uterine leiomyoma Hunan Yi Ke Da Xue Xue Bao 1999;24(1):29-32

The expression of insulin-like growth factor-I (IGF-I) was measured at the mRNA and protein level in myometrium and fibroids from women with and without preoperative treatment with a gonadotrophin-releasing hormone (GnRH) agonist for 3 months, from post-menopausal women, from pregnant women and in myometrium from women without fibroid disease. Women with menstrual periods were classified according to the phase of the cycle. In tissues from non-treated premenopausal women, IGF-I mRNA expression was significantly higher in fibroids than in myometrium, with no differences related to phase of the menstrual cycle. In post-menopausal women and in GnRH agonist-treated women responding to treatment, similar mRNA expression was seen in myometrium and fibroids but the concentrations were lower than in untreated premenopausal women. The IGF-I mRNA value in fibroids from pregnant women was higher than in any other group and myometrium from pregnant women exhibited higher mRNA expression than myometrium from non-treated premenopausal women. The IGF-I protein was more abundant in fibroids than in myometrium of non-treated premenopausal and of pregnant women and in both tissues the concentration was significantly higher in the group of pregnant women. The IGF-I protein concentrations in fibroids and myometrium from GnRH agonist-treated and post-menopausal women were similar to those from premenopausal non-treated women. **High sex steroid concentrations in pregnant and non-pregnant women of fertile age seem to be associated with a higher expression of IGF-I in fibroids than in myometrium, suggesting that IGF-I contributes to the selective growth advantage of these tumours.**

Englund K, Lindblom B, Carlstrom K, Gustavsson I, Sjoblom P, Blanck A. Gene expression and tissue concentrations of IGF-I in human myometrium and fibroids under different hormonal conditions. Mol Hum Reprod 2000 Oct;6(10):915-20

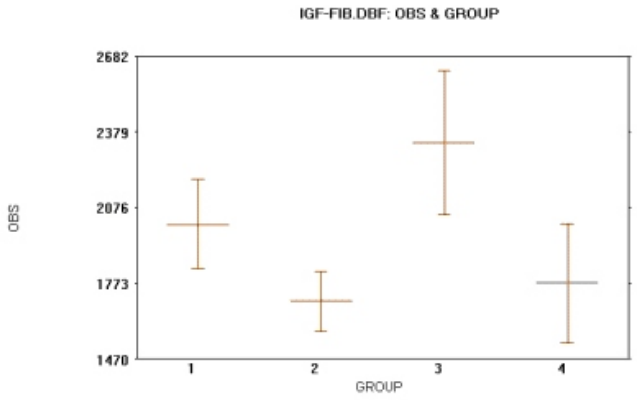
OBJECTIVE: Our purpose was to determine whether insulin-like growth factors I and II preferentially stimulate uterine leiomyoma cells versus myometrial cells in monolayer culture. STUDY DESIGN: Leiomyomas and normal myometrium were obtained at hysterectomy from five premenopausal women. Specimens were enzymatically digested for use in primary monolayer cell cultures. By use of serum-free media, insulin-like growth factor I or II was added in 1, 10, and 100 ng/ml concentrations to both cell types with the

patient serving as her own control. Cell number, prolactin production, and proliferative index values were measured on day 15 of cell culture. RESULTS: Significant increases in cell number were found in the leiomyoma cultures (p < 0.05) treated with 10 and 100 ng/ml insulin-like growth factors I but not with insulin-like growth factors II. Neither factor exerted a stimulatory effect on myometrial cells. CONCLUSION: **Insulin-like growth factors I preferentially stimulates leiomyoma cells in monolayer culture.** These results suggest an autocrine-paracrine role in vivo for this factor in conjunction with gonadal steroids in promoting leiomyoma growth.

Strawn EY Jr, Novy MJ, Burry KA, Bethea CL. Insulin-like growth factor I promotes leiomyoma cell growth in vitro. Am J Obstet Gynecol 1995 Jun;172(6):1837-43; discussion 1843-4

OBJECTIVE: To determine plasma levels of insulin-like growth factor-I (IGF-I), CA-125, estrone (E1), E2, and P in women with uterine leiomyomas compared with normal women. DESIGN: Women with leiomyomas were compared with normal women (control). SETTING: University Department of Obstetrics and Gynecology. PATIENTS: Fifty-one premenopausal women with uterine myomas > 14 weeks gestation and 30 normal fertile women (controls) were studied. Peripheral blood samples were obtained before myomectomy or hysterectomy and during the nonmenstruating phase in the controls. MAIN OUTCOME MEASURES: Plasma levels of E1, E2, P, CA-125, and IGF-I were determined by specific and sensitive RIAs and immunoradiometric assays. RESULTS: Plasma IGF-I levels were 2,006 +/- 185 mU/mL (mean +/- SEM, n = 35) and 2,335 +/- 287 mU/mL (n = 16) in women with leiomyomas during the follicular and luteal phases, respectively, whereas the corresponding values for normal women were 1,702 +/- 120 (n = 30) and 1,774 +/- 239 mU/mL (n = 30). Similarly, plasma CA-125 levels were unchanged in women with leiomyomas (myomas: 18.8 +/- 2.4, 21.5 +/- 3.7 U/mL; normal: 15.9 +/- 1.5, 15.8 +/- 1.3 U/mL during follicular and luteal phases, respectively). Women with leiomyomas had plasma E1, E2, and P levels during the follicular phase (91.9 +/- 11.5 pg/mL; conversion factor to SI unit, 3.699; 94.6 +/- 19.0 pg/mL; conversion factor to SI unit, 3.671; and 1.5 +/- 0.4 ng/mL; conversion factor to SI unit, 3.180, respectively) and the luteal phase (105.8 +/- 11.2 pg/mL; conversion factor to SI unit, 3.699; 128.7 +/- 24.8 pg/mL; conversion factor to SI unit, 3.671; and 9.6 +/- 1.6 ng/mL; conversion factor to SI unit, 3.180) similar to normal women. CONCLUSION: Plasma levels of IGF-I, CA-125, E1, E2, and P are normal in women with leiomyomas.

**Plasma Igf-1 in Women with and Without Uterine Fibroids**




**Group I – women with fibroids, follicular phase**

**Group II – women without fibroids, follicular phase**

**Group III – women with fibroids, luteal phase**

**Group IV – women with fibroids, follicular phase**

Because of low number of subjects, these data did not reach a statistical significance, but the trend is remarkable. The comparable groups had no overlapping values, a fact not commented upn by the authors.

Dawood MY, Khan-Dawood FS. Plasma insulin-like growth factor-I, CA-125, estrogen, and progesterone in women with leiomyomas. Fertil Steril 1994 Apr;61(4):617-21

## Benign Prostatic Hypertrophy

OBJECTIVES: To examine the relationship between insulin-like growth factor-1 (IGF-1), insulin-like growth factor binding protein-3 (IGFBP-3), and body mass index and prostate volume, as a surrogate marker for benign prostatic hyperplasia, in a community-based sample of black men. Epidemiologic studies examining the role of IGF-1 and IGFBP-3 suggest that increased levels of serum IGF-1 and decreased levels of serum IGFBP-3 are associated with an increased risk of prostate cancer. Few studies have examined these factors with respect to benign prostatic hyperplasia, and these have been limited to white men. METHODS: The study population consisted of a sample of 364 black men, 40 to 79 years of age, residing in Genesee County, Michigan. Men with prostate cancer or prior prostate surgery were excluded. All subjects completed a clinical examination, which included a complete urologic examination with transrectal ultrasonography, anthropometric measurements, and serum assays for IGF-1 and IGFBP-3. RESULTS: Multivariable regression models demonstrated that prostate volume increased with increasing age ($P < 0.0001$) and body mass index ($P = 0.03$). IGFBP-3 rather than IGF-1 was positively associated with increasing prostate volume ($P = 0.003$). CONCLUSIONS: This is the largest study describing the relationships between IGF-1, IGFBP-3, and body mass index and prostate volume, and the only study in black men. Although **earlier studies demonstrated an association between IGF-1 and prostate cancer risk, our findings indicate that**

**IGFBP-3 is more relevant for prostate enlargement, suggesting that IGF-1 and IGFBP-3 may play different pathophysiologic roles in benign and malignant prostatic conditions.**

**Sarma AV, Jaffe CA, Schottenfeld D, Dunn R, Montie JE, Cooney KA, Wei JT. Insulin-like growth factor-1, insulin-like growth factor binding protein-3, and body mass index: clinical correlates of prostate volume among Black men. Urology 2002 Mar;59(3):362-7**

## Other Adverse effects of the Insulin/IGF-1 combination

Some other possible effects of the growth-abnromalities promoted by insulin and Igf-1 are:

- Elevated serum uric acid
- Acne - via overgrowth of the keratin around the pores
- Early menarche
- Epithelial cell cancers
- Increased stature - via overgrowth of the bones along their long axes
- Myopia - via unnatural elongation of the eyeball
- Cutaneous papillomas
- Acanthosis nigricans
- Male vertex balding

Comp Biochem Physiol A Mol Integr Physiol. 2003 Sep;136(1):95-112. Hyperinsulinemic diseases of civilization: more than just Syndrome X.Cordain L, Eades MR, Eades MD.

# Insulin resistance, appetite, and abdominal obesity

## The appetite hormones

Two recently discovered hormones help to regulate the appetite.

- Leptin, secreted by the fat cells (white adipose tissue)
- Ghrelin, secreted by the empty stomach wall.

### Leptin

Hormone secreted by the white adipose tissue. This tissue is for readily storable, easily retrievable fat. It is most promonent around the abdomen, both around the mesentery and around the trunk. Because this tissue secretes a hormone, some scientists rightly consider it collectively to be an endocrine organ.

- Normally, leptin is secreted as the fat cells fill with fat. it signals that the "ready-fuel" tank is full.
- It is also secreted in response to the binding of insulin, signaling that nutrients are being stored away, and that starvation is not immanent.

Leptin's two targets are the **hyppothalamus** and the **pancreas**

- Rising leptin tell the hypothalamus that the ready-reserve of fat is adequate. The hypothalamus responds by **increasing fat burning** from the white adipose tissue and by **reducing the appetite.**
- The hypothalamus triggers fat burning in the white adipose tissue through sympathetic stimulation via adrenalin – adrenalin receptors on the white fat cells cause increased metabolism in that tissue. Notice the classical endocrine negative feedback loop.
- Leptin, rising as insulin binds to the fat cells, sends a feedback signal to the pancreatic beta cells, reducing insulin secretion.

So, normally:

- Low fat storage = low leptin from fat cells, increased appetite, and reduced metabolism of fat.
- High fat storage = high leptin levels, decreased appetitie, and increased metabolism of fat.
- Normally, there is a daily cycle. Leptin peaks in the late evening, and is at its lowest point upon waking. Thus normally, appetite is at its lowest before bed, and fat burning is at its highest during sleep.

### Dysregulation, phase I. Disrupted appetite cycle

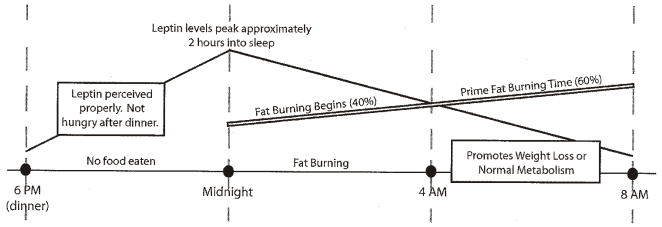
High glycemic carbohydrates ***early in the day*** cause the leptin cycle to be disrupted. It peaks earlier in the day, and then declines. There is a larger appetite for dinner, and then food cravings after dinner and at bedtime.

## Dysregulation, phase II. Leptin resistance

- In response to a high glycemic diet, high insulin surges, and also to stored fat from overeating, leptin levels become greatly ***elevated***. The hypothalamus and pancreas ***develop leptin resistance*** by shutting down receptors. The fat tank is full, but the hypothalamus reads it as empty. The hypothalamus, thinking the body is starving, increases the appetite, and decreases the metabolism, putting the individual into hibernation mode despite the fat cells already being engorged.
- The pancreas, which normally reduces its insulin in response to rising leptin, also develops leptin resistance, and continues to secrete insulin when it would normally stop. Hyperinsulinemia with and insulin resistance are the result.
- Finally, the white adipose tissue develops adrenalin resistance, and does not burn fat despite plenty of adrenalin being around.

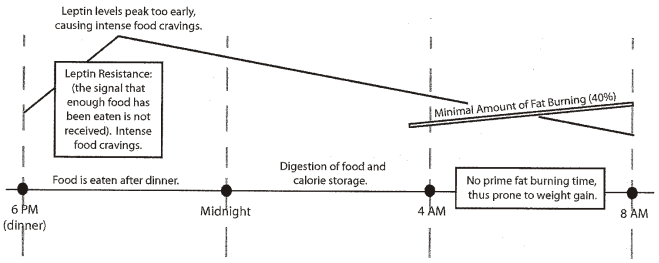
Normal Leptin Function after Dinner

Figure 8A




Leptin Resistance

Figure 8B




The sympathetic system may do flip flops, first trying to shut down fat burning and then trying to stimulate it, but regardless of the mode, the white adipose tissue does not burn the fat. The cells most susceptible to this phenomenon are around the abdomen, and thus the ***abdominal obesity*** of the Metabolic Syndrome.

Note that insulin resistance may be caused by many other things, already discussed. Hyperinsulinemia may also cause hyperleptinemia, and then the hyperleptinemia may cause leptin resistance in the pancreas and furthur aggravate the hyperinsulinemia and insulin resistance. This is another vicious-cycle dysregulation triggered initially by high glycemic carbohydrates.

Chart from: Richards BJ. *Mastering Leptin.* Minneapolis: Wellness Resources Books, 2004

## Ghrelin

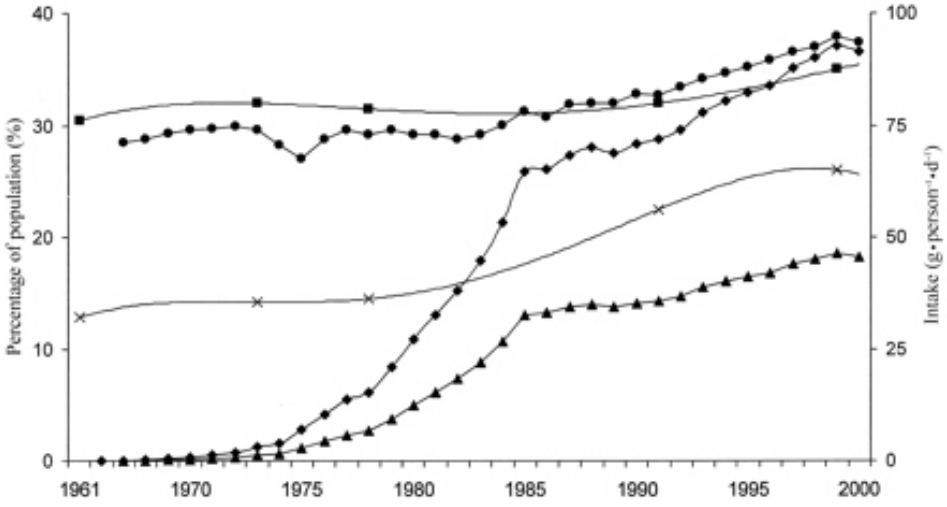
- Ghrelin is secreted by cells in the stomach wall.
- Normally eating suppresses ghrelin, and an empty stomach secretes it freely.
- Ghrlein stimulates appetite,
- Ghrelin is a potent stimulator of growth hormone, with the growth hormone promoting protein sparing and fat burning.

## Fructose and the appetite hormones

Fructose was introduced into the Amerian food supply as a sweetener during the 1970s. It quickly supplanted sucrose as the most common sweetener in processed foods. Following by about ten years, America saw a dramatic rise in rates of overweight, obesity, and diabetes. some authors have propsed that the epidemic was caused, among other factors, by the increasing amounts of fructose in the food supply.

**Fructose compared to an equal number of calories from glucose promotes leptin less and suppresses ghrelin less. Both responses were lowered by more than 60%.**

Americans consume on average 130+ calories from fructose per day, with 20% of Americans consuming more than 300 calories. The introduction of fructose into the food supply thus introduced empty calories which fails to suppress the appetite, leading to increased caloric consumption.




Estimated intakes of total fructose (•), free fructose (black triangle), and high-fructose corn syrup (HFCS, diamond) in relation to trends in the prevalence of overweight (black square) and obesity (x) in the United States.

George A Bray, Samara Joy Nielsen and Barry M Popkin. Bray GA, Nielsen SJ, Popkin BMConsumption of high-fructose corn syrup in beverages may play a role in the epidemic of obesity. American Journal of Clinical Nutrition, Vol. 79, No. 4, 537-543, April 2004

# Growth Hormone

"The Protein-sparing hormone"

## Basic functions

- **Increases protein synthesis in every cell**
- Promotes the release of fat for fuel from the cells
- Shift the cellular fuel from glycogen-glucose to fat
- Promotes insulin sensitivity

**Secreted in response to:**

- An empty or enptying stomach, via stimulation from the **ghrelin** hormone
- Dietary amino acids (promote glucagon, GH, AND insulin)
- Exercise **-- secretion increases with exercise intensity**
- Slow wave (deep) sleep

**Bottom line:** Growth hormone preserves protein reservoirs in the body by switching fuel burning away from the protein-gluconeogenesis pathway. It promotes building of the lean muscle mass and burning of the fat mass.

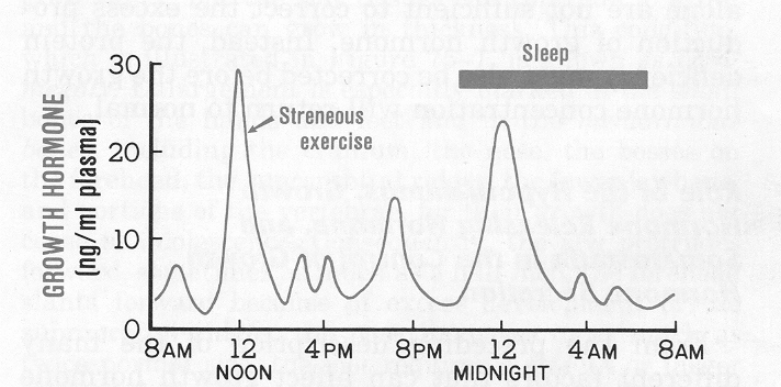
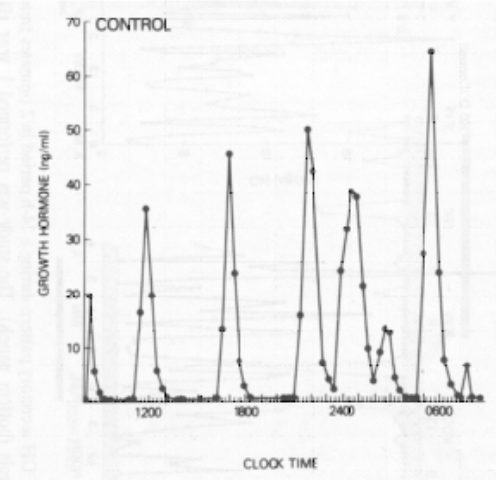



**Figure 75–5.** Typical variations in growth hormone secretion throughout the day, illustrating the especially powerful effect on secretion caused by strenuous exercise, and illustrating also the high rate of growth hormone secretion that occurs during the first few hours of deep sleep.

Notice the pulsatile secretion. Although the peaks of secretion may vary, the duration is usually about 90 minutes. The exception is the longer curve during deep sleep.

## Growth hormone declines with age

The result in the increased tendency to loss of lean body weight and the increase of fat with age.



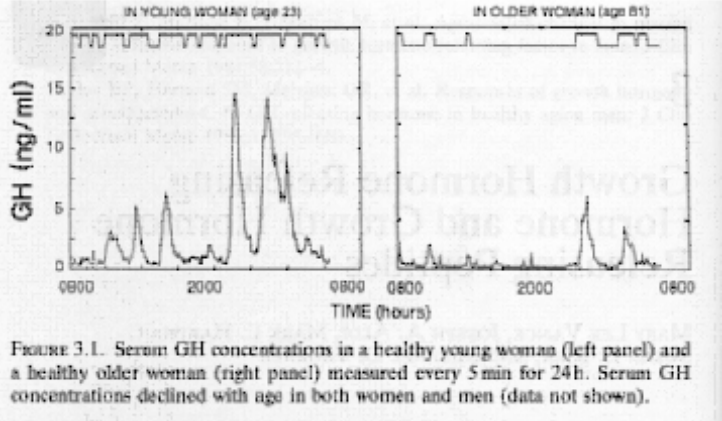




FIGURE 3.1. Serum GH concentrations in a healthy young woman (left panel) and a healthy older woman (right panel) measured every 5 min for 24 h. Serum GH concentrations declined with age in both women and men (data not shown).

Left: The growth hormone cycle in a young child. Notice that the peaks reach 30-65 ng/ml. also notice the prolonged levels of secretion during deep sleep.

Right: The growth hormone cycle in middle age and in elder years. Notice that the peaks in middel age are greatly reduced from youth, and are nearly non-existent in the elder.

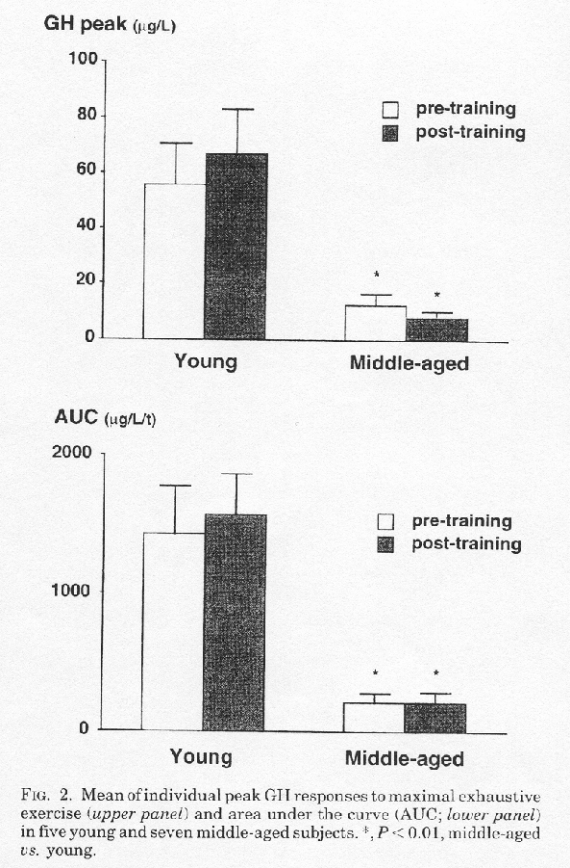



FIG. 2. Mean of individual peak GH responses to maximal exhaustive exercise (*upper panel*) and area under the curve (AUC; *lower panel*) in five young and seven middle-aged subjects. *, $P < 0.01$, middle-aged *vs.* young.

In middle age the growth hromone secretion to exercise is greatly reduced.

Zaccaria M, Vernier M, Piazza P, Noventa D, Ermoloa A. Blunted growth hormone response to maximal exercise in middle-aged vs young subjects and no effect of endurance training. J Clin Endocrinol Metab 84(7):2303-23-7

## Exercise and growth hormone

- GH response to exercise lasts abut 90 minutes.
- Intensity or duration of exercise does not change the length of the GH curve.
- Intensity, as measured by % of lactate threshhold, increases the peak of GH secreted during the 90 minute surge
- A GH curve may be suppressed and cut short by a surge of insulin/Igf-1

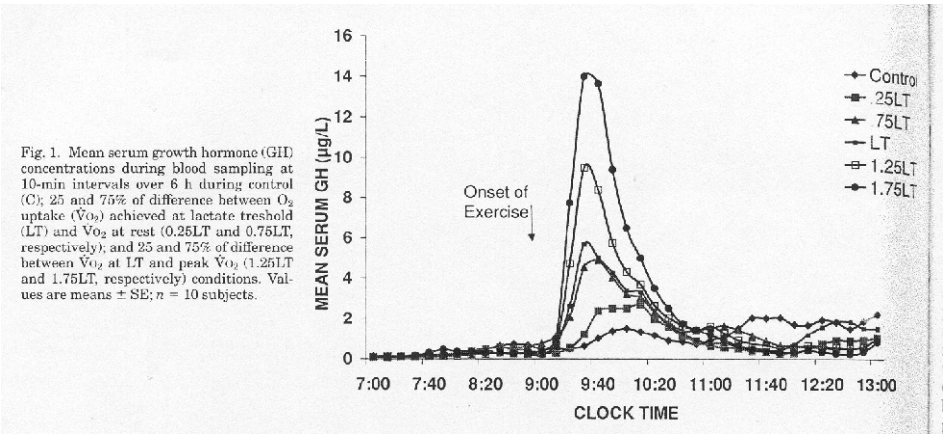
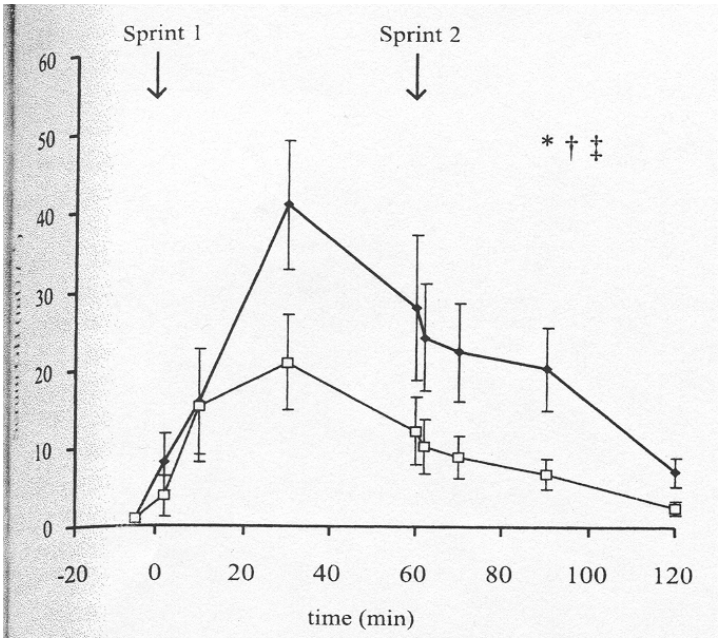



Fig. 1. Mean serum growth hormone (GH) concentrations during blood sampling at 10-min intervals over 6 h during control (C); 25 and 75% of difference between $O_2$ uptake ($\dot{V}O_2$) achieved at lactate treshold (LT) and $\dot{V}O_2$ at rest (0.25LT and 0.75LT, respectively); and 25 and 75% of difference between $\dot{V}O_2$ at LT and peak $\dot{V}O_2$ (1.25LT and 1.75LT, respectively) conditions. Values are means ± SE; $n$ = 10 subjects.

Notice that GH secretion increases only slightly between 75% of the lactate threshhold and 100% of lactate threshhold. It increased almost 60% more when simply exceeding the lactate threshhold by 25%, and more than doubles at 75% beyond the LT.

Pritzlaff CJ, Wideman L, Weltman JY, Abbott RD, et al. Impact of acute exercise intensity on pulsatile growth hormone release in men. *J Appl Physiol.* 1999 Aug;87(2):498-504.




4. Serum growth hormone (GH) concentrations at rest and ing 1 h of recovery after two 30-s maximal cycle ergometer sprints the fast (◆) and slow (□) trials. Values are means ± SE. *Sprint in effect, $P < 0.05$. †Time main effect, $P < 0.01$. Trial main effect, 0.08 (not significant). ‡Sprint × time interaction effect, $P < 0.01$.

The bottom curve on this graph shows a response that would be typical of a 30 minute jog. the upper curve shows the response to a 30-second all-out sprint. Notice that in either case, the GH duration will be about 90 minutes, but that the intensity of the exercise generates more GH. In this trial, the GH cruve is extended out toward 120 minutes because a second sprint was done at 60 minutes. Notice that the second sprint during the 90 minute spike from the first had little effect.

Stokes KA, Nevill ME, Hall GM, Lakomy HKA. Growth hormone responses to repeated maximal cycle ergometer exercise at different pedaling rates. *J Appl Physiol* 92:602-608

## Spaced exercise bouts produce more GH than sequential ones

Repeated exercise bouts during the day, but spaced well-apart in time, produce significantly greater total GH secretion

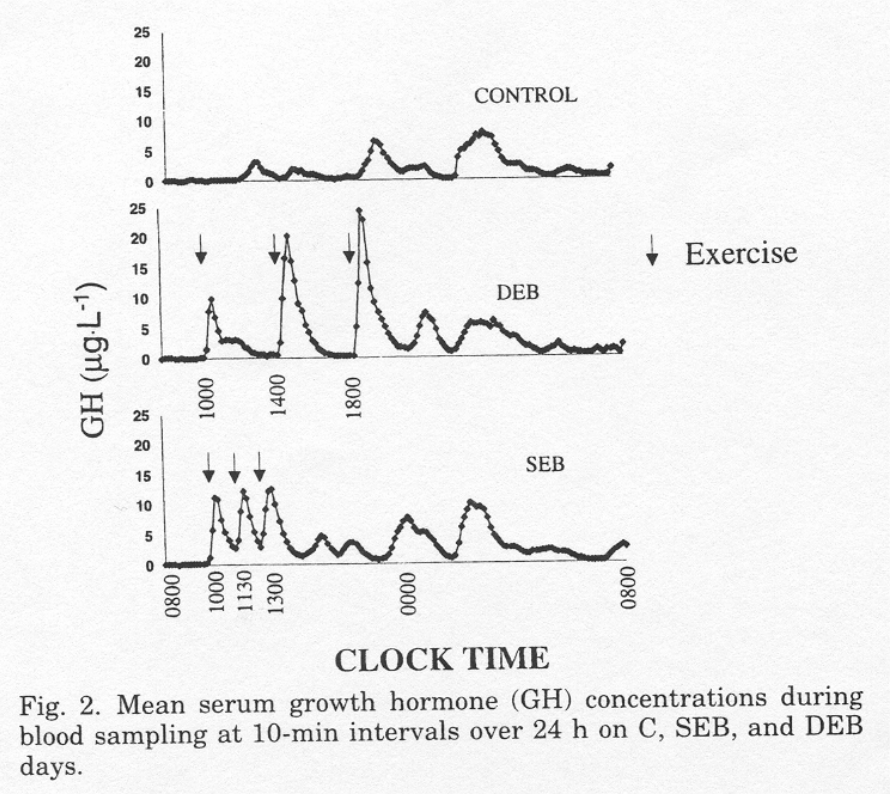



Fig. 2. Mean serum growth hormone (GH) concentrations during blood sampling at 10-min intervals over 24 h on C, SEB, and DEB days.

In this trial, SEB = sequential exercise bouts. In the bottom graph, a new exercise bout was begun at the 90 minute mark after the previous one. For the DEB= delayed exercise bout, in the middle graph, exercise periods were spaced at 4-hours intervals. Notice the increasing GH intensity with each successive bout.

Kanaley JA, Weltman JY, Veldhuis JD, Rogol AD et al. Human growth hormone response to repeated bouts of aerobic exercise. *J Appl Physiol*. 1997 Nov;83(5):1756-61

**See also in the chapter on Metabolic Dysregulation, that GH response to exercise is blunted in obesity.**

**Therapeutic preview: Short bursts of high intensity exercise, repeated throughout the day, will produce GH in much greater quantity than a single bout of aerobic exercise.**

## Walking exercise

Although public health recommendations over the last twenty years have emphasized aerobic exercise in 30-40 minute bouts 3-4 times a week, simple walking exercise confers almost as much benefit on cardiovascular risk. In addition:

- 30-40 minutes of moderate walking reduces heart disease risk by 40%
- The same exercise lowers cancer risk by about 35%
- Patient compliance with walking is much better than with aerobic exercise. Despite decades of health advice, 75% of Americans do not get the 30-40 minutes of aerobic exercise 3-4 times per week recommended.
- Patients are much more likely to engage in walking every day than in more intense exercise.
- The benefits of walking exercise are equal or better when it is broken up into multiple 10-minute sessions thatn if engaged in all at once.
- The benefits of walking are not due to changes in insulin resistance, with is not much affected by walking exercise.

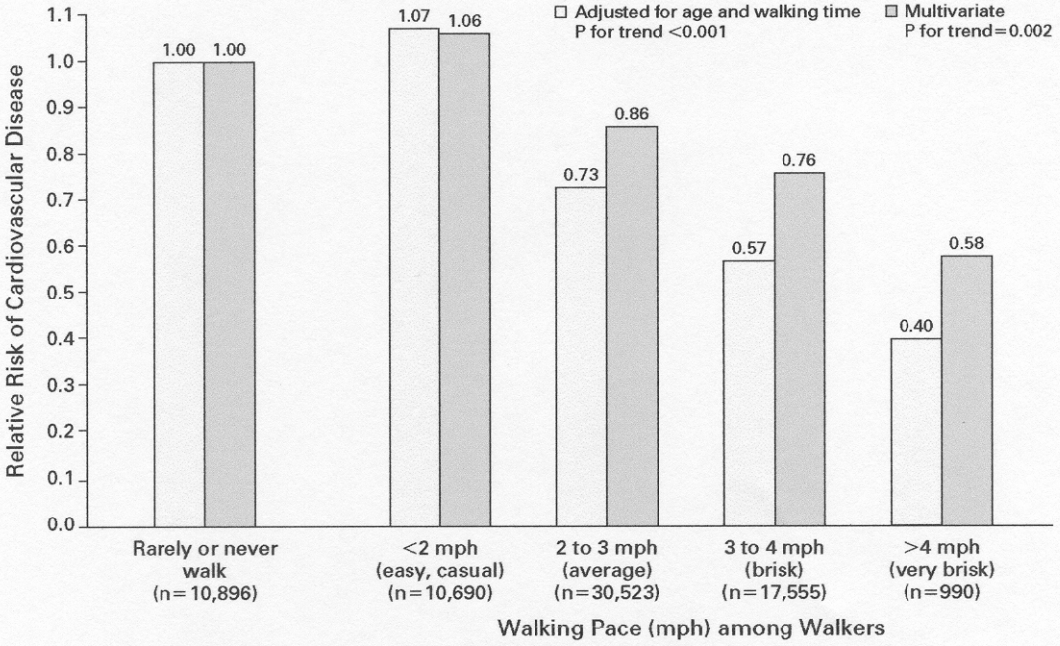



**Figure 4.** Multivariate Relative Risk of Cardiovascular Disease and Relative Risk Adjusted for Age and Walking Time, According to Walking Pace.

Multivariate relative risks were adjusted for age, time spent walking, smoking status (0, 1 to 14, 15 to 24, or ≥25 cigarettes per day), race or ethnic group, level of education, annual family income, body-mass index, waist-to-hip ratio, level of alcohol intake, parental history of premature myocardial infarction, age at menopause, use or nonuse of hormone-replacement therapy, percentage of calories from saturated fat, number of servings of fruit and vegetables per day, and dietary fiber intake. To convert values for distance to kilometers, multiply by 1.6.

Manson J, Greenland P, LaCroix AZ, Stefanick ML, et al. Walking Compared with vigorous exercise for the prevention of cardiovascular events in women. *NEJM* 347(10):716-725

## Bottom Line

**The ideal exercise routine to maximize GH effects and reduce insulin resistance would include:**

- A base of walking 30-90 minutes most days
- Walking at a "brisk but comfortable" pace
- Walking broken up into multiple short segments rather than one long one. Note that 10-15 minute brisk walks are easier to work into a busy modern schedule.
- Intermittent burst-type maximal exercise, such as a sprint, bike sprint, or short bout with weights.
- The burst exercise may be from 30 seconds to 5 minutes, and may be integrated into a walking session.
- A short session of burst exercise 2 hours after the evening meal will clear nutrients from the blood and rpepare for fat burning during sleep.

# Stress, Sleep, and Insulin Resistance

We can see **three major endocrinological states** in the human:

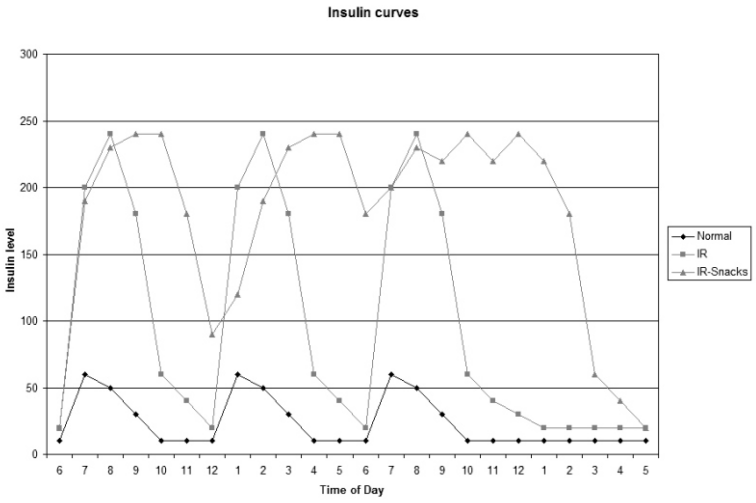
- The baseline state. Glucagon and growth hormone are the normal hormones. The stomach is empty, and the individual is preferentially burning fat. The individual may be in ketosis.
- The post-meal state. Insulin and IGF-1 are the dominant hormones. Glucose is the predominant fuel. GH and its effects are suppressed.
- The stress state. Cortisol and or adrenalin are the controlling hormones, the preferred fuel is glucose, which in this state may be derived from protein through gluconeogenesis. Insulin is moderately elevated in response to the elevations of glucose from the stress hormones. The stress hormones induce a level of insulin resistance.

According to our physiological nature, we are designed for long periods of the baseline state, with short periods of the post-meal or the stress states. Severe metabolic problem may arise when the individual is in either the prolonged "fed" stateor prolonged stress.

- Elevated cortisol from endurance type stress, sleep loss, etc. can induce insulin resistance at the level that it is found in gestational diabetes.
- Individuals with pre-diabetic insulin resistance may flip into full blown diabetes under the influence of cortisol.
- Insulin spikes cause counterregulatory spikes of cortisol and/or adrenalin in order to prevent hypoglycemia

Prolonged and chronic hyperinsulinemia causes a corresponding chronic hypercortisolemia.

- This is essentially an endocrine civil war between insulin, which is trying to lower blood glucose, and cortisol, which is trying to elevate it.
- Because the insulin block the release of fuels from the cell, and the cortisol demands more fuel, the result is a gnawing appetite for carbohydrates. This typically occurs at the 2 hour point after meals
- This may eventually cause adrenal exhaustion.




Thus, the post-meal and the stress states become superimposed, and become the dominant baseline state, supplanting the normal GH dominated state. The muscle mass wastes, fat accumulates, and insulin resistance proceeds to do its damage to the system.

The chart shows a normal insulin curve, an insulin-resistant one, and one where compensatory snacking causes a permanent state of insulin elevation.

# Pathophysiology of sleep debt and Sleep therapeutics

## Introduction

The state of sleep debt includes profound changes in the endocrine, cardiovascular, and immune systems and natural treatments for these conditions, without correcting the underlying sleep debt are sure to fail. Thus herbal nervines and hypnotics, administered in the context of lifestyle changes to induce recuperative sleep and establish normal sleep duration and depth, become critical to the successful practice of herbalism in chronic disease. Sleep debt has become a major obstacle to cure, to some extent present in the majority of patients.

## Some physiological effects of sleep deprivation

"Normal" average sleep duration was about 9 h per night in 1910, and reamined close to this until 1960. Since 1960 the average has fallen to about 7.5 h currently. Approximately 1/3 of the population sleeps 6 hours or less per night. To meet the demands of around-the-clock production, many shift workers sleep, on average, less than 5 h per work day.

Bliwise DL. Historical change in the report of daytime fatigue. Sleep 1996; 19: 46264.

Broman JE, Lundh LG. Hetta J. Insufficient sleep in the general population. Neurophysiol Clin 1996; 26: 3039

Kripke DF, Simons R, Garfinkel L, Hammond E. Short and long sleep and sleeping pills: is increased mortality associated? Arch Gen Psychiatry. 1979;36:103-116.

National Sleep Foundation (NSF). 2000 Omnibus Sleep in America Poll. Washington, DC: NSF; 2000. Available at: http://www.sleepfoundation.org/publications/2000poll.html Accessibility verified February 6, 2003.

Some studies have shown that participants cannot adapt to a progressive curtailment of their usual sleep period by 2-3 h per night, experiencing substantial alterations in mood and vigilance.

Dinges D, Pack F, Williams K, et al. Cumulative sleepiness, mood disturbance, and psychomotor vigilance performance decrements during a week of sleep restricted to 4-5 hours per night. Sleep 1997; 20: 26777.

In general, sleep loss will result in performance deficits, including increased variability in performance, slowed physical and mental reaction time, increased errors, decreased vigilance, impaired memory, and reduced motivation and laxity.

Dinges DF, Kribbs NB. Performing while sleepy: Effects of experimentally induced sleepiness. In: Monk TH, ed. Sleep, Sleepiness, and Performance. New York: Wiley, 1991.

Brain metabolism slowed by 7%, as measured by brain uptake of glucose.

Spiegel K, Leproult R, Van Cauter, E Impact of sleep debt on metabolic and endocrine function Lancet 1999 354: 1435-1439

Thomas M, Balkin T, Sing H, Wesensten N, Belenky G. 14th European Congress on Sleep Research 1332. Madrid: Blackwell Science, 1998.

## Endocrine effects

Recent studies show that underlying the cognitive impairment of sleep debt is a profound endocrine dysregulation.

Van Cauter E, Spiegel K. Hormones and metabolism during sleep. In: Schwartz WJ, ed. Sleep science: integrating basic research and clinical practice. Monogr Clin Neurosci 1997; 15: 14474.

Spiegel K, Leproult R, Van Cauter, E Impact of sleep debt on metabolic and endocrine function Lancet 1999 354: 1435-1439

## Thyroid hormone

Thyroid hormone levels rose during the 4-day period above. Long term effects have not been measured, but chronic overstimulation of the thyroid could cause chronic thyroid disease.

Spiegel K, Leproult R, Van Cauter, E Impact of sleep debt on metabolic and endocrine function Lancet 1999 354: 1435-1439

## Growth hormone levels

Growth hormone normally surges in the first several hours of sleep, during slow wave brain activity in the deep stages of sleep. If the slow wave portion of sleep is curtailed, growth hormone production is also depressed. And in those with sleep deprivation, trials inducing slow wave sleep also restore growth hormone secretion.

Van Cauter E. Slow wave sleep and release of growth hormone. JAMA 2000 Dec 6;284(21):2717-8

Van Cauter E, Copinschi G. Interrelationships between growth hormone and sleep. Growth Horm IGF Res 2000 Apr;10 Suppl B:S57-62

Spiegel K, Leproult R, Colecchia EF, L'Hermite-Baleriaux M, Nie Z, Copinschi G, Van Cauter E. Adaptation of the 24-h growth hormone profile to a state of sleep debt. Am J Physiol Regul Integr Comp Physiol 2000 Sep;279(3):R874-83

Van Cauter E, Leproult R, Plat L. Age-related changes in slow wave sleep and REM sleep and relationship with growth hormone and cortisol levels in healthy men. JAMA 2000 Aug 16;284(7):861-8

## Cortisol levels

Afternoon and early evening cortisol levels rose significantly in the sleep debt phase. This may reflect decreased efficacy of the negative-feedback regulation of the hypothalamo-pituitary-adrenal axis.

Leproult R, Colecchia EF, L'Hermite-Baleriaux M, Van Cauter E. Transition from dim to bright light in the morning induces an immediate elevation of cortisol levels. J Clin Endocrinol Metab 2001 Jan;86(1):151-7

Van Cauter E, Leproult R, Plat L. Age-related changes in slow wave sleep and REM sleep and relationship with growth hormone and cortisol levels in healthy men. JAMA 2000 Aug 16;284(7):861-8

## Immune function is also impaired

In several studies sleep deprivation resulted in impaired immune function, especially of natural killer cells, essential to defense against viral infection and cancer. This was found with even modest sleep deprivation, such as denying sleep during 10 PM and 3 AM, or between 3AM and 7 AM.

Dinges DF, Douglas SD, Hamarman S, Zaugg L, Kapoor S. Sleep deprivation and human immune function. Adv Neuroimmunol 1995; 5: 97110.

One trial demonstrated a reduced response to influenza immunization in subject in a state of sleep debt.

Spiegel K, Sheridan JF, Van Cauter E. Effect of sleep deprivation on response to immunizaton. JAMA 2002 Sep 25;288(12):1471-2

Inflammatory chemicals are increased

**Insulin resistance and cardiovascular disease.**

Impaired carbohydrate tolerance. One trial found a glucose clearance rate depressed by 40% after 4 days of restriction of sleep to four hours a night. The measurement is comparable to that found in gestational diabetes. Responses to a morning glucose tolerance test fit the criteria for impaired glucose tolerance.

Spiegel K, Leproult R, Van Cauter, E Impact of sleep debt on metabolic and endocrine function Lancet 1999 354: 1435-1439

**Such changes have been linked to age-related insulin resistance and memory loss.**

Van Cauter E, Leproult R, Kupfer DJ. Effects of gender and age on the levels and circadian rhythmicity of plasma cortisol. J Clin Endocrinol Metab 1996; 81: 246873.

Kern W, Dodt C, Born J, Fehm HL. Changes in cortisol and growth hormone secretion during nocturnal sleep in the course of aging. J Gerontol 1996; 51A: M39.

**Glucose tolerance is decreased during sleep debt**

Scheen AJ, Van Cauter E. The roles of time of day and sleep quality in modulating glucose regulation: clinical implications. Horm Res 1998;49(3-4):191-201

Scheen AJ, Byrne MM, Plat L, Leproult R, Van Cauter E. Relationships between sleep quality and glucose regulation in normal humans. Am J Physiol 1996 Aug;271(2 Pt 1):E261-70

**Abdominal pattern obesity**

Scheen AJ. Clinical study of the month. Does chronic sleep deprivation predispose to metabolic syndrome? Rev Med Liege 1999 Nov;54(11):898-900

**Increased tendency of blood to clot.**

Meade TW, Chakrabarti R, Haines AP, North WR, Stirling Y. Characteristics affecting fibrinolytic activity and plasma fibrinogen concentrations. Br Med J 1979 Jan 20;1(6157):153-6

**Increased triglycerides**

Costa G. The impact of shift and night work on health. Applied Ergonomics 1996; 27: 9-16.

Morgan LM, Aspostolakou F, Wright J, Gama R. Diurnal variations in peripheral insulin resistance and plasma non-esterified fatty acid concentrations: a possible link? Ann Clin Biochem 1999; 36: 447-50.

**Obesity, both in adults . . .**

Parkes KR. Shift work and age as interactive predictors of body mass index among offshore workers. Scand J Work Environ Health 2002 Feb;28(1):64-71

**. . .and children**

Child Care Health Dev 2002 Mar;28(2):163-70 A dose-response relationship between short sleeping hours and childhood obesity: results of the Toyama Birth Cohort Study. Sekine M, Yamagami T, Handa K, Saito T, Nanri S, Kawaminami K, Tokui N, Yoshida K, Kagamimori S.

## Hypertension

Lusardi P, Zoppi A, Preti P, Pesce RM, Piazza E, Fogari R. Effects of insufficient sleep on blood pressure in hypertensive patients: a 24-h study. Am J Hypertens 1999 Jan;12(1 Pt 1):63-8

## Myocardial infarction

2 or more days/week with <5 hours of sleep were also associated a 200-300% increase in heart attack (5-10 times the risk of having high cholesterol)

Y Liu and H Tanaka Overtime work, insufficient sleep, and risk of non-fatal acute myocardial infarction in Japanese men Occupational and Environmental Medicine 2002;59:447-451

In a group of women, those reporting less than five hours of sleep per night had an 82% increase in cardiovascular events. Those sleeping fewer than six hours had a 30% increase. Note that these risk are high than those for moderately elevated total cholesterol or LDL cholesterol.

Najib T. Ayas, MD; David P. White, MD; JoAnn E. Manson, MD, DrPH; et al. A Prospective Study of Sleep Duration and Coronary Heart Disease in Women Arch Intern Med. 2003;163:205-209

The effects of sleep deprivation can be induced either by disruption of the quantity of sleep, or its quality. Chronic light restless sleep without a deep sleep phase results in many of the above changes. Disruption of sleep quality commonly accompanies jet lag, night shift work, and lifestyle activities that do not conform to the natural circadian rhythm of light and dark. And a diurnal-nocturnal pattern of activity and rest.

## Sleep debt

Experimental extension of the time spent in bed to 14 h per day over 1month showed that a normal 8 h night does not meet the sleep needs of healthy young adults, who may carry a substantial sleep debt even in the absence of obvious efforts to curtail sleep.

Wehr TA, Moul DE, Barbato G, et al. Conservation of photoperiod-responsive mechanisms in humans. Am J Physiol 1993; 265: R84657.

## Physiological influences on sleep

In a normal daily physiological rhythm, the hormone melatonin begins to rise in the early evening and reaches a peak at 4-6 AM. The body temperature follows the opposite course, and begins to decline as the melatonin increases, and is at its lowest point when melatonin peaks. The most important factor setting this rhythm is exposure to light, which depresses melatonin. The body temperature low point at 4-6 AM can be shifted later by exposure to even moderate light (such as in the typical home living room) after sunset.

Zeitzer JM, Dijk DJ, Kronauer R, Brown E, Czeisler C. Sensitivity of the human circadian pacemaker to nocturnal light: melatonin phase resetting and suppression. J Physiol 2000; 526: 695-702.

Factors that raise body temperature after sunset, such as exercise or heavy meals, or hot baths near bedtime, can also disrupt the cycle.

The deepest sleep normally occurs during the first 3 hours of sleep, and during this time growth hormone surges at a rate about equivalent to light aerobic exercise. GH promotes regeneration of the tissues and immune system, and healing and repair of the lean body mass. This surge may be blocked if carbohydrates are eaten within 3 hours of going to bed, (via the GH blocking effects of insulin) or if sleep is not deep enough. Valium and related drugs cut off the deep stages of sleep, and may block this function of growth hormone.

Night shift work can have persistent negative effects on health due to the inability of the human organism to adapt fully to a daily rhythm of activity and rest that is out of synch with the daily alteration of light and dark.

Rajaratnam S  Arendt J  Health in a 24-h society Lancet 2001; 358: 999-1005

Problems among shiftworkers include sleep disorders (which can become chronic), gastrointestinal disease, increased incidence of cardiovascular disease, lipid intolerance evidenced by increased triacylglycerol concentrations, and possibly an increase in late-onset diabetes.

Costa G. The impact of shift and night work on health. Applied Ergonomics 1996; 27: 9-16.

Morgan LM, Aspostolakou F, Wright J, Gama R. Diurnal variations in peripheral insulin resistance and plasma non-esterified fatty acid concentrations: a possible link? Ann Clin Biochem 1999; 36: 447-50.

## A routine for establishing healthy sleep

This routine is especially helpful for re-establishing a healthy 8 1/2 to 9 1/2 hour sleep cycle in an individual who has chronically not been sleeping well, or who is suffering from the after effects of night shift work or jet lag.

- Select a time to go to bed so you can get 8 2 to 9 2 hours of sleep before the need to arise in the morning. Any hour of sleep before 11 PM is especially beneficial, and any hour of wakefulness after 1 AM is especially detrimental.

- Engage in some outdoor activity during the bright daylight hours around noon, even if it is only a 20 minute walk on the lunch hour. Bright natural light suppresses melatonin, and help to establish the normal daily rhythm, with the melatonin rising again as sleep approaches. If possible, do your daily exercise in the daylight hours before 1 PM. This allows the body=s metabolism to cool down before sleep. Physical exercise after sunset may be detrimental to sleep.

- A brief late-afternoon nap is OK. 20 minutes is ideal. Don=t engage in physical exercise or intense exciting activity after the nap.

- Have an early dinner, and be sure the stomach is empty before going to bed. 5-6 hours after the last meal is optimal, but at least 3 hours is necessary. The body metabolism increases in response to food, and this elevation can promote insomnia.

- Don't engage in intense mental activity for at least 2 hours before bedtime. Light reading is OK.

- Turn off all bright lights as soon as possible after sunset, and very strictly for the last hour before bedtime. Use gentle candlelight instead of bright room light if possible.

- In the last 45-90 minutes before bed, take a Aneutral bath.@ (Not a hot bath) In a neutral bath, the water temperature should be 92-97 degrees F. It should feel somewhere between natural temperature and slightly warm to the individual. Add warm water as necessary to keep the bath from feeling cool. A treatment for insomnia could last from 15-60 minutes. During the last part of the bath, let the water cool down somewhat so it feels cool to the touch. The bath room should be dimly lit, as with candlelight. A few drops of lavendar essential oil may be added to the bath. Soft pleasant music may also be played. This treatment cools and slows the metabolism, while relaxing the nervous system. Lie down and rest in a horizontal position as soon as possible after the bath.

- Take a dose of mild sedative herbs 30-60 minutes before bed.

- Get horizontal for 30-60 minutes before going to sleep (after the bath if you take one). Read or watch television lying down. Remember, keep the lights dim.

- At the time you set to go to sleep, take another dose of sedative herbs, turn off all lights, draw the blinds or curtains if the moon is bright, and don=t turn on any lights again until morning light comes. Say a prayer, release the events of day to the Creator, make thanks for the good things of the day. Lie down in bed and relax. Think about natural things that you love B animals, plants, trees, beautiful places in nature. Soft music may be played as you are going to sleep.

- If you wake up before 8 2 hours, roll over and go back to sleep. For recovery from sleep deficit, stay in bed for at least 9 2 hours, and take a twenty-minute nap in the late afternoon.

- Eat a substantial breakfast with abundant protein, and try to consume 80% of your daily protein requirements at breakfast and lunch. Protein raises by heat production.

- This routine will usually re-establish the sleep-wake cycle within 3 days.

## Case study: Sleep debt and insulin resistance

A 52 year-old man with insulin resistance syndrome, but no diabetes or abnormal glucose tolerance, attempted to remain in bed ten or more hours per night for fourteen days. His fasting blood glucose had been between 100 and 105 each time he measured it during the previous three weeks. He was fatigued and stressed and reported insomnia. After coaching on sleep hygiene, including the patient instructions on page four, he attempted to remain in bed for ten or more hours per night for fourteen days. The accompanying table shows the hours actually slept and the fasting blood glucose each morning. The average blood glucose reading fell by more than ten points during the period of increased rest. The before and after readings were within the range of normal blood glucose, according to current standards, but the change may have significantly lowered heart disease risk. Hoogwerf et al explored coronary heart disease risk at levels of fasting blood glucose within the normal range, and found a nearly 20% increase in cardiovascular disease risk as glucose readings rose from the mid-eighties to the mid-nineties (Hoogwerf et al). The three-night period of extended sleep necessary to shift the metabolism initially in this case is typical. The blood glucose rise in the middle of the period when the sleep fell to eight hours may demonstrate that this individual requires more than eight hours of sleep per night to maintain normal metabolism.

| Day | Hours slept | Fasting glucose |
|---|---|---|
| 1 | 10 | 103 |
| 2 | 10.5 | 105 |
| 3 | 11 | 81 |
| 4 | 9.5 | 86 |
| 5 | 9.5 | 94 |
| 6 | 8.5 | 92 |
| 7 | 8.0 | 88 |
| 8 | 8.0 | 102 |
| 9 | 9.0 | 99 |
| 10 | 10.0 | 91 |
| 11 | 9.5 | 92 |
| 12 | 9.5 | 98 |
| 13 | 9.0 | 86 |
| 14 | 9.5 | 91 |

# Stages of Insulin Resistance Syndrome

We need to identify the true stages of insulin resistance, so we have some baseline against which to measure the results of our clinical interventions. The contemporary "normals" were devised more than a century after 100lbs or more of added sugar per capita also became "normal." Hunter gatherers woudl be classified as "super-normal" according to modern standards, but the hunter gatherer norms are routinely achievable for some indicators with the methods taught in this course.

## Stage 1 Hunter-gatherer normal

**Blood glucose**

“Normal” fasting glucose, per modern standards = 75-100 mg/dl

However, heart disease risk begins to rise as soon as blood glucose rises above 90 mg/dl with the increase in rise from a 85 to 95 at 119%, adjusting for other known risk factors.

Hoogwerf, BJ et al Blood glucose concentrations <= 125 mg/dl and Coronary Heart Disease Risk Am J Cardio 89;2002:596-599

"The Paleolithic diet of our ancestors, which consisted of lean meats, vegetables and small amounts of whole grains, nuts, seeds and fruits, is estimated to have generated blood glucose levels between 60 and 90 mg/dL."

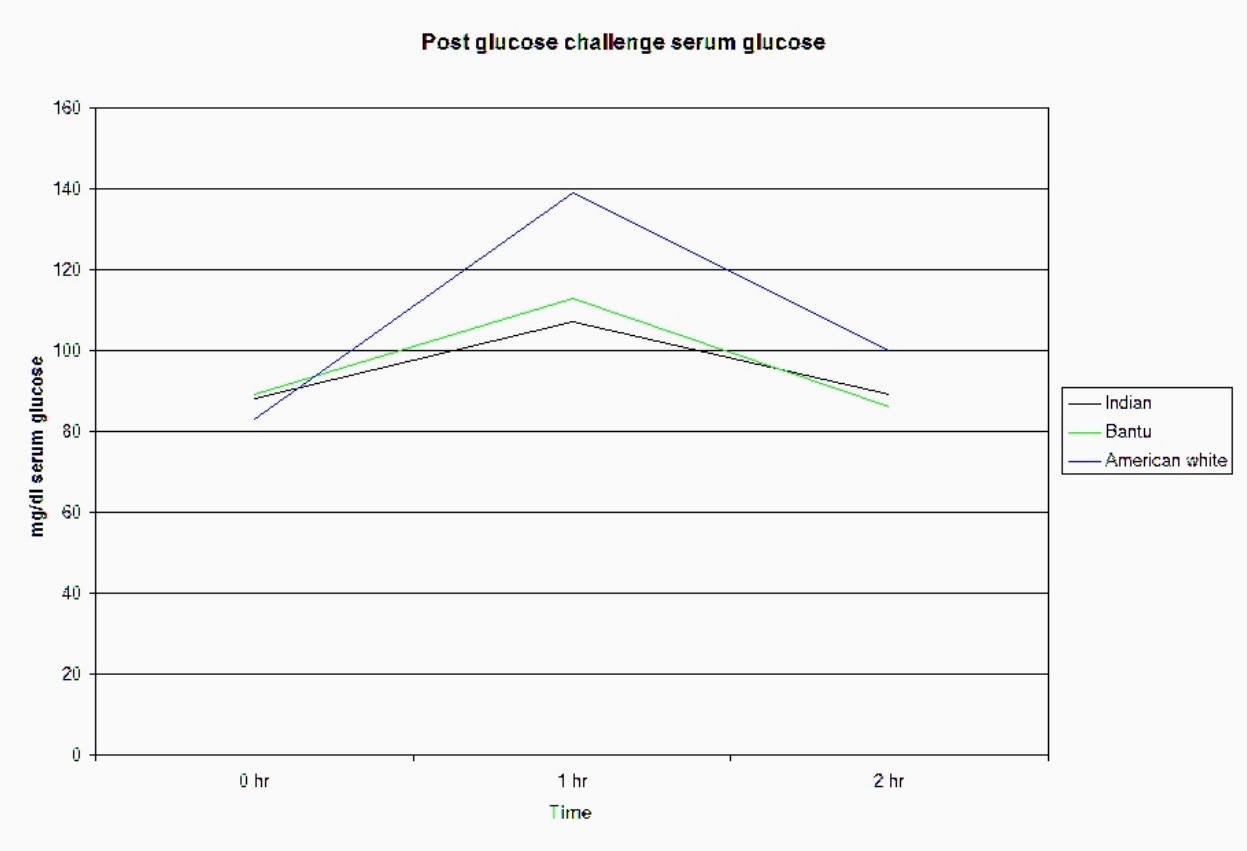
Brand-Miller J, et al. The glucose revolution. Newport (RI) Marlowe andCo.; 1999.

**“Normal” Glucose Tolerance per modern diagnostic standards**

| | |
|---|---|
| Fasting | 75-100 |
| One-hour post 100 g oral glucose | < 195 |
| Two hour | < 140 |

**Glucose levels after 100 ml glucose challenge**

| | 0 | 60 | 120 |
|---|---|---|---|
| American white | 83 +/- 4 | 139 +/- 5.8 | 100 +/- 5.6 |
| Indian | 88 +/- 9.5 | 107 +/- 31 | 89 +/- 21 |
| Eskimo | 77 +/- 9.8 | ——— | 86.3 +/- 19.2 |
| Bantu | 89 +/- 3 | 113 +/- 6 | 86 +/- 9 |
| Yanomama | 86 +/- 13 | 86.5 +/- 17.3 | 90 +/- 26 |




**The two traditional groups (American Indian and Afican Bantu) have similar blood glucose responses to a glucose challenge, which is markedly lower than that of a "normal" group of whites without clinical insulin resistance or diabetes according to contemporary standards.**

**Percentile levels of glucose two hours after a glucose load.**

| | | 25 | 50 | 75 | 90 | 95 |
|---|---|---|---|---|---|---|
| Bedford, England | | | | | | |
| 50 grams glucose | | | | | | |
| both sexes | | 77 | 99 | 113 | 128 | 149 |
| | | | | | | |
| Eskimos | | | | | | |
| 100 grams glucose | | | | | | |
| | male | 61 | 71 | 82 | 101 | 114 |
| | female | 73 | 86 | 103 | 124 | 146 |
| | | | | | | |
| Alaskan Indian | | | | | | |
| 100 grams glucose | | | | | | |
| | male | 71 | 84 | 90 | 97 | 102 |
| | female | 78 | 83 | 94 | 129 | 155 |


Spielman RS, Fajans SS, Neel JV, Pek S, Floyd JC, Oliver WJ.Glucose tolerance in two unacculturated Indian tribes of Brazil. Diabetologia 1982; 23: 90-3.

Mouratoff. GJ, et al. Diabetes mellitus in Athabaskan Indians in Alaksa Diabetes 1969 Jan;18(1):29-32

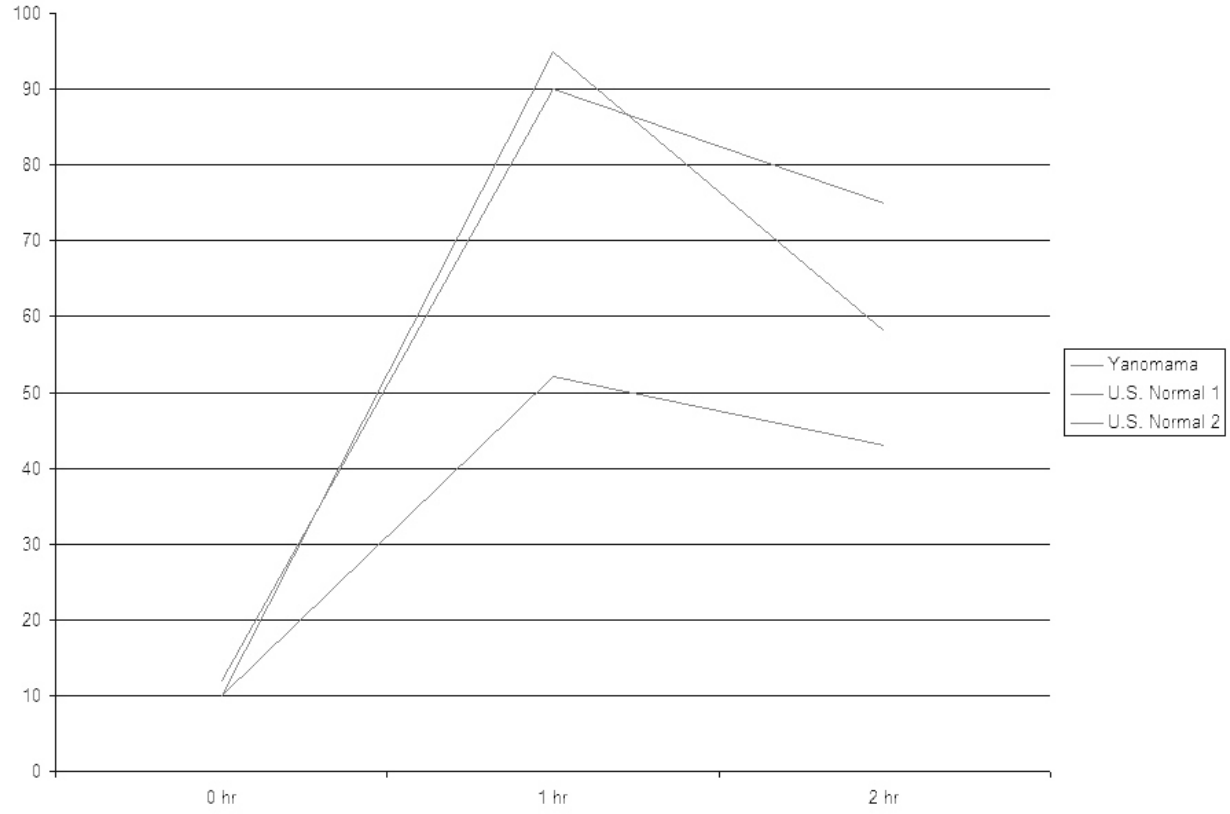
Mouratoff GJ, Carroll NV, Scott EM. Diabetes mellitus in Eskimos. JAMA. 1967 Mar 27;199(13):961-967

Merimee TJ, Rimoin DL, Cavalli-Sforza Metabolic Studies in the African Pygmy J Clin Invest 51;1972:395-401

## Insulin

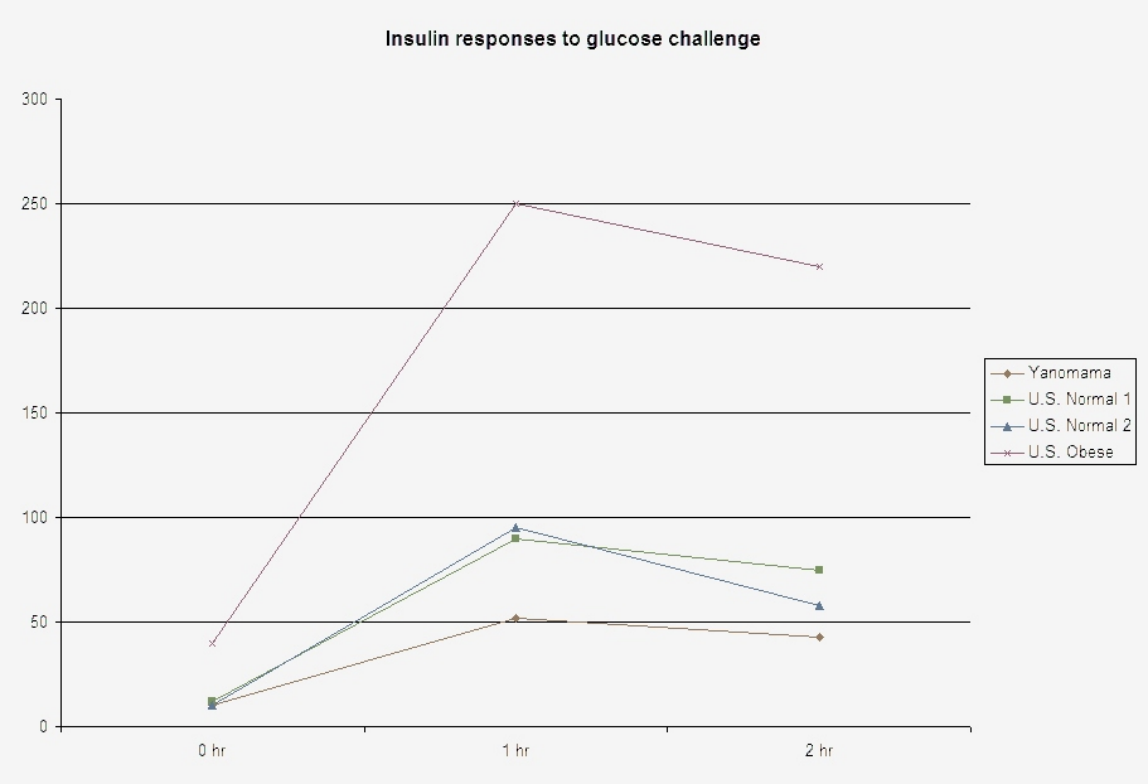
The Yanomama Indians of South America exhibit a greatly blunted response to a glucose tolerance test compared to modern subjects. They also exhibit a lower insulin response. The Yanomama may not be typical of hunter-gatherers because they have a high carbohydrate diet, with “cooking bananas” (plantain) and “yams” as their chief source of calories. Thus they may have higher insulin levels, some level of insulin resistance, and other h-g groups may have even better insulin curves relative to American "normals."

| **Minutes post 100g oral glucose** | **0** | **60** | **120** |
|---|---|---|---|
| Normal, US (Porth) | 5-20 | 90 | 75 |
| Normal, US (Speilman et al) | 10.4 +/- 4.5 | 95.0 +/- 47.2 | 57.2 +/- 21.9 |
| Obese, US | 40 | 250 | 220 |
| Obese diabetic, US | 50 | 180 | 220 |
| Yanomama | 10.5 +/- 5.1 | 52.5 +/- 34.9 | 42.9 +/- 32 |




**The top two curves are from clinically "normal" modern U.S. whites**

**The bottom curve is from brazilian Yanomama Indians**




**This is the same data as the previous graph, but with the top curve added. It represents the typical insulin cirve in obesity with insulin resisstance but no diabetes. Yanomama-type insulin responses are attanable in modern patients with dietary and exercise modification.**

## Triglycerides

### Conventional normal

Before Fall 2001 = < 200

Now = < 150

### Gunter-gatherer normal

The dietary habits of present hunter-gatherer populations reveal the impact of a Westernized diet on both TG and cholesterol and suggest that a desirable TG is < 100 mg/dl.

Miller M. The epidemiology of triglyceride as a coronary artery disease risk factor. Clin Cardiol 1999 Jun;22(6 Suppl):II1-6

**Blood Pressure**

Lifelong low blood pressure is the rule among primitive peoples

1929: Average blood pressure for all 97 men over age 60 in a group of 1000 Kenyan tribesmen was 105/60

1949: Average blood pressure in Eskimo men aged 50-59 102/76

The Western Diseases, Their Emergence and Prevention by Trowell and Burkitt. Harvard Univ Press, 1981; ISBN: 0674950208

**Obesity**

Pattern in traditional studies in body weight peak at age 25, then gradual decline

Pattern in modern society is steady slow increase from age 25, until some wasting after age 80.

The Western Diseases, Their Emergency and Prevention by Trowell and Burkitt. Harvard Univ Press, 1981; ISBN: 0674950208

**Stage 1 Normal**

Fasting blood glucose <90

2-hour post glucose challenge < 110

Insulin < 10

Triglycerides < 100

Blood pressure declining with age; =<115/75 in a 40 year old; =<110/70 in a 50 year old.

Weight declining with age: Peak weight at age 25.

**Stage 2 Borderline dysfunction (60-80% of modern population)**

Insulin resistance indicators within modern "normal" parameters

Fasting blood glucose 90-100

2-hour post glucose >110, <140

Any degree of hypoglycemia at 2-5 hours

Fasting insulin 10-20

Triglycerides 100-150

Blood pressure =>120/80 to 130/90 in an individual over 50 years old

Body Weight > Age 25 weight.

**Stage 3 Overt Insulin resistance (40% of modern population by age 60)**

Fasting blood glucose 100-120

2 hour post glucose => 140

Blood glucose < 60 at 2-5 hours post challenge

Fasting insulin > 20 (Nichols Institute)

Tryglycerides > 150

HDL <40 male <50 female

Blood pressure > 135/95

Waist > 35 (female) > 40 male

Waist:hip ratio >= .8 female >= 1 male

**Stage 4 Diabetes (5-8% of modern population – white; higher in blacks, Hispanics, Native Americans)**

Fasting blood glucose >120

Any post glucose challenge > 195

For Dr Ravnskov's information on cholesterol and saturated fat, see:
http://www.ravnskov.nu/cholesterol.htm

# Syndrome X Therapeutic Triangle

**Exercise to maximize**
**growth hormone effects**

**A low glycemic diet**
**to minimize insulin effects**

**Supplementation with all**
**factors that reduce**
**insulin resistance**

**(rest, sleep)**

## Dietary Inteventions for Syndrome X

### Satiation is essential

Conventional model = Calories in/calories out

In reality = Satiation + nutritional requirements ——> Appetite ———> Calories in

Thermogenic set point plus activity ——-> calories out

So: ***Selection of a diet that maximizes thermogenesis and satiation along with nutrient density*** may promotes weight loss without restriction of the appetite.

### Protein and fiber increase satiation

Many trials show an increase in satisfaction with higher protein or fiber intake. The NAS states that up to 35% of calories may be taken from protein. That amounts to 180-200 grams of protein for most people. This is consistent with nutritional anthropology.

Institute of Medicine of the National Academies. Dietary References Intakes: Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids. Washington: National Academy Press, 2002

### Protein increases thermogenesis

A group of overweight or mildly obese men were fed 29% of energy as fat, 29% as protein, and 42% carbohydrate vs 28% fat and 11% protein, and 61% carbohydrate for four days. The diets contained the same calories of energy. The subjects on the high protein diets were satisfied to the point that they had trouble finishing their meals. Those obtaining the protein from meat increased their daily caloric output by 3.9%. Those consuming soy protein increased thermogenesis by 1.9%

Mikkelsen PB, Toubro S, Astrup A.Effect of fat-reduced diets on 24-h energy expenditure: comparisons between animal protein, vegetable protein, and carbohydrate. Am J Clin Nutr. 2000 Nov;72(5):1135-41

Another trial found that ad libitum protein consumption, in the form of lean meat, increased weight loss in a group of subjects on a low fat diet.

Skov AR, Toubro S, Ronn B, Holm L, Astrup A. Randomized trial on protein vs carbohydrate in ad libitum fat reduced diet for the treatment of obesity. Int J Obes Relat Metab Disord. 1999 May;23(5):528-36.

### Fat is neutral to thermogenesis, and its relationship to satiation is controversial

Fat has more calories per gram than either protein or carbohydrate (9 vs 4) a fact that is cited when promoting low fat diets for weight loss. Many authors state that fat is more satisfying that carbohydrate, because it delays stomach emptying, but research studies do not support a greater satiation.

Institute of Medicine of the National Academies. Dietary References Intakes: Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids. Washington: National Academy Press, 2002

Subjectively, patients state that more fat is more satisfying, and this may be only in relationship to high glycemic carbohydrates, which increase hunger.

Despite population trials that show a correlation between fat consumption and cardiovascular disease, healthy fats in the absence of high glycemic carbohydrates, have no effect on insulin or insulin resistance. Trials in athletes have shown that increasing fat in the diet to 50% has no adverse effect on blood lipids.

High quality olive oil might be taken ad libitum, as up to 35% calories from fat have proven to reduce second heart attacks and lower hypertension.

Yudkin found that ad libitum fat permission did not greatly increase fat consumption in dieting subjects

### Carbohydrates reduce thermogenesis

Mikkelsen PB, Toubro S, Astrup A.Effect of fat-reduced diets on 24-h energy expenditure: comparisons between animal protein, vegetable protein, and carbohydrate. Am J Clin Nutr. 2000 Nov;72(5):1135-41

Raben A, Vasilaras, TH, Moller AC, Astrup, A. Sucrose compared with artificial sweeteners: different effects on ad libitum food intake and body weight after 10 wk of supplementation in overweight subjects. Am J Clin Nutr 2002:76(4);721-729

### High Glycemic carbohydrates increase appetite

Ludwig DS. The glycemic index: physiological mechanisms relating to obesity, diabetes, and cardiovascular disease. JAMA. 2002 May 8;287(18):2414-23. Review.

Nicholson AL, Yudkin J.The nutritional value of low-carbohydrate diet used in the treatment of obesity. Proc Nutr Soc. 1969 Mar;28(1):13A.

Yudkin, J This Slimming Business. London, MacGibbon and Kee, 1958

## Phase I Preparation

**Useful interventions to break the cycle of insulin resistance and prepare for carbohydrate withdrawal are:**

- Chromium nicotinate or glycinate, 200 mcg tid or qid can dramatically reduce sugar cravings in most individuals
- Correcting macronutrient or micronutrient deficiencies that may lead to "false" carbohydrate cravings may also help. Magnesium citrate, 200 mg tid or qid.
- Eating a low-glycemic, high protein breakfast

Compliance with the above is easy, and each intervention helps break the vicious cycle of insulin resistance. Most notably, these three together will dramatically reduce carbohydrate cravings in many people

## Phase II Restriction of added sugars.

Added sugars make up, on average about 15% of caloric intake in the U.S, and up to 25% in some individuals. The National Academy of Sciences has suggested 25% as an upper limit, indicating that perhaps 50% of the population should reduce their intake of added sugars. The NAS ignored previous research on the ill effects of high glycemic carbohydrates on various risk factors for cardiovascular or immune disease, in the absence of a weight of scientific evidence that satisfied them. They focused instead on research demonstrating that nutritional deficiencies increase as added sugars rise about 25% of caloric intake.

Institute of Medicine of the National Academies. Dietary References Intakes: Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids. Washington: National Academy Press, 2002

University of London in the 1950's researchers experimented with low carbohydrate diets. The primary intervention was that subject were instructed to restrict added sugars, and to eat protein and fat according to their appetite. The result was that:

- Carbohydrate consumption fell by 140 grams
- Total caloric intake fell by 800 kcal
- No significant change in the consumption of protein or fat.

Nicholson AL, Yudkin J.The nutritional value of low-carbohydrate diet used in the treatment of obesity. Proc Nutr Soc. 1969 Mar;28(1):13A.

Yudkin, J This Slimming Business. London, MacGibbon and Kee, 1958

Some recent research supports this indirectly. Researchers in Denmark investigated the effects of adding 5.3 ounces of sucrose to the diet of obese patients, and compared this to an artificial sweetener placebo. After ten weeks, the patients receiving the sucrose gained 3.5 lbs compared to a loss of 2.2 lbs in the artificial sweetener group. Systolic and diastolic blood pressure rose by 3.8 and 4.1 mm Hg respectively in the sugar group, and dropped by 3.1 and 1.2 mm Hg in the artificial sweetener group.

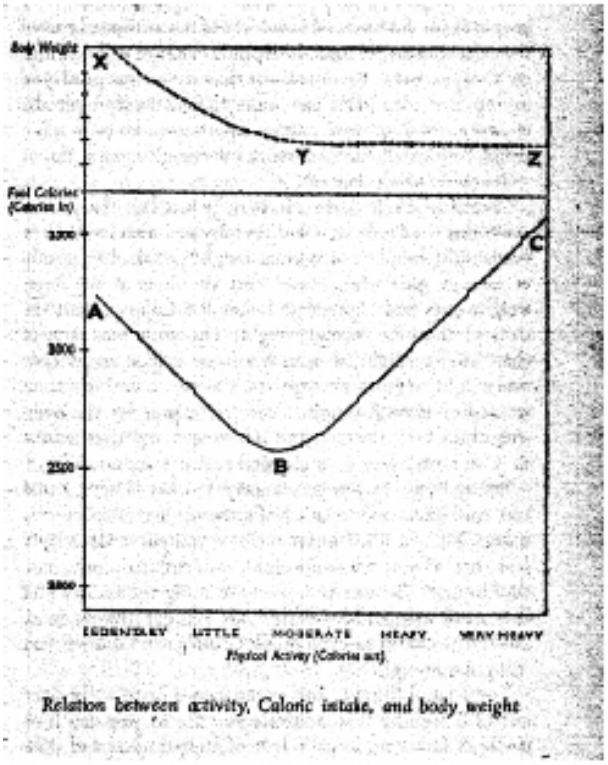
Raben A, Vasilaras, TH, Moller AC, Astrup, A. Sucrose compared with artificial sweeteners: different effects on ad libitum food intake and body weight after 10 wk of supplementation in overweight subjects. Am J Clin Nutr 2002:76(4);721-729

- Compliance may be difficult due to carbohydrate addiction, or due to caloric restriction if sugar intake is high. Thus nutritious foods that also satiate the appetite must be allowed ad libitum. Increasing protein or fiber have been shown separately to improve satiation.
- Patients may be allowed to eat as much protein and fat as they have an appetite for, paying attention to the quality of the fat.

**Introduction of a moderate exercise program may also decrease food cravings.**

30-60 minutes walking per day, in multiple sessions is OK



Relation between activity, Caloric intake, and body weight

This chart shows weight loss (top curve) and caloric consumption (bottom curve) at different levels of exercise intensity (bottom axis). As subjects increased from sedentary to moderate activity, their voluntary caloric intake declined, and they lost weight. Increasing activity beyond moderate resulted in higher caloric intake, and no improvement in weight loss.

Yudkin, J This Slimming Business. London, MacGibbon and Kee, 1958

The client may inadvertantly substitute other high glycemic binge foods, such as dried fruits or bananas, so provision with satisfying snack foods in a must.

## Phase III Non-ketotic restriction of high glycemic starchy foods

- Further restriction of grains and potatoes, with a corresponding increase in protein, fiber, and fat and permissible ad-libitum foods.
- Increase intensity of exercise to include brief growth-hormone promoting bursts of resistance exercise.
- Increase overall consumption of fats as healthy fats.

## Phase IV Ketogenic diet

The Atkins model, latest revision: Atkins R. *Dr Atkins New Diet Revolution* New York: M Evans and Company, 2002. Or South Beach Diet. Similar to Atkins, but with more veggies (eventually) and less saturated fat.

**Key elements:**

- < 20 grams a day carbohydrates until ketosis is established
- Ketosis is maintained for 2 weeks
- Plenty of water (8 glasses) when in ketosis.
- Very low glycemic carbohydrates are reintroduced gradually. Emphasis is on dark leafy greens, berries , and low glycemic fruit.
- Exercise is a key component
- Supplements are a key component
- This phase requires intensive support.

**LC diet and serum lipids**

To determine the effects of carbohydrate restriction (CR) with and without soluble fiber on lipoprotein metabolism, 29 men participated in a 12-wk weight loss intervention. Subjects were matched by age and BMI and randomly assigned to consume 3 g/d of either a soluble fiber supplement (n=14) or placebo (n=15) with a macronutrient energy distribution of approximately 10% carbohydrate, approximately 65% fat, and approximately 25% protein. Because the groups did not differ in any of the variables measured, all data were pooled and comparisons were made between baseline and 12 wk. After 12 wk, subjects had a mean weight loss of 7.5 kg ($P<0.001$), and abdominal fat was reduced by 20% ($P<0.001$). PlasmaLDL cholesterol and triglycerides (TG) were significantly reduced by 8.9 and 38.6%, respectively. Similarly, apolipoproteins C-I (-13.8%), C-III (-21.2%) and E (-12.5%) were significantly lower after the intervention. In contrast plasmaHDL-cholesterol concentrations were increased by 12% ($P<0.05$). Changes in

plasma TG were positively correlated with reductions in large (r=0.615, P<0.01) and medium VLDL particles (r=0.432, P<0.05) and negatively correlated with LDLdiameter (r=-0.489, P<0.01). Changes in trunk fat were positively correlated with medium VLDL (r=0.474, P<0.0) and small LDL (r=0.405, P<0.05) and negatively correlated with large HDL (r=-0.556, P<0.01). We conclude that weight loss induced by CR favorably alters the secretion and processing of plasma lipoproteins, rendering VLDL, LDL, and HDL particles associated with decreased risk for atherosclerosis and coronary heart disease.

Wood RJ, Volek JS, Liu Y, Shachter NS, Contois JH, Fernandez ML.Carbohydrate restriction alters lipoprotein metabolism by modifying VLDL, LDL,and HDL subfraction distribution and size in overweight men. J Nutr. 2006 Feb;136(2):384-9.

**LC diet in type II diabetes**

We recently reported that in subjects with untreated type 2 diabetes mellitus, a5-week diet of 20:30:50 carbohydrate-protein-fat ratio resulted in a dramatic decrease in 24-hour integrated glucose and total glycohemoglobin compared with a control diet of 55:15:30. Body weight, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and serum ketones were unchanged; insulin and nonesterified fatty acids were decreased. We now present data on other hormones and metabolites considered to be affected by dietary macronutrient changes. The test diet resulted in an elevated fastingplasma total insulin-like growth factor 1, but not growth hormone. Urinary aldosterone was unchanged; free cortisol was increased, although not statistically. Urinary pH and calcium were unchanged. Blood pressure, creatinine clearance, serum vitamin B12, folate, homocysteine, thyroid hormones, and uric acid were unchanged. Serum creatinine was modestly increased. Plasma alpha-amino nitrogen and urea nitrogen were increased. Urea production rate was increased such that a new steady state was present. The calculated urea production rate accounted for 87% of protein ingested on the control diet, but only 67% on the test diet, suggesting net nitrogen retention on the latter. The lack of negative effects, improved glucose control, and a positive nitrogen balance suggest beneficial effects for subjects with type 2 diabetes mellitus at risk for loss of lean body mass.

Nuttall FQ, Gannon MC. The metabolic response to a high-protein, low-carbohydrate diet in men with type 2 diabetes mellitus.Metabolism. 2006 Feb;55(2):243-51.

**LC diet, ECG, and insulin resistance**

OBJECTIVE: To assess whether shortening of the corrected QT (QTc) interval is most closely associated with changes in weight, insulin resistance, or free fatty acids (FFAs) (or some combination of these factors). METHODS: We randomized 75 severely obese subjects without diabetes to either a low-carbohydrate or a conventional low-fat weight-loss diet for 6 months. We measured QTc, insulin sensitivity, body mass index, and FFAs at baseline and at 6 months. Analysis was performed to determine whether improvement in weight, in insulin resistance, or in FFAs has the greatest effect on reducing the QTc interval. RESULTS: "Completers" of both the low-carbohydrate diet (N = 25) and the low-fat diet (N = 22) had a decrease in weight, but the weight loss was greater in the low-carbohydrate group. A statistically significant decrease in QTc from baseline was observed only in the low-carbohydrate group. QTc in the low-carbohydrate group correlated with improvement in insulin resistance, but this finding was

not significant after correction for the greater weight loss. FFAs or weight loss was not correlated with QTc in either dietary group. CONCLUSION: Low-carbohydrate dieting is associated with a greater decrease in the QTc interval in comparison with low-fat dieting. Improvements in insulin resistance seem to have a relatively weak mechanistic role, and a decrease in FFAs has no apparent role in the reduction of the QTc interval.

Seshadri P, Samaha FF, Stern L, Chicano KL, Daily DA, Iqbal N.Free fatty acids, insulin resistance, and corrected qt intervals in morbid obesity: effect of weight loss during 6 months with differing dietary interventions. Endocr Pract. 2005 Jul-Aug;11(4):234-9.

**High fat, High protein, and High carb diets**

AIMS/HYPOTHESIS: A diet low in saturated fatty acids and rich in wholegrains, vegetables and fruit is recommended in order to reduce the risk of obesity, cardiovascular disease and type 2 diabetes mellitus. However there is widespread interest in high-fat ("Atkins Diet") and high-protein ("Zone Diet") alternatives to the conventional high-carbohydrate, high-fibre approach. We report on a randomised trial that compared these two alternative approaches with a conventional diet in overweight insulin-resistant women. METHODS: Ninety-six normoglycaemic, insulin-resistant women (BMI >27 kg/m(2)) were randomised to one of three dietary interventions: a high-carbohydrate, high-fibre (HC) diet, the high-fat (HF) Atkins Diet, or the high-protein (HP) Zone Diet. The experimental approach was designed to mimic what might be achieved in clinical practice: the recommendations involved advice concerning food choices and were not prescriptive in terms of total energy. There were supervised weight loss and weight maintenance phases (8 weeks each), but there was no contact between the research team and the participants during the final 8 weeks of the study. Outcome was assessed in terms of body composition and indicators of cardiovascular and diabetes risk. RESULTS: Body weight, waist circumference,triglycerides and insulin levels decreased with all three diets but, apart from insulin, the reductions were significantly greater in the HF and HP groups than in the HC group. These observations suggest that the popular diets reduced insulin resistance to a greater extent than the standard dietary advice did. When compared with the HC diet, the HF and HP diets were shown to produce significantly ($p<0.01$) greater reductions in several parameters, includingweight loss (HF -2.8 kg, HP -2.7 kg), waist circumference (HF -3.5 cm, HP -2.7 cm) and triglycerides (HF -0.30 mmol/l, HP [corrected] -0.22 mmol/l). LDL cholesterol decreased in individuals on the HC and HP diets, but tended to fluctuate in those on the HF diet to the extent that overall levels were significantly lower in the HP group than in the HF group (-0.28 mmol/l, 95% CI 0.04-0.52, $p=0.02$). Of those on the HF diet, 25% showed a >10% increase in LDL cholesterol, whereas this occurred in only 13% of subjects on the HC diet and 3% of those on the HP diet. CONCLUSIONS/INTERPRETATION: In routine practice a reduced-carbohydrate, higher protein diet may be the most appropriate overall approach to reducing the risk of cardiovascular disease and type 2 diabetes. To achieve similar benefits on a HC diet, it may be necessary to increase fibre-rich wholegrains, legumes, vegetables and fruits, and to reduce saturated fatty acids to a greater extent than appears to be achieved by implementing current guidelines. The HF approach appears successful for weight loss in the short term, but lipid levels should be monitored. The potential deleterious effects of the diet in the long term remain a concern.

McAuley KA, Hopkins CM, Smith KJ, McLay RT, Williams SM, Taylor RW, Mann JI.Comparison of high-fat and high-protein diets with a high-carbohydrate diet ininsulin-resistant obese women. Diabetologia. 2005 Jan;48(1):8-16. Epub 2004 Dec 23.

## Atkins diet and seizures

The ketogenic diet is effective for treating seizures in children with epilepsy. The Atkins diet can also induce a ketotic state, but has fewer protein andcaloric restrictions, and has been used safely by millions of people worldwide for weight reduction. Six patients, aged 7 to 52 years, were started on the Atkins diet for the treatment of intractable focal and multifocal epilepsy. Five patients maintained moderate to large ketosis for periods of 6 weeks to 24 months; three patients had seizure reduction and were able to reduce antiepileptic medications. This provides preliminary evidence that the Atkins diet may have a role as therapy for patients with medically resistant epilepsy.

Kossoff EH, Krauss GL, McGrogan JR, Freeman JM. Efficacy of the Atkins diet as therapy for intractable epilepsy. Neurology. 2003 Dec 23;61(12):1789-91.

## Depression during the withdrawal period

Currently, the carbohydrate-restricted diet is very popular. Atkins' book, Dr.Atkins' Diet Revolution, has sold millions in its more than 25 years of existence. His book promotes the carbohydrate-restricted diet, which focuses on the consumption of proteins and fats as primary calorie and energy sources, while severely restricting carbohydrates. However, when carbohydrates are restricted from the diet, the body's primary energy source is reduced considerably. Therefore, the purpose of this study was to compare the psychological responses to exercise of individuals when on a carbohydrate restrictive diet and when on a noncarbohydrate restrictive diet. For this study, 17 participants practiced a noncarbohydrate-restricted diet for three weeks and the carbohydrate-restricted diet for three weeks, while maintaining previous exercise habits. After each exercise session, the participants completed the Physical Activity Affect Scale, which measures Positive Affect, Negative Affect, Tranquility, and Fatigue. Simple one-way analyses of variance indicated significant treatment differences (ps<.05) relative to Negative Affect, Positive Affect, and Fatigue. The results of the study indicate as pred icted, that, when a person restricts carbohydrates from the diet, he will experience more fatigue, more negative affect, and less positive affect in response to exercise than those individuals who are not restricting carbohydrates.

Butki BD, Baumstark J, Driver S. Effects of a carbohydrate-restricted diet on affective responses to acute exercise among physically active participants.Percept Mot Skills. 2003 Apr;96(2):607-15.

## LC diet and CVD risk factors (6 and 12 months)

BACKGROUND: Despite the popularity of the low-carbohydrate, high-protein, high-fat (Atkins) diet, no randomized, controlled trials have evaluated its efficacy. METHODS: We conducted a one-year, multicenter, controlled trial involving 63 obese men and women who were randomly assigned to either a low-carbohydrate, high-protein, high-fat diet or a low-calorie, high-carbohydrate, low-fat (conventional) diet. Professional contact was minimal to replicate the

approach used by most dieters. RESULTS: Subjects on the low-carbohydrate diet had lost more weight than subjects on the conventional diet at 3 months (mean [+/-SD], -6.8+/-5.0 vs. -2.7+/-3.7 percent of body weight; P=0.001) and 6 months (-7.0+/-6.5 vs. -3.2+/-5.6 percent of body weight, P=0.02), but the difference at 12 months was not significant (-4.4+/-6.7 vs. -2.5+/-6.3 percent of body weight, P=0.26). After three months, no significant differences were found between the groups in total or low-density lipoprotein cholesterol concentrations. The increase in high-density lipoprotein cholesterol concentrations and the decrease in triglyceride concentrations were greater among subjects on the low-carbohydrate diet than among those on the conventional diet throughout most of the study. Both diets significantly decreased diastolic blood pressure and the insulin response to an oral glucose load. CONCLUSIONS: The low-carbohydrate diet produced a greater weight loss (absolute difference, approximately 4 percent) than did the conventional diet for the first six months, but the differences were not significant at one year. The low-carbohydrate diet was associated with a greater improvement in some risk factors for coronary heart disease. Adherence was poor and attrition was high in both groups. Longer and larger studies are required to determine the long-term safety and efficacy of low-carbohydrate, high-protein, high-fat diets.

Foster GD, Wyatt HR, Hill JO, McGuckin BG, Brill C, Mohammed BS, Szapary PO, Rader DJ, Edman JS, Klein S. A randomized trial of a low-carbohydrate diet for obesity. N Engl J Med. 2003 May 22;348(21):2082-90.

**LC diet effects on weight and cardiovascular risk factors (6 months)**

BACKGROUND: The effects of a carbohydrate-restricted diet on weight loss and risk factors for atherosclerosis have been incompletely assessed. METHODS: We randomly assigned 132 severely obese subjects (including 77 blacks and 23 women) with a mean body-mass index of 43 and a high prevalence of diabetes (39 percent) or the metabolic syndrome (43 percent) to a carbohydrate-restricted (low-carbohydrate) diet or a calorie- and fat-restricted (low-fat) diet. RESULTS: Seventy-nine subjects completed the six-month study. An analysis including all subjects, with the last observation carried forward for those who dropped out, showed that subjects on the low-carbohydrate diet lost more weight than those on the low-fat diet (mean [+/-SD], -5.8+/-8.6 kg vs. -1.9+/-4.2 kg; P=0.002) and had greater decreases in triglyceride levels (mean, -20+/-43percent vs. -4+/-31 percent; P=0.001), irrespective of the use or nonuse of hypoglycemic or lipid-lowering medications. Insulin sensitivity, measured only in subjects without diabetes, also improved more among subjects on the low-carbohydrate diet (6+/-9 percent vs. -3+/-8 percent, P=0.01). The amount of weight lost (P<0.001) and assignment to the low-carbohydrate diet (P=0.01) wereindependent predictors of improvement in triglyceride levels and insulin sensitivity. CONCLUSIONS: Severely obese subjects with a high prevalence of diabetes or the metabolic syndrome lost more weight during six months on a carbohydrate-restricted diet than on a calorie- and fat-restricted diet, with a relative improvement in insulin sensitivity and triglyceride levels, even after adjustment for the amount of weight lost. This finding should be interpreted with caution, given the small magnitude of overall and between-group differences in weight loss in these markedly obese subjects and the short duration of the study. Future studies evaluating long-term cardiovascular outcomes are needed before a carbohydrate-restricted diet can be endorsed.

Samaha FF, Iqbal N, Seshadri P, Chicano KL, Daily DA, McGrory J, Williams T, Williams M, Gracely EJ, Stern L.A low-carbohydrate as compared with a low-fat diet in severe obesity. N Engl J Med. 2003 Sep 4;349(10):1000-2; author reply 1000-2.

### LC diet and hormonal effects

The few studies that have examined body composition after a carbohydrate-restricted diet have reported enhanced fat loss and preservation of lean body mass in obese individuals. The role of hormones in mediating this response is unclear. We examined the effects of a 6-week carbohydrate-restricted diet on total and regional body composition and the relationships with fasting hormone concentrations. Twelve healthy normal-weight men switched from their habitual diet (48% carbohydrate) to a carbohydrate-restricted diet (8% carbohydrate) for 6 weeks and 8 men served as controls, consuming their normal diet. Subjects were encouraged to consume adequate dietary energy to maintain body mass during the intervention. Total and regional body composition and fasting blood samples were assessed at weeks 0, 3, and 6 of the experimental period. Fat mass was significantly (P <or=.05) decreased (-3.4 kg) and lean body mass significantly increased (+1.1 kg) at week 6. There was a significant decrease in serum insulin (-34%), and an increase in total thyroxine (T(4)) (+11%) and the free T(4) index (+13%). Approximately 70% of the variability in fat loss on the carbohydrate-restricted diet was accounted for by the decrease in serum insulin concentrations. There were no significant changes in glucagon, total or free testosterone, sex hormone binding globulin (SHBG), insulin-like growth factor-I (IGF-I), cortisol, or triiodothyronine (T(3)) uptake, nor were there significant changes in body composition or hormones in the control group. Thus, we conclude that a carbohydrate-restricted diet resulted in a significant reduction in fat mass and a concomitant increase in lean body mass in normal-weight men, which may be partially mediated by the reduction in circulating insulin concentrations.

Volek JS, Sharman MJ, Love DM, Avery NG, Gomez AL, Scheett TP, Kraemer WJ.Body composition and hormonal responses to a carbohydrate-restricted diet. Metabolism. 2002 Jul;51(7):864-70.

## Growth-Hormone Maximizing exercise routine

- 2-3 minute (or more) burst-type exercise in am on rising
- No-carb or lo-carb breakfast
- (30 minutes of walking during day)
- Add sprints to normal jogging, swimming, cycling routines
- 2 minute burst-type exercise at 2 hours after evening meal
- Reliably lowers lingering post-prandial blood glucose levels by 20-40 points
- No food after exercise and before bed.

- Normal 2-3 hour GH surge during first hours of slow wave sleep.

## Diet and Supplements

**“The Oil Change’**

- Omit all refined oils, especially that hidden in processed foods
- High quality olive oil ad libitum
- Moderate butter and ghee
- 1-3 Tsp emulsified cod liver oil, or sardines
- Good quality nuts and seeds ad libitum
- Sesame tahini ad lib.
- 60% of calories for 6-12 weeks

**Supplements**

- Multiple vitamin with vitamin B
- Magnesium 600-800 citrate, or ionic magnesium
- Zinc 20-40 mg
- Manganese 2-5 mg
- Chromium nicotinate, glycinate 400-1000 mcg
- Carnitine 500-2000 mg
- Full complement of trace elements, food-based in seaweed.

**Full complement of antioxidants:**

- Vitamin E 100 iu bid
- Vitamin C 500 mg bid
- C oenzyme Q-10 60 mg bid
- Alpha-lipoic acid 200 mg bid
- Selenium 100 mcg bid

## Results

Results of the above treatments (without the added effects of herbs) are usually evident within one week.

- rapid loss of water weight
- rapid reduction of hypertension
- sustained weight loss of ½ - 1 lb per week
- reduced food cravings and appetite
- improved mental clarity
- improved energy level, steadier throughout the day.
- better tolerance of stress.
- radically improved glycemic control in diabetics. (One patient brought 2-hour post-meal blood glucose levels from 225+ down to the 90s within 8 days. A type I diabetic brought insulin requirements from 25+ to below 5 in 3 weeks.)
- No long term clinical trials have been done, but, presumably, reduced risk for the chronic diseases of civilization.

# Syndrome X Case

| Age | Wt | Waist | Hip | W/H | TG | HDL | TG/HDL | TC | TC/HDL | LDL | Note |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 40 | 156 | 33 | 36 | 0.91 | n | n | n | n | n | n | athlete |
| 43 | 198 | 40 | 40 | 1 | n | n | n | 208 | n | n | Wt gain |
| 45 | 218 | 44 | 43 | 1.02 | 225 | 33 | 6.8 | 240 | 7.2 | 162 | Initiate Ornish Diet |
| 45 | 212 | 43 | 42 | 1.02 | 440 | 29 | 15.1 | 202 | 6.9 | 85 | Quit diet |
| 48 | 230 | 45 | 44 | 1.02 | 325 | 31 | 10.5 | 245 | 7.9 | 153 | Stress; Hypercortisolemia; Athletic still Bone spurs. |
| 49 | 228 | 45 | 44 | 1.02 | 255 | 37 | 6.9 | 242 | 6.5 | 154 | Regular exercise FBG = 104 |
| 50 | 242 | 47 | 44 | 1.04 | | | | | | | 140/90 avg 170/115 high Intermittnet DM |
| 50.5 | 232 | 45 | 44 | 1.01 | 315 | 31 | 10.1 | 210 | 6.8 | 116 | |
| 51 | 228 | 46 | 44 | 1.02 | 341 | 30 | 11.3 | 225 | 7.5 | 140 | Cognitive Difficulties; Lower carbs More protein |
| 51.5 | Initiate aggressive program of supplementation, very low carb, and resistance exercise | | | | | | | | | | |
| 52 | 204 | 42 | 43 | 0.97 | 120 | 34 | 3.5 | 230 | 6.7 | 172 | CAD on Ultrafast CT; Hypoglycemia on OGTT |
| 52.5 | 198 | 40 | 42 | 0.95 | 140 | 43 | 3.3 | 218 | 5.1 | 147 | bone spurs gone |
| 52.7 | 195 | 39.5 | 42 | 0.94 | 91 | 39 | 2.3 | 219 | 5.6 | 162 | MI; / stent |
| 54 | 210 | 42 | 43 | .98 | 147 | 36 | 4.0 | 245 | 6.8 | 165 | Reinitiated diet, Exercise, with ad lib fruit |
| 55 | 187 | 38 | 40 | .95 | 119 | 35 | 3.4 | 218 | 6.2 | 148 | GH maximizing exercise |
| 57 | 202 | 40 | 42 | .95 | 102 | 45 | 2.27 | 232 | 5.2 | 152 | continue routine |

# Ketosis

"Ketones" = ketone bodies = acetacetate, beta-hydroxybutyrate, and acetone.

- ketogenesis = production of ketones by the liver
- ketonemia = buildup of ketones in the blood
- ketonurea = the appearance of ketones in the urine
- ketoacidosis = extremely elevated ketone bodies due to insulin lack, in IDDM

Under the influence of glucagon:

In liver: Fatty acids –> Acetyl-CoA –> ketone bodies (Poor fuel for liver, so most goes to blood

In blood: Some ketones to urine, some excreted in lungs as acetone

In extrahepatic tissues: ketone bodies –> Acetyl CoA –> Citric Acid cycle –> energy

(insulin dependent)

- Ketones are a fuel – not a waste product.
- The are a preferred fuel by the brain.
- May be used by parts of the brain and by muscle.
- Humans may remain in ketosis indefinitely without documented adverse effects provided protein, essential fatty acid, and micronutrient requirements are met, and the pancreas secretes adequate baseline insulin levels.
- Ketones stimulate insulin secretion from the pancreas, and insulin is necessary for their utilization as fuel.
- In ketoacidosis, insulin is deficient or completely lacking, and is not available to turn off the release of free fatty acids from the cells or to permit use of ketones as fuel. As fatty acid levels rise unchecked, so does ketosis, and eventually the acidic ketones cause death by pathologically acidifying the blood.

**Ketosis of starvation**

First stage – glycogen depletion

Second stage – liver utilization of fatty acids increases

Third stage – liver reduces the rate of fatty acid burning and shifts metabolism preferentially toward ketone formation. As fatty acid utilization doubles, ketone body formation increases fivefold

Fourth stage – brain and muscle shift metabolism to reduce glucose utilization and increase ketone utilization as fuel.

**Arterial concentration of fuels during progressive fasting**

| | 15 hours | 60 hours | 120 hours |
|---|---|---|---|
| **Glucose*** | 478.4 | 345.7 | 326.8 |
| **Acetoacetate*** | 9.1 | 57.9 | 64.6 |

* micromoles/100 ml

Dietze, G., Wicklmayr M., Mehnert, H. On the key role of ketogenesis for the regulation of glucose homeostasis during fasting: intrahepatic control, ketone levels, and peripehral pyruvate utilization. In: SÖling H and Suefert C Biochemical and clinical aspects of ketone body metabolism. StuttgartL Thieme, 1978

**Ketosis of exercise**

Untrained individuals can develop marked ketosis following 1-2 hours of intense exercise. The state resembles the ketosis of starvation. It is non-pathological

The ketosis is relatively lower in trained individuals through two probably mechanisms – less prouduction by the liver and greater utilization by the muscles.

Trained individuals' muscles become adapted to burning fatty acids. The result is prolonged time before muscles and liver glycogen is depleted. In some cases, liver glycogen content remains unchanged or 30 minutes or more.

| **Untrained** | **Trained** |
|---|---|
| Depletion of liver glycogen | Depletion is delayed |
| Elevated free fatty acids | muscle can use the fatty acids in preference to glycogen |
| decrease in plasma insulin | less of a decrease |
| increase in plasma glucagon | less of an increase |
| muscle poorly adapted to ketone fuel | muscle better adapted to ketones as fuel |
| => higher blood ketones | => less high blood ketones |

Holloszy J.O., Winder, W.W., Fitts, R.H., Rennie, M.J. Postexercise ketosis: protective effect of training. In: SÖling H and Suefert C Biochemical and clinical aspects of ketone body metabolism. StuttgartL Thieme, 1978

**Ketosis of low carbohydrate diet**

Most studies of ketogenic diets have lasted for 14 days or less, and have been characterized by umpleasant symptoms: lethargy, nausea, and depression. Longer trials show a period of adaptation lasting from 2-3 weeks, with some indication that physiological adaptation may continue for at least six weeks.

Phinney, S.D., Horton, E.S., Sims, E.A.H., et al. Capacity for moderate exercise in obese subjects after adaptation to a hypocaloric ketogenic diet. J Clin Invest 1980; 66:1152-1161

Nine lean males were fed a control diet for a week, and then a diet with identical calories and protein, but less than 20grams of carbohydrate per day. There was an initial loss of nitrogen balance (due to gluconeogenesis) which was regained after one week. At the end of four weeks, the fasting blood glucose fell by 7% without evidence of hypoglycemia. Whole body glucose utilization fell by 30%. Insulin levels fell by 10%. T-3 fell by 40%. Total Cholesterol rose from 159 to 208 mg/dl. Hdl cholesterol was unchanged. Triglycerides fell from 107 to 79 mg/dl. Kidney and liver function remained normal. All subjects remained on the diet and remained in ketosis for the full 28 days. Subjective symptoms includes

- Mild lethargy in most participants for 7-10 days
- Early transient inability to maintain training schedules in 3 athletes
- Decreased stool volume and frequency
- Mild constipation in 3 subjects
- No nausea, diarrhea, or flatulence

Phinney S.D., Bistrian, B.R., Wolfe, R.R., Blackburn, G.L. The human metabolic response to chronic ketosis without caloric restriction: physical and biochemical adaptation. Metabolism 1983: 32(8)

A longer trial of 668 morbidly obese outpatients on a ketogenic high protein diet ran for an average of 31 weeks, with 17 of those on the ketogenic diet. Average weight loss was 40 kg Physiological parameters changed:

| | **Entry average** | **Final average** |
|---|---|---|
| Systolic BP | 135 | 124 |
| Diastolic BP | 87 | 79 |
| Blood sugar | 97 | 82 |
| Triglycerides | 133 | 95 |
| Cholesterol | 225 | 232 |
| Uric acid | 5.9 | 6.3 |

The only side effects were mild adaptation symptoms during the first weeks of the diet, and a transient hair loss in a small number of the patients.

**Prolonged ketosis and exercise performance**

A group of elite cyclists athletes were kept on a ketogenic diet without caloric restriction for four weeks. After a period of adaptation, there was no degradation of performance over the 28 days.

The performance was accomplished despite a 3-4 fold reduction in the use of glucose or glycogen as fuel, with fatty acids becoming the predominant muscle fuel.

Phinney SD, Bistrian BR, Evans WJ, Gervino E, Blackburn GL. The human metabolic response to chronic ketosis without caloric restriction: preservation of submaximal exercise capability with reduced carbohydrate oxidation. Metabolism. 1983 Aug;32(8):769-76.

### Side effects

Side effects are benign – no serious effects have been recorded in ketogenic protein sparing diets. Most of the effects appear during the initial period of adaptation to the diet. One trial measured a decline in cognitive performance on a caloric restricted ketogenic diet compared to a non-ketogenic control. The decline occured during the first week of the trial.

Wing RR, Vazquez JA, Ryan CM. Cognitive effects of ketogenic weight-reducing diets. Int J Obes Relat Metab Disord 1995 Nov;19(11):811-6

### Ketogenic diet for seizures

Ketogenic diets have been used continuously for more than 70 years to control intractable seizures not responsive to drug therapy. The classic ketogenic diet for seizures is described as the “4:1" diet (four parts fat: one part carbohydrate: one part protein) and more recently a diet composed of 60% medium chain triglycerides has been used. Caloric intake varies from study to study, and there is no consistent policy on supplementation of vitamins or minerals. In most trials, patients continue with anti-seizure medication.

### Control of seizures

All published trials of ketogenic diets show some efficacy at reducing seizures, and in some cases eliminating them. Different seizure types appear to respond equally. Some sample trials:

A study of 13 epileptic patients between the ages of 1 and 19 years old for an average of 22 months resulted in improvement in 100% of the children according the EEG measurements, greater than a 50% reduction in crises om 85% of the children, and complete control in 30.8 % of the children. Side effects were minimal.

Panico LR, Demartini MG, Rios VG, Carniello MA. The ketogenic diet in infantile refractory epilepsy: electroclinical response, complications and secondary effects. Rev Neurol 2000 Aug 1-15;31(3):212-20

Another trial of 48 patients resulted in more than half of the patients experiencing a 90% reduction in seizures within 45 days.

Katyal NG, Koehler AN, McGhee B, Foley CM, Crumrine PK. The ketogenic diet in refractory epilepsy: the experience of Children’s Hospital of Pittsburgh. Clin Pediatr (Phila) 2000 Mar;39(3):153-9

Similar results were found in another trial

Acta Paediatr Taiwan 1999 Mar-Apr;40(2):97-100 Clinical experience of ketogenic diet on children with refractory epilepsy. Mak SC, Chi CS, Wan CJ.

## Mechanisms

"The mechanism of action of the ketogenic diet appears to rely on a fundamental change in the brain's metabolism from that of a glucose-based energy substrate to a ketone-based substrate. . . . The change in seizure threshold appears to occur without affecting the brain's ability to carry out its normal complex functions. . . . The ketogenic diet is successful in controlling or ameliorating a broad spectrum of seizure types and etiologies. Perhaps then, common metabolic pathways, independent of seizure type, are used in the initiation and spread of electrical seizures.

Swink TD, Vining EP, Freeman JM. The ketogenic diet: 1997. Adv Pediatr 1997;44:297-329

## Glutamate/aspartate

The metabolism of glutamate and aspartate, excitatory amino acids in the brain, may be involved with the mechanism. Researchers note that a reduction in the rate of glutamate transformation to aspartate occurs on a ketogenic diet. Conversion of glutamate to excitatory GABA is increased. The uptake of non-excitatory amino acids into the brain is increased, resulting in "dumping" of glutamate from the brain.

Yudkoff M, Daikhin Y, Nissim I, Lazarow A, Nissim I. Ketogenic diet, amino acid metabolism, and seizure control. J Neurosci Res 2001 Dec 1;66(5):931-40

Yudkoff M, Daikhin Y, Nissim I, Lazarow A, Nissim I. Brain amino acid metabolism and ketosis. J Neurosci Res 2001 Oct 15;66(2):272-81

Yudkoff M, Daikhin Y, Nissim I, Grunstein R, Nissim I. Effects of ketone bodies on astrocyte amino acid metabolism. J Neurochem 1997 Aug;69(2):682-92

## Implications for carbohydrate addiction

The mechanism by which ketosis lowers brain excitability may describe critical features of carbohydrate addiction and withdrawal. The addiction may be to the more excitable brain state under the exclusive use of glucose as fuel, secondary to a high carbohydrate diet, a recent historical innovation. Habituation to the exclusive glucose fuel state may result in decline of substrates in the brain and muscle to utilize ketosis, a condition which may be exacerbated by high glycemic load, fasting or post prandial glucose and/or insulin habitually elevated at levels exceeding hunter-gatherer norms. The unpleasant period of adaptation when ketosis is reintroduced is effectively a withdrawal period from carbohydrate addiction, and an obstacle to be dealt with clinically when attempting to alter diets in carbohydrate-addicted patients.

The symptom of appetite loss common to patients on ketogenic diets may also be viewed in reverse. If the ability to easily utilize either glucose of ketones for fuel is lost through habituation to a high carbohydrate diet, then abnormally increased appetite is a symptom of carbohydrate adaptation, and may contribute to obesity and related conditions caused by high caloric diets.

# Do ketones necessarily cause acidosis?

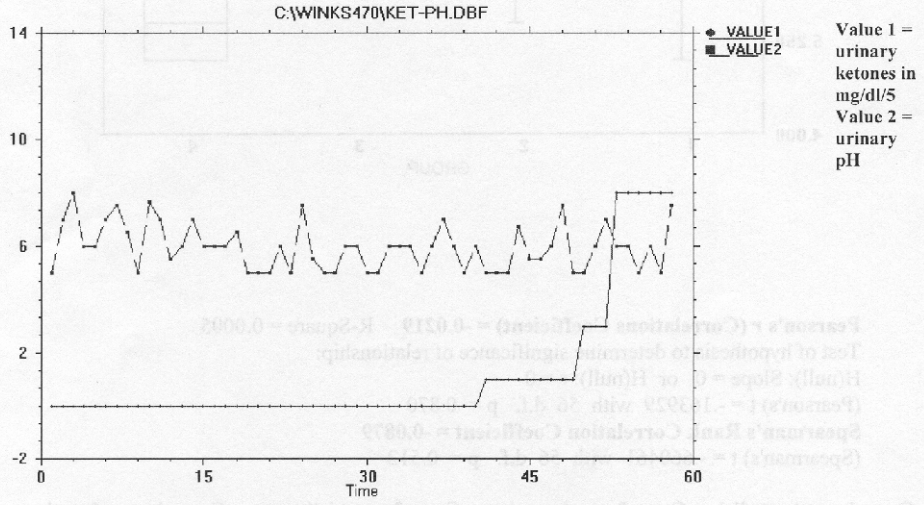
**7. Does normal ketosis acidify the system beyond the normal buffering capacity?**

52 year-old male with insulin resistance but no diabetes on an intermittnet ketogenic diet took urinary and ketone readings with Beyer Multistix 10 SG for a period of 3 weeks. The journal showed whether each reading was A) within 3 hours after a meal B) within 2 hours after moderate exercise or C) none of the above.

**Summary of readings for urinary pH at urinary ketones readings between 0 and 40 mg/dl**

WINKS 4.70 BASIC Edition April 15,2004

| | |
|---|---|
| N = 58 | Missing or Deleted = 0 |
| Mean = 5.93793 | St. Dev (n-1) = 0.86411 |
| Median = 6.00 | St. Dev (n) = 0.85663 |
| Minimum = 5.00 | S.E.M. = 0.11346 |
| Maximum = 8.00 | Variance = 0.74669 |
| Sum = 344.40 | Coef. Var. = 0.14552 |




**Value 1 = urinary ketones in mg/dl/5**
**Value 2 = urinary pH**

The coefficient variable shows a near perfect non-correlation between extent of ketosis and urinary pH.

# Diabetes Mellitus

**DM = insulin deficiency absolute or relative to tissue resistance,, with disturbed carbohydrate, fat, and protein metabolism.**

**Type I = IDDM - Insulin dependent** formerly called juveline onset. Beta cells in pancreas produce either no or else insufficient insulin to prevent hyperglycemia. May be autoimmune or idiopathic.

- Some viral
- In some cases is autoimmunity to milk protein or to bovine insulin

**Type II - NIDDM - Non Insulin Dependent.** Secondary to insulin resistance. Usually a condition of hyperinsulinemia, but the elevated insulin is insufficient to overcome the exaggerated insulin resistance.

In later stages can progress to insulin insufficiency as pancreas "burns out."

May be subdivied into Nonobese NIDDM and Obese NIDDM (90% of NIDDM), useful clinically because nonobese NIDDM is unlikely to develop ketoacidosis. Abdominal obesity is the key measurement = abdomen great that the waist in a male, or abdomen greater than 80% of waist in a female. Bernstein theorizes that non-obese NIDDM may be a low grade IDDM, where the patient can still produce some insuline, but not enough.

**Other**

May be due to pancreatic diseases, hormonal irregularities, genetic defects, drug side effects.

**Gestational**

Occurs during pregnancy. Should be considered as prediabetic. Increased risk of NIDDM within 5 years. See chart of progression below.

**Diagnostic Tests**

**Fasting Blood glucose.**

- Most people rigidly control somewhere between 80 and 90mg/dl, with most near 85.
- Official normal is 75-100.
- 100-126 is **prediabetes**
- **DM** now officially starts at 126. The figure was 145 as recently at 15 years ago, so some older physicians may not appreciate the significance of prediabetes.
- Diabetic complications may occur as 120, per Bernstein.

**Hemoglobin A1-C (Glycosylated hemoglobin)**

Measures long term blood sugar control.

- Measures amount of hemoglobin that is bound to serum glucose proteins. This normal function is exaggerated in habitual hyperglycemia.
- Upper quartile of normal range (4-6 units) is associated with Syndrome X pathologies.

**Oral Glucose tolerance test (GTT or OGTT)**

- Should measure both glucose and insulin after rapid administration of 100 g of glucose to a fasting patient.
- Glucose normals are <195 mg/dl at one hour, <160 at 90 minutes, and <140 at two hours. The high normal here may be too high, per Bernstein
- Many individuals begin dumping glucose into the urine at about 180 mg/dl.

**Cortisone GTT** = blood sugar (and insulin) curves following administration of cortisone plus glucose.

- This test may be the best early indicator of NIDDM
- Cortisone induces insulin resistance

| | **Early Insulin resistance** | **Prediabetes** | **NIDDM** |
|---|---|---|---|
| Fasting glucose | normal | usually normal | high |
| Fasting insulin | high | high | high |
| GTT glucose | normal | may be normal, but abnormal during pregnancy, stress | abnormal |
| GTT insulin | high | high | high |
| Cortisone GTT glucose | normal | abnormal | abnormal |

Note: Only about 40% of Syndrome X patients progress to an abnormal GTT. About 10% of the U.S. population reaches NIDDM., with only half of these diagnosed.

The patient progresses from prediabetes to diabetes gradually with intermittnet loss of control periods of stress

- specific dietary indescretions
- fasting levels may be normal when taken at doctor's office, but abnormal at other times.
- first loss of control shows with 1 hour post meal readings > 195, with fasting levels either normal or prediabetic

- loss of control of fasting levels is final stage

**Implications:** Individuals with insulin resistance, and especially with pre-diabetes, should monitor their glucose readings, fasting, post-meal, and at times of stress. It is also useful for the prediabetic to do their own "glycemic index" informally by observing the effects of certain foods, snacks, or meals on their blood sugar. This will catch, the "silent" slide of prediabetes to diabetes, and is an indispensable aid to patient motivation and inspiration to control their diet.

**See Insulin Index Article on Data Disk**

**Complications of diabetes**

Most important: The older theory of diabetic damage is entirely related to the adverse effects of hyperglycemia. With current understanding, hyperglycemia is only part of the picture, with insulin, IFG-1, GH deficiency, cortisol excess, systemic inflammation, etchaving as great a role. The bottom line: simple control of hyperglycemia is essential, but is insufficient. Hyperinsulinemia and its dysregulatory consequences must also be corrected to prevent damage.

**Theories of pathology** (none definitively proven)

**Overloading of the polyol (sorbitol) pathway**

This biochemical pathway is present in some cells (the lens of the eye for one).

- Glucose from the blood is transformed first into sorbitol and then into fructose.
- The firrst conversion is easy, but the second is more difficult.
- With abnormally high blood glucose, more sorbitol is made than can be changed into fructose.
- Sorbitol builds up within the cell and impairs its function or destroys it.
- This is the pathology of diabetic cataracts and may be involved in other complications as well

**Formation of abnormal glycoproteins** = protein-glucose complexes, AGEs

- Normally occur in basement membranes of capillaries and small vessels.
- Excess blood glucose may cause formation of abnormal glycoproteins, contributing to vascular problems associated with diabetes

**Oxygen starvation of tissues**

- Hemoglobin, the oxygen carrying molecule in the red blood cell, may become altered, and less able to release oxygen.
- Specifically, a glucose molecule becomes incorporated into the hemoglobin molecule in the place of another normal amino acid (valine).

**Bottom line:** In all pathologies, effective normalization of blood sugar is the only way to prevent complications. If this can't be quickly acheived by natural means, medications may be necessary, at least until insulin resistance is otherwise lowered.

## Presenting symptoms

**The "three poly's"**

- polyhuria (frequent urination)
- polydipsia (excessive thirst)
- polyphagia (excessive hunger)

  The above are often not all present even when blood sugar is high. Thirst is often the first sign.

**Other:** poor wound healing, thrush, fungal infections, urinary tract infections

**IDDM** = Weight loss and hunger, or ketoacidosis and coma

**NIDDM** = sometimes fatigue is only cause for visit to practitioner. Obesity is typical rather than weight loss.

## Acute complications

**Ketoacidosis** and coma – More typical of IDDM. Fruity smell on breath. Stress may precipitate. Requires emergency administration of insulin and fluids. Insulin lack prevents ketone-fuel use by cells, with radical buildup of ketones causing acidosis.

**Hyperosmolar hyperglycemic nonketotic coma (HHNK)** More typical of NIDDM. Mortality is 40-70%. Blood glucose 600+ ; Dehydration. Seizures and other neurological problems.

**Hypoglycemia** (also called insulin reaction) (BG < 50 mg/dl) Typical of IDDM who has taken too much insulin or not eaten. Headache, confusion, coma, seizures all possible. Requires administration of glucose or sugary snack.

**Bottom line:** All diabetics must be under a physicians care. Herbalists are not trained to prevent or treat such complications.

## Chronic complications

**Peripheral neuropathy** (not in CNS). 60-70% develop. May cause impotence, gastroparesis, parasthesias.

**Kidney damage** 20-50% develop this. Leading cause of kidney dialysis

**Retinopathy** – 85% develop. Leading cause of blindness in US.

**Vascular changes.** Atherosclerosis. Coronary artery disease, Stroke

**Poor wound healing** – foot ulcers

**Susceptibility to infection.**

# Diabetes Therapeutics

1. First and foremost, to maintain normal blood sugar levels around the clock.

ABSTRACT : BACKGROUND : The low-carbohydrate, ketogenic diet (LCKD) may be effective for improving glycemia and reducing medications in patients with type 2 diabetes. METHODS : From an outpatient clinic, we recruited 28 overweight participants with type 2 diabetes for a 16-week single-arm pilot diet intervention trial. We provided LCKD counseling, with an initial goal of <20 g carbohydrate/day, while reducing diabetes medication dosages at diet initiation. Participants returned every other week for measurements, counseling, and further medication adjustment. The primary outcome was hemoglobin A1c. RESULTS : Twenty-one of the 28 participants who were enrolled completed the study. Twenty participants were men; 13 were White, 8 were African-American. The mean [+/- SD] age was 56.0 +/- 7.9 years and BMI was 42.2 +/- 5.8 kg/m2. Hemoglobin A1c decreased by 16% from 7.5 +/- 1.4% to 6.3 +/- 1.0% ($p < 0.001$) from baseline to week 16. Diabetes medications were discontinued in 7 participants, reduced in 10 participants, and unchanged in 4 participants. The mean body weight decreased by 6.6% from 131.4 +/- 18.3 kg to 122.7 +/- 18.9 kg ($p < 0.001$). In linear regression analyses, weight change at 16 weeks did not predict change in hemoglobin A1c. Fasting serum triglyceride decreased 42% from 2.69 +/- 2.87 mmol/L to 1.57 +/- 1.38 mmol/L ($p = 0.001$) while other serum lipid measurements did not change significantly. CONCLUSION : The LCKD improved glycemic control in patients with type 2 diabetes such that diabetes medications were discontinued or reduced in most participants. Because the LCKD can be very effective at lowering blood glucose, patients on diabetes medication who use this diet should be under close medical supervision or capable of adjusting their medication.

Yancy WS Jr, Foy M, Chalecki AM, Vernon MC, Westman EC. A low-carbohydrate, ketogenic diet to treat type 2 diabetes. *Nutr Metab* (Lond). 2005 Dec 1;2:34.

**Bernsteins "Laws of small Numbers"**

**Law of carbohydrate estimation:**

It's almost impossible to estimate actual grams of carbohydrate to more accuracy than 20% (FDA allows margin of error, natural variance in food, imprecision in portion control) 20% is best case and 40% is likely at least sometimes.

1 gram error in estimation raises or lowers blood glucose by 5 mg/dl

If your bowl of pasta contains 150 grams of carbohydrate, and you're 20% off, then that's 30 grams error or a blood sugar swing of = or - 150 mg/dl, and your 85 mg/dl blood sugar is now somewhere between 0 and 235 mg/dl.

If your meal contains 15 grams of CHO in a salad, and you're 20% off, then that's 3 grams of error, 15 mg/dl + or - and your BG stays between 65 and 100 mg/dl.

Bottom line: Glycemic control is impossible without using only low amounts of CHO

**Law of insulin estimation** (for IDDM)

For those using insulin, there si also a variation in the amount absorbed, due to dose estimation, changes in pharmacokinetics, etc, with a usual variation of 30-40%

1 unit of insulin will lower blood sugar by 40 mg/dl

If the insulin dose is 20 units, a 40% variation will be 8 units, for a BG variation of 320 mg/dl, and accurate glycemic control is possible.

If the insulin dose is 4 units, the variation is greatly reduced.

Bottom line: minimizing the insulin dose is not only valuable, accurate glycemic control may be impossible without it. Herbs may help this, but CHO restriction ensures it. Medications may be more accurate in their hypoglycemic effect than herbs, and control with either drugs or herbs is impossible if large CHO numbers are involved.

**Complication in NIDDM diabetics:** Stomach stretch reflex causes first an insulin surge, followed by a blood sugar drop, followed by a glucagon surge, followed by a blood sugar rise, which, due to insulin resistance and/or relative insulin deficiency, rises out of control. Thus a person can eat a head of lettuce, filling the stomach with nothing but roughage, and have BG shoot up over 300 mg/dl (an actual case).

Bottom, bottom line: Diabetics in order to control BG levels have to eat a very-low CHO diet, with -no- fast-acting CHO's (ie only from low on the glycemic index), and even then, eat frequent small meals rather than a few large ones.

Book that all diabetic patients (and those treating them) must read: ***Dr. Bernsetin's Diabetes Solution: a Complete Guide to Achieveing Normal Blood Sugars.***, by Richard Bernstein ISBN: 0-316-09344-0

## Treat complications

See chapter on Herbs for Insulin Resistance. The insulin stimulants may be used in type I diabetes

A. Support with glycemic control, to try to lower insulin or other drug doses.

B. Retinopathy

*Vaccinium myrtillus* Bilberry concentrate, or dietary blueberries in significant amounts.

- Powerful antioxidant, plus other constituents, protect microcirculation in peripheral vascular system. Can rapidly and effectively reduce or delay diabetic retinopathy.
- One of the few herbs for which standardization is essential. Amounts of protective constituents vary as low as zero in some berries.
- Dose: 300-600 mg of standardized extract. Expensive.

*Gingko biloba* leaf

- Same as above, protects microcirculation.

- Also some antithrombotic effect.
- Dose of standardized extract is 160-240 mg/day, compared to 80mg day as a standard dose for cerebrotonic effects.

**Neuropathy.**

- Must achieve glycemic control. Neuropathy often will reverse somewhat.
- B-vitamin complex in high doses.
- Capsicum annum: liniments may help with pain.
- L-carnitine: 300 mg tid

# Herbs and insulin resistance

by Paul Bergner

**Abstract:** The increasing recognition of the pathological effects of hyperinsulinemia with and without loss of glycemic control has led to the search for agents that increase insulin sensitivity in preference to those that stimulate insulin secretion or inhibit liver production or release of glucose in order to lower blood glucose in Type II diabetes (NIDDM) or to improve the profile of hyperinsulinemia and dyslipidemia in insulin resistance syndrome without diabetes. The mechanisms of action of pharmaceutical drugs and twelve herbal medicines that lower blood glucose are reviewed. *Panax ginseng, Gymnema sylvestre, Brickellia spp Vaccinium spp* and *Syzygium jambolana* appear to lower blood glucose through undesirable mechanisms. *Panax quinquefolius, Foeniculum vulgare, Grifola spp Momordica charantia, Ocimum spp and Cinnamomum cassia* may act at least in part by increasing insulin sensitivity in the tissues.

**Introduction**

Insulin resistance has been recognized as the root pathology underlying Type II diabetes (Non Insulin Dependent Diabetes Mellitus, or NIDDM) for decades, but only in recent years has insulin resistance syndrome (IRS) without loss of control of blood glucose been recognized as a major disease pathology in its own right. When the cells become resistant to the effects of insulin, the pancreas secretes larger amounts, and for a longer period of time. Figure 1 shows typical insulin curves after a glucose challenge in a variety of patients. The top curve is for an individual who may have perfectly normal fasting and post-meal blood glucose levels. The second curve shows a similar individual whose IRS has progressed to loss of glycemic control. This patient still has hyperinsulinemia, with the added pathological burden of elevated blood glucose. Both patients have elevated and prolonged insulin curves compared to the third curve, for an individual with both normal insulin and blood glucose levels. Research from the last decade has demonstrated that such elevated insulin, with accompanying metabolic factors, is a root cause of many of the diseases of modern civilization even in the absence of overt diabetes.

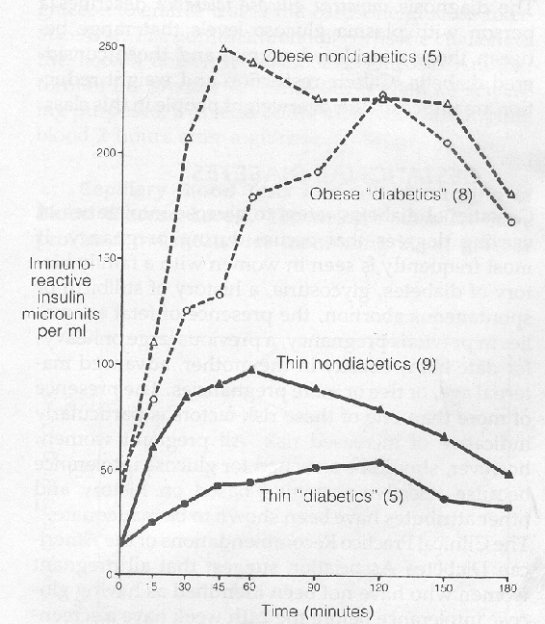



**FIG. 46-3.** Mean absolute insulin responses in both thin and obese patients with diabetes during a 3-hour (100-g) oral glucose tolerance curve. (Bagdade, J. D., Biermann, E. L., & Porter, D. [1967]. The significance of basal insulin levels in evaluation of the insulin response to glucose in diabetic and nondiabetic subjects. *Journal of Clinical Investigation [New York], 46*(10), 1553.)

## Figure 1

**Pathophysiology of hyperinsulinemia**

In normal metabolism, as insulin rises after a meal, or in response to stress-related hyperglycemia during periods of stress, it triggers release of insulin-like growth factor (IGF-1) from the liver. This in turn suppresses growth hormone, and IGF-1 effects combine with those of insulin for a net anabolic effect on cells. The combination of elevated or prolonged insulin secretion in IRS, the accompanying excessive and prolonged secretion of IGF-1, with extended suppression of growth hormone can have powerful pathological effects on the tissues. Some chronic conditions related to insulin resistance and compensatory hyperinsulin- emia, but with normal glycemic control, are listed below.

Obesity

Hypertension

Atherosclerosis

Elevated triglycerides with depressed HDL cholesterol

Increasing the tendency of the blood to clot

Heart attacks and strokes

Polycystic ovarian syndrome

Elevated IGF-1 accompanying insulin resistance may also be related to the pathology of cancers of the breast, prostate, and colon.

All the above may occur in an individual with normal control of blood sugar. In NIDDM, elevated blood glucose may add to the damage, but simple reduction of blood glucose will not remedy the problem. Both insulin and blood glucose must be lowered, preferably by correcting the original resistance of the cells to the effects of insulin. Glycemic control in diabetes attained through stimulation of insulin in a patient who is already hyperinsulinemic may worsen the prognosis of the disease or threaten serious hypoglycemic episodes. Agents that suppress liver production or release of glucose have historically led to liver disease in some patients, and at least three leading drugs in this category had to be pulled from the market due to hepatotoxicity.

Natural methods to increase insulin sensitivity

Drug or herbal treatments to correct insulin resistance and hyperinsulinemia are irrational as permanent cures, because the syndrome is easily treated with lifestyle and dietary modification. A combination of reduction of carbohydrates in the diet, regular moderate activity including cross training to tone multiple muscle systems, and supplementation with nutritional factors known to increase insulin rapidly improve measures of insulin resistance, including glycemic control in NIDDM. Some nutritional factors that may increase insulin sensitivity are listed below.

Chromium picolinate, 200-400 mcg twice a day

Cod Liver Oil for a dose of docosohexaenoic acid (DHA) equivalent to 2-4 grams/day

B-Complex, in the form of a multivitamin

Magnesium, 600-1000 mg/day

Zinc, 30-60 mg/day

## Drug actions

Drugs or herbs that lower blood glucose may do so in the following ways:

Reduce glucose absorption from the intestine. This must be viewed as a poor substitute for reducing carbohydrates in the diet.

Inhibit liver enzymes that release glucose from the liver. This may be either through suppression of the release of glucose from glycogen, or of manufacture of glucose through gluconeogenesis. Drugs of this class have potential liver toxicity as a side effect. This action does not address the underlying pathology of insulin resistance, but creates a disease condition in the liver to balance the disease condition in the cells.

Stimulate insulin production or release from the pancreas. This approach may lower blood glucose, but actually worsens the underlying pathology. Figure 1 shows that insulin is already pathologically elevated in NIDDM. The hyperinsulinemia itself is pathogenic and produces many of the destructive symptoms of NIDDM. Stimulating it further may also hasten the ultimate exhaustion of the pancreas. Drugs which powerfully elevate insulin also increase the risk of fatal hypoglycemic events.

Increase insulin sensitivity. If a drug or herb is used for IRS or NIDDM, this should be the preferred effect. This should not, however, be expected to take the place of normal nutritional components or normal activity that decreases insulin resistance.

### Pharmaceutical drugs

The quest for oral hypoglycemic agents was to prevent the inconvenience of insulin injections. For most of the later twentieth century the focus was on lowering blood glucose, without particular regard to the mechanism. With a growing understanding of insulin resistance as the underlying mechanism of a syndrome that is pathological in itself whether or not it includes loss of glycemic control, the focus in the recent decade has been to identify drugs that increase insulin sensitivity.

### Guanidine derivatives

The first oral hypoglycemic drugs were guanidine derivatives. These may have a combination effect of suppression of sugar production in the liver and increase in insulin sensitivity in the cells. The first drugs in the class, buformine and phenformine, were discontinued due to adverse effects on the liver. The current main drug in this category is metformin (Glucophage).

### Sulfonureas

The next generation of oral hypoglycemics are the sulfonureas. These increase pancreatic insulin, and symptomatically reduce blood sugar. These drugs can cause life-threatening hypoglycemia. They also elevate triglycerides, a normal consequence of hyperinsulinemia. They hasten the degeneration of the pancreatic insulin-producing cells in NIDDM. They are contraindicated in pre-diabetic insulin resistance due to the tendency to cause hypoglycemia.

### Thiazolidinediones

Troglitazone (Rezulin) was widely heralded in the mid-nineties as an insulin-sensitizing agent, but eventually was withdrawn from the market after nearly 100 cases of acute Liver Failure developed in people taking it (Graham et al.).

### Metformin

Metformin (Glucophage) is a guanidine derivative that inhibits liver production of glucose via gluconeogenesis, and also increases the insulin sensitivity of the peripheral tissues. It does not cause hyperinsulinemia or hypoglycemia and may be the most appropriate drug therapy where a drug is required to control blood glucose. It is widely promoted as an insulin sensitizer, but it also acts on the liver, has multiple side effects, and may cause death in individuals with impaired kidney function, a common condition in diabetes.

A study of representatives of the guanidine derivative and sulfonureas in 1971 found that although they improved control of blood glucose, they significantly increased deaths from cardiovascular causes relative to giving insulin alone (Cornfield; Schor; University Group Diabetes Program.).

## Herbs

Many herbs have been used to treat diabetes or its symptoms in areas of the world and in eras when diabetes was present. Diabetes apparently first appeared in ancient Egypt, followed later in the grain farming valleys of India, China, and Mesopotamia. The first recorded case in European history appears to be in the 1600s in Holland, following by a few decades the opening of the first sugar refinery in Europe in that country. Some of these herbs reduce blood glucose, and others treat the symptoms of diabetes without lowering blood glucose. Considering current understanding of insulin resistance, the same discrimination should be used when selecting herbs that lower blood glucose as when selecting drugs. Herbs that lower blood glucose by increasing insulin sensitivity may also be useful in IRS without diabetes. Many historical and currently popular herbs for lowering blood sugar do so through worsening the underlying state of hyperinsulinemia.

### Panax

Various studies of both Asian and American ginseng have shown improvement in aspects of glycemic control in animals and humans. The mechanisms are not clear, but at least some

constituents of Panax ginseng promote insulin production and release, and improvements in control of blood of glucose may be at the expense of stimulating hyperinsulinemia (Waki et al.; Kimura et al.).

A low dose of P. ginseng (100-200 mg) extract was given to 36 diabetic subjects for 8 weeks. The test groups showed improvements in fasting blood glucose and increases in daily activity and exercise. No mechanism was suggested for the activity, but there was no change in serum lipids in the ginseng group. If the action were through improving insulin sensitivity, a drop in serum triglycerides would be expected, so it appears that ginseng acts through methods other than the optimal increase of insulin sensitivity in the peripheral tissues (Sotaniemi et al.).

Administration of an oral preparation of unprocessed roots of P. ginseng in mice reduced blood glucose. The mechanisms suggested were through inhibition of intestinal glucose absorption, and suppressing liver production of glucose, the latter being an undesirable mechanism for long term use (Chung et al.).

A preparation of P. ginseng rootlets lowered blood glucose in animals, and the suggested mechanisms were inhibition of intestinal absorption of glucose, and an increase in insulin sensitivity. P. ginseng rootlets are considered a separate medicine from the root in Chinese herbalism, with rootlet actions resembling the yin tonic American ginseng (Panax quinquefolius) rather than the more stimulating chi and yang tonifying effects of P. ginseng (Chung et al.).

One-gram doses of American ginseng reduced the area under the blood glucose curve in human volunteers without diabetes. The effect was statistically significant, but was slight, from 12-19% of the area under the curve. The ginseng had to be given at least 40 minutes before the glucose challenge to be effective, and a 3 gram dose provided no improved results over a 1 gram dose (Vuksan et al. 2001).

The same researchers found a clinically significant fall in the peak glucose level at the 2 hour point in patient with NIDDM, with administration of 3 grams of P. quinquefolius – blood glucose at the 2 hour point was 60% lower in the panax group than the placebo group (Vuksan et al. 2000b).

In an earlier trial, in both insulin-resistant diabetics and non-diabetic overweight individuals, the researchers found that a 3 gram dose given 40 minutes before a glucose challenge reduced the area under the post-meal glucose curve by just less than 20% (Vuksan et al. 2000a).

No mechanism has been suggested for the activity of American ginseng. The demonstrated insulin secretagogue effects constituents of P.ginseng roots suggest that it should be avoided in the treatment of insulin resistance. Insulin-sensitizing P. ginseng rootlets are generally not available in the U.S. herb market, but their traditional use as an analogue to P. quinquefolius at least suggests that P. quinquefolius should be used in preference to P. ginseng for insulin resistance syndromes

Panax species in low doses (< 1 gram) may play an important role in the treatment of either IRS or NIDDM due to their role as adaptogens, providing energy and support for increased exercise and for dietary changes. .

**Gymnema**

Gymnema sylvestre is a traditional Ayurvedic and Arabic medicine used for diabetes since antiquity in India (Nadkarni) and Egypt (El Gammel). Clinical trials have shown that it can lower blood sugar in both Insulin Dependent Diabetes (IDDM) and NIDDM (Shanmugasundaram et al.; Baskaran et al.). Typical conventional dose: 10 to 15 ml per day of a 1:1 extract or Gymnema tablets 4000 mg 3 daily. Research into the mechanism of action in animals suggests that the plant delays the absorption of glucose from the intestine (Yoshikawa et al.; Shimizu et al.). Consistent results in petri dish, animal and human trials demonstrate that it increases insulin secretion (Persaud et al.), raises serum insulin (Shanmugasundaram et al.; Baskaran et al.), and does not act through increasing insulin sensitivity in the tissues (Tominaga et al.). Older research show that the plant can induce hypoglycemia in normal animals (Nadkarni). Thus gymnema has qualities in common with the sulfonurea drugs. It lowers blood sugar by worsening the underlying disease process of hyperinsulinemia.

**Vaccinium**

The leaves of Vaccinium myrtillus and related species (blueberry, bilberry) have been used to treat diabetes and its complications since antiquity in Egypt (El Gammel). They are also used in Central European folk medicine (Weiss; Petlevski). The use for diabetes in the U.S. appears to have been first recorded in the 1930s, when researchers found it used Swiss-American folk medicine, and verified a blood sugar lowering effect; by the 1960s it had entered into common usage as a treatment for elevated blood sugar in the U.S. via the health foods industry (Crellin and Philpott). In both traditional and contemporary literature, distinction has to be made between use of the leaf and the berry. Vaccinium berry and its flavonoid extracts are used to treat the vascular damage of diabetes without altering insulinemic or glycemic status (Savickiene et al.).

No studies appear to describe a mechanism for the action of the leaf, but Weiss reports research showing that long-term use can cause severe hydroquinone poisoning and states that it is not appropriate for chronic use. Weiss does not state the form or dose that may cause poisoning. Appalachian herbalist Tommie Bass states that the dose he recommended was several hands full of the leaf in a gallon of water to make tea and makes no observation of toxicity (Crellin and Philpott).

**Oplopanax**

Oplopanax horridum (devil's club) has a reputation among contemporary herbalists as a plant that can lower blood sugar in diabetes. The first report of this historically was based on an anecdote in British Columbia where a native coming to a hospital for surgery suddenly developed the symptoms of diabetes. The physician enquired and it seems that the man had been

taking devil's club. The doctor postulated that the devils club was effectively treating the diabetes, and when the plant was withdrawn in the hospital, the full disease emerged. The case was written up and published in a Canadian medical journal. The problem with this particular anecdote is that borderline NIDDM often appears only under conditions of stress, and then disappears when the stress is removed. An aboriginal man admitted to a hospital for anesthesia and surgery could have been experiencing severe stress, and this could have caused the emergence of the symptoms of NIDDM rather than withdrawal of the oplopanax. Subsequent clinical trials have found no effect of oplopanax on either blood sugar or insulin (Justice; Thommassen et al.).

A review of the older ethnobotanical literature on oplopanax turned up only a single reference to it use in diabetes: one native informant reported that she remembered a white woman taking the plant for diabetes (Thie). Subsequently, it appears that in recent decades use of the plant among natives for diabetes has become common (Thommassen et al.), and it appears from the published studies that the plant benefits patients subjectively in some way unrelated to glycemic control (Justice; Thommassen et al.).

Because oplopanax has no demonstrated action of blood glucose or insulin there is no rationale for using it to treat underlying insulin resistance syndrome.

**Brickellia**

Brickelia grandiflora (progidiosa) and related species are used in popular medicine in Mexico and the Southwest U.S. to control elevated blood sugar in diabetes (Moore). Research in Mexico suggests that the mechanism is through stimulation of insulin from the pancreas (Peres-Gutierrez). Extracts were given to diabetic and normal mice. As expected, the extract lowered blood sugar in the diabetic mice, but also lowered blood sugar by 40% in the normal mice. An agent acting to normalize insulin resistance would not be expected to do this, while the result is typical of an agent that either stimulates insulin release or decreases liver release of glucose. In humans with normal blood glucose, Brickellia rapidly induces the symptoms of hypoglycemia.

**Syzygium**

Syzygium jambolana, fructus (S. cumini, Eugenia jambolana Lam, Eugenia cumini Druce, Myrtus cumini Linn), common name Jambul, has been used in traditional Egyptian (El Gammel), Unani (Said), and Ayurvedic medicine (Kar et al.; Grover et al. 2001; Rathi) to treat diabetes. The activity has been confirmed in some animal trials (Kar et al.; Grover et al., 2001; Rao and Rao), but not in others. The plant part used may be important. The leaf decoction was found ineffective in diabetic animals (Pepato et al.) and in non-diabetic human volunteers (Teixeira et al. 2000). A tea of the seeds was ineffective in animals (Teixeira et al. 1997). Powders or decoctions of the dried seeds were effective in animals in another trial (Grover et al. 2000). The fruit pulp was effective in another animal trial (Achrekar et al.). Research into the mechanisms of action of Syzygium are contradictory, with some animal trials showing an inhibition of the liver enzymes that release blood glucose (Grover et al. 2000) or stimulating insulin secretion

(Achrekar et al.), and one trial showed a lowered insulin response to a fructose challenge (Vikrant et al. 2001).

## Herbs that may enhance insulin sensitivity

### Trigonella

In a trial of a fenugreek extract (Trigonella foenum-gracium) in twenty-five patients with Type II diabetes, a trial group of thirteen patients received one gram a day of an evaporated hydro-alcoholic extract of fenugreek seeds for two months. At the end of the period, blood sugar responses to a meal were significantly lower in the fenugreek group. Insulin secretion was also lower, as were serum triglycerides (TG). HDL cholesterol was improved., and a standard measure of insulin sensitivity showed increased insulin sensitivity (Gupta et al.).

Dose of powder has varied in different trials from 18 grams (Sowmya and Rajyalakshmi) to 100 grams (Sharma 1990) with several trials giving 25 grams (Sharma, Sarkar et al.). Long term compliance can therefore be difficult. In some clinical trial in India, the powder was mixed into chipati flour for easier compliance. In several trials, an evaporated hydro-alcoholic extract was effective (Gupta et al.), as was an aqueous extract (Abdel-Barry).

### Cinnamomum

Chinese diabetes researchers investigating traditional formulas for diabetes discovered that a formula based on cinnamon and prepared aconite (quei fu di huang wan) lowered blood glucose in test animals. The formula suppressed the production of glucose in the liver in a manner similar to that of metformin. They then separately tested the cinnamon and the aconite. Both herbs lowered glucose, the aconite by suppressing gluconeogenesis, and the cinnamon by some other unidentified mechanism (Cheng et al.).

Studies at the U.S. Department of Agriculture suggest that cinnamon acts in some manner to potentiate the action of insulin on the target cell (Berrio et al.; Broadhurst et al.; Khan et al.). Other researchers found that cinnamon components help to activate specific cellular responses to insulin (Imparl-Radosevish et al.; Jarvill-Taylor et al.) thus increasing insulin sensitivity.

A clinical trial published in December of 2003 showed that modest doses of cinnamon can have a powerful effect on both insulin and blood glucose. Volunteers with Type 2 diabetes were given one, three, or six grams of cinnamon powder a day, in capsules after meals.All responded within weeks, with fasting blood glucose levels that were on average 24 per cent lower than a control group. Some achieved normal blood sugar levels. When the cinnamon was removed, blood glucose began to rise back to its original levels. Triglyceride levels, a marker for insulin levels, fell by 30% (Khan, Safdar, et al).

## Grifola

Maitake mushroom (Grifola spp.) has been shown in animals to lower both blood glucose and insulin (Talpur; Manohar; Horio; Kubo). It improves many aspects of hyperinsulinemia, including blood sugar, HBA1C (a measure of long term glycemic control) (Talpur et al.), insulin levels, and triglycerides (Talpur et al.; Kubo et al.). Two case reports have appeared in the literature suggesting that grifola polysaccharides in moderate doses may completely replace conventional antidiabetic drugs (Konno). The animal trials indicate that either the powder of maitake or a water extract may be effective. The mechanism seems only to involve an increase in insulin sensitivity.

## Momordica charantia

Momordica charantia (bitter melon) has been in continuous use since antiquity to treat diabetes in Ayurvedic, Unani, and Egyptian medicine (Grover et al. 2002; El Gammel). Many trials have verified its use to lower blood glucose in experimental animals (Kar; Miora; Vikrant), and the property has been confirmed in humans, where the plant lowered blood glucose in 86% of diabetic patients tested (Ahmad). It has also been shown to reduce diabetic pathological endpoints in animals, such as cataract (Rathi) and kidney damage (Grover et al., 2001). It appears to act by increasing insulin sensitivity in the peripheral tissues (Miura et al.). Momordica prevents both hyperinsulinemia and hypertriglyceridemia (Vikrant et al.).

## Ocimum

Various species of basil (Ocimum species) have been used in traditional medicine to treat diabetes, including O. sanctum (Kar et al.; Grover et al.), O. canum (Nyarko et al.), O. gratissimum (Aguiyi et al.) and O ablum (Agrawal et al.). A number of trials have demonstrated a hypoglycemic effect in animals (Kar et al.; Nyarko et al.; Vats et al.; Aguiyi et al.; Chattopadhyay; Rai et al.). An anti-hyperglycemic effect has been confirmed on both fasting and post-prandial blood glucose in a human clinical trial (Agrawal et al.). Studies in animals (Chattopadhyay et al.) and humans (Viseshakul et al.) suggest that its action is through increasing insulin sensitivity in the cells.

## Opuntia spp and Caffea arabica

See notes following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## Caffea arabica

BACKGROUND: In western populations, coffee consumption is associated with a reduced risk for type 2 diabetes; however, the effect of green, black, and oolong teas is unclear. OBJECTIVE: To examine the relationship between consumption of these beverages and risk for diabetes. DESIGN: Retrospective cohort study. SETTING: 25 communities across Japan. PARTICIPANTS: A total of 17,413 persons (6727 men and 10,686 women; 49% of the original study population) who were 40 to 65 years of age; had no history of type 2 diabetes, cardiovascular disease, or cancer at the baseline lifestyle survey; and completed the 5-year follow-up questionnaire. There was no difference in body mass index levels at baseline between respondents and nonrespondents. MEASUREMENTS: Questionnaire on consumption of coffee; black, green, and oolong teas; and physician-diagnosed diabetes. RESULTS: During the 5-year follow-up, there were 444 self-reported new cases of diabetes in 231 men and 213 women (5-year event rates, 3.4% and 2.0%, respectively). Consumption of green tea and coffee was inversely associated with risk for diabetes after adjustment for age, sex, body mass index, and other risk factors. Multivariable odds ratios for diabetes among participants who frequently drank green tea and coffee (> or =6 cups of green tea per day and > or =3 cups of coffee per day) were 0.67 (95% CI, 0.47 to 0.94) and 0.58 (CI, 0.37 to 0.90), respectively, compared with those who drank less than 1 cup per week. No association was found between consumption of black or oolong teas and the risk for diabetes. Total caffeine intake from these beverages was associated with a 33% reduced risk for diabetes. These inverse associations were more pronounced in women and in overweight men. LIMITATIONS: Diabetes was self-reported, no data were available on consumption of soda, and the follow-up rate was low. CONCLUSIONS: Consumption of green tea, coffee, and total caffeine was associated with a reduced risk for type 2 diabetes.

Iso H, Date C, Wakai K, Fukui M, Tamakoshi A; JACC Study Group.The relationship between green tea and total caffeine intake and risk forself-reported type 2 diabetes among Japanese adults. *Ann Intern Med.* 2006 Apr 18;144(8):554-62.

OBJECTIVE: Coffee has several metabolic effects that could reduce the risk of type 2 diabetes. Our objective was to examine the effects of coffee consumption on glucose tolerance, glucose and insulin levels. RESEARCH DESIGN AND METHODS: A subsample of subjects aged 45 to 64 years in 1987 and in 1992 from the population-based FINRISK study (12,287 individuals) was invited to receive the standard oral glucose tolerance test at baseline. Plasma samples were taken after an overnight fast, and a two-hour oral glucose tolerance test was administered. Fasting and two-hour plasma glucose and insulin were measured in 2434 subjects with data on coffee use and potential confounders. RESULTS: After adjustment for potential confounding factors (age, body mass index, systolic blood pressure, occupational, commuting and leisure time physical activity, alcohol and tea drinking, smoking), coffee consumption was significantly and inversely associated with fasting glucose, two-hour plasma glucose, and fasting insulin in both men and women. Coffee consumption was significantly and inversely associated with impaired fasting glucose, impaired glucose regulation, and hyperinsulinemia among both men and women and with isolated impaired glucose tolerance among women. CONCLUSIONS: In this cross-sectional analysis, coffee showed positive effects on several glycemia markers.

Bidel S, Hu G, Sundvall J, Kaprio J, Tuomilehto J.Effects of coffee consumption on glucose tolerance, serum glucose and insulin levels--a cross-sectional analysis. *Horm Metab Res.* 2006 Jan;38(1):38-43.

OBJECTIVE: High habitual coffee consumption has been associated with a lower risk of type 2 diabetes, but data on lower levels of consumption and on different types of coffee are sparse. RESEARCH DESIGN AND METHODS: This is a prospective cohort study including 88,259 U.S. women of the Nurses' Health Study II aged 26-46 years without history of diabetes at baseline. Consumption of coffee and other caffeine-containing foods and drinks was assessed in 1991, 1995, and 1999. We documented 1,263 incident cases of confirmed type 2 diabetes between 1991 and 2001. RESULTS: After adjustment for potential confounders, the relative risk of type 2 diabetes was 0.87 (95% CI 0.73-1.03) for one cup per day, 0.58 (0.49-0.68) for two to three cups per day, and 0.53 (0.41-0.68) for four or more cups per day compared with nondrinkers (P for trend <0.0001). Associations were similar for caffeinated (0.87 [0.83-0.91] for a one-cup increment per day) and decaffeinated (0.81 [0.73-0.90]) coffee and for filtered (0.86 [0.82-0.90]) and instant (0.83 [0.74-0.93]) coffee. Tea consumption was not substantially associated with risk of type 2 diabetes (0.88 [0.64-1.23] for four or more versus no cups per day; P for trend = 0.81). CONCLUSIONS: These results suggest that moderate consumption of both caffeinated and decaffeinated coffee may lower risk of type 2 diabetes in younger and middle-aged women. Coffee constituents other than caffeine may affect the development of type 2 diabetes.

van Dam RM, Willett WC, Manson JE, Hu FB.Coffee, caffeine, and risk of type 2 diabetes: a prospective cohort study in younger and middle-aged U.S. women. Diabetes Care. 2006 Feb;29(2):398-403.

CONTEXT: Emerging epidemiological evidence suggests that higher coffee consumption may reduce the risk of type 2 diabetes. OBJECTIVE: To examine the association between habitual coffee consumption and risk of type 2 diabetes and related outcomes. DATA SOURCES AND STUDY SELECTION: We searched MEDLINE through January 2005 and examined the reference lists of the retrieved articles. Because this review focuses on studies of habitual coffee consumption and risk of type 2 diabetes, we excluded studies of type 1 diabetes, animal studies, and studies of short-term exposure to coffee or caffeine, leaving 15 epidemiological studies (cohort or cross-sectional). DATA EXTRACTION: Information on study design, participant characteristics, measurement of coffee consumption and outcomes,

adjustment for potential confounders, and estimates of associations was abstracted independently by 2 investigators. DATA SYNTHESIS: We identified 9 cohort studies of coffee consumption and risk of type 2 diabetes, including 193 473 participants and 8394 incident cases of type 2 diabetes, and calculated summary relative risks (RRs) using a random-effects model. The RR of type 2 diabetes was 0.65 (95% confidence interval [CI], 0.54-0.78) for the highest (>or=6 or >or=7 cups per day) and 0.72 (95% CI, 0.62-0.83) for the second highest (4-6 cups per day) category of coffee consumption compared with the lowest consumption category (0 or <or=2 cups per day). These associations did not differ substantially by sex, obesity, or region (United States and Europe). In the cross-sectional studies conducted in northern Europe, southern Europe, and Japan, higher coffee consumption was consistently associated with a lower prevalence of newly detected hyperglycemia, particularly postprandial hyperglycemia. CONCLUSIONS: This systematic review supports the hypothesis that habitual coffee consumption is associated with a substantially lower risk of type 2 diabetes. Longer-term intervention studies of coffee consumption and glucose metabolism are warranted to examine the mechanisms underlying the relationship between coffee consumption and type 2 diabetes.

van Dam RM, Hu FB. Coffee consumption and risk of type 2 diabetes: a systematic review. JAMA. 2005 Jul 6;294(1):97-104.

AIMS/HYPOTHESIS: Coffee contains several substances that may affect glucose metabolism. The aim of this study was to evaluate the relationship between habitual coffee consumption and the incidence of IFG, IGT and type 2 diabetes. METHODS: We used cross-sectional and prospective data from the population-based Hoorn Study, which included Dutch men and women aged 50-74 years. An OGTT was performed at baseline and after a mean follow-up period of 6.4 years. Associations were adjusted for potential confounders including BMI, cigarette smoking, physical activity, alcohol consumption and dietary factors. RESULTS: At baseline, a 5 cup per day higher coffee consumption was significantly associated with lower fasting insulin concentrations (-5.6%, 95% CI -9.3 to -1.6%) and 2-h glucose concentrations (-8.8%, 95% CI -11.8 to -5.6%), but was not associated with lower fasting glucose concentrations (-0.8%, 95% CI -2.1 to 0.6%). In the prospective analyses, the odds ratio (OR) for IGT was 0.59 (95% CI 0.36-0.97) for 3-4 cups per day, 0.46 (95% CI 0.26-0.81) for 5-6 cups per day, and 0.37 (95% CI 0.16-0.84) for 7 or more cups per day, as compared with the corresponding values for the consumption of 2 or fewer cups of coffee per day (p=0.001 for trend). Higher coffee consumption also tended to be associated with a lower incidence of type 2 diabetes (OR 0.69, CI 0.31-1.51 for >/=7 vs </=2 cups per day, p=0.09 for trend), but was not associated with the incidence of IFG (OR 1.35, CI 0.80-2.27 for >/=7 vs </=2 cups per day, p=0.49 for trend). CONCLUSIONS/INTERPRETATION: Our findings indicate that habitual coffee consumption can reduce the risk of IGT, and affects post-load rather than fasting glucose metabolism.

van Dam RM, Dekker JM, Nijpels G, Stehouwer CD, Bouter LM, Heine RJ; Hoorn study.Coffee consumption and incidence of impaired fasting glucose, impaired glucose tolerance, and type 2 diabetes: the Hoorn Study. Diabetologia. 2004 Dec;47(12):2152-9. Epub 2004 Dec

AIMS/HYPOTHESIS: Several studies have reported that coffee has a protective effect against the development of type 2 diabetes. However, few of these studies used the standard glucose tolerance test to diagnose type 2 diabetes. The aim of this study was to investigate the relationship between coffee and green tea consumption and glucose tolerance status as determined using a 75-g OGTT. METHODS: We performed a cross-sectional study of 3224 male officials of the self-defence forces. Glucose tolerance status was determined in accordance with the 1998 World Health Organization criteria, and average intakes of coffee and green tea over the previous year were assessed by a self-administered questionnaire. The

figures obtained were adjusted for BMI, physical activity and other factors. RESULTS: A total of 1130 men were identified as having glucose intolerance (IFG, IGT or type 2 diabetes). Compared with those who did not consume coffee on a daily basis, fasting and 2-h post-load plasma glucose levels were 1.5% and 4.3% lower in those who drank 5 cups of coffee or more per day respectively. The adjusted odds ratios of glucose intolerance for categories of <1, 1-2, 3-4 and >/=5 cups of coffee per day were 1.0 (referent), 0.8 (95% CI 0.6-1.0), 0.7 (95% CI 0.6-0.9) and 0.7 (95% CI 0.5-0.9) respectively (p=0.0001 for trend). No clear association was observed between green tea drinking and glucose tolerance status. CONCLUSIONS/INTERPRETATION: Coffee consumption may inhibit postprandial hyperglycaemia and thereby protect against the development of type 2 diabetes mellitus.

Yamaji T, Mizoue T, Tabata S, Ogawa S, Yamaguchi K, Shimizu E, Mineshita M, Kono Coffee consumption and glucose tolerance status in middle-aged Japanese men. Diabetologia. 2004 Dec;47(12):2145-51. Epub 2004 Dec 15.

Recent prospective epidemiology links heavy coffee consumption to a substantial reduction in risk for type 2 diabetes. Yet there is no evidence that coffee improves insulin sensitivity and, at least in acute studies, caffeine has a negative impact in this regard. Thus, it is reasonable to suspect that coffee influences the risk for beta cell "failure" that precipitates diabetes in subjects who are already insulin resistant. Indeed, there is recent evidence that coffee increases production of the incretin hormone glucagon-like peptide-1 (GLP-1), possibly owing to an inhibitory effect of chlorogenic acid (CGA -- the chief polyphenol in coffee) on glucose absorption. GLP-1 acts on beta cells, via cAMP-dependent mechanisms, to promote the synthesis and activity of the transcription factor IDX-1, crucial for maintaining the responsiveness of beta cells to an increase in plasma glucose. Conversely, the "glucolipotoxicity" thought to initiate and sustain beta cell dysfunction in diabetics can suppress expression of this transcription factor. The increased production of GLP-1 associated with frequent coffee consumption could thus be expected to counteract the adverse impact of chronic free fatty acid overexposure on beta cell function in overweight insulin resistant subjects. CGA's putative impact on glucose absorption may reflect the ability of this compound to inhibit glucose-6-phosphate translocase 1, now known to play a role in intestinal glucose transport. Delayed glucose absorption may itself protect beta cells by limiting postprandial hyperglycemia -- though, owing to countervailing effects of caffeine on plasma glucose, and a paucity of relevant research studies, it is still unclear whether coffee ingestion blunts the postprandial rise in plasma glucose. More generally, diets high in "lente carbohydrate", or administration of nutraceuticals/pharmaceuticals which slow the absorption of dietary carbohydrate, should help preserve efficient beta cell function by boosting GLP-1 production, as well as by blunting the glucotoxic impact of postprandial hyperglycemia on beta cell function.

McCarty MF. A chlorogenic acid-induced increase in GLP-1 production may mediate the impact of heavy coffee consumption on diabetes risk. Med Hypotheses. 2005;64(4):848-53.

**Plants containing chlorogenic acid**

| | | | |
|---|---|---|---|
| Coffea arabica L. -- Coffee | Seed | 100,000 ppm | DUKE1992A |
| Helianthus annuus L. -- Girasol, Sunflower | Seed | 28,000 ppm | DUKE1992A |
| Vaccinium corymbosum L. -- Blueberry | Fruit | 3,000 ppm | |

**Bottom line:**

For an individuals with insulin resistance or diabetes who is habituated to coffee, removing it is not only not a priority, but could be harmful.

For those not habituated to coffee, promotion of dietary consumption of blueberries in the amount of 4-8 oz per day would be the more beneficial recommendation.

**Opuntia spp.**

To find out if commercial capsules with dried nopal (prickle-pear cactus, Opuntia ficus indica may have a role in the management of diabetes mellitus, three experiments were performed: 30 capsules where given in fasting condition to 10 diabetic subjects and serum glucose was measured through out 3 hours; a control test was performed with 30 placebo capsules. OGTT with previous intake of 30 nopal or placebo capsules was performed in ten healthy individuals. In a crossover and single blinded study 14 diabetic patients withdrew the oral hypoglycemic treatment and received 10 nopal or placebo capsules t.i.d. during one week; serum glucose, cholesterol and tryglycerides levels were measured before and after each one-week period. Five healthy subjects were also studied in the same fashion. Opuntia capsules did not show acute hypoglycemic effect and did not influence OGTT. In diabetic patients serum glucose, cholesterol and tryglycerides levels did not change with Opuntia, but they increased with placebo ($P < 0.01$ glucose and cholesterol, P = NS triglycerides). In healthy individuals glycemia did not change with nopal, while cholesterol and triglycerides decreased ($P < 0.01$ vs. placebo). The intake of 30 Opuntia capsules daily in patients with diabetes mellitus had a discrete beneficial effect on glucose and cholesterol. However this dose is unpractical and at present it is not recommended in the management of diabetes mellitus.

Frati Munari AC, Vera Lastra O, Ariza Andraca CR.[Evaluation of nopal capsules in diabetes mellitus] [Article in Spanish]Gac Med Mex. 1992 Jul-Aug;128(4):431-6. 2: Prostaglandins Leukot Essent Fatty Acids. 2003 Jul;69(1):61-6.

BACKGROUND: Besides others pectin, a soluble fibre, has been reported to be effective in lowering cholesterol levels in both animals and man with hyperlipidemia as well as being able to slow carbohydrate absorption and hence reduce the postprandial rise in blood glucose and serum insulin in patients with type-II diabetes. Aim of this pilot study was to assess the effect of prickly pear consumption on glucose- and lipid metabolism. DESIGN: In 24 non-diabetic, non-obese males (aged 37-55 years) suffering from primary isolated hypercholesterolemia (n = 12; group A) or combined hyperlipidemia (n = 12; group B) respectively, the influence of prickly pear pectin (Opuntia robusta)-intake on glucose- and lipid metabolism was examined. After an 8 week pre-running phase with a 7506 KJ step-I diet (phase I), 625 KJ were replaced by prickly pear edible pulp (250 g/day) for 8 further weeks (phase II). RESULTS: Prickly pear leads to a decrease of total cholesterol (12%), low-density lipoprotein-cholesterol (15%), apolipoprotein B (9%), triglycerides (12%), fibrinogen (11%), blood glucose (11%), insulin (11%) and uric acid (10%), while body weight, high-density lipoprotein-cholesterol, apolipoprotein A-I, and lipoprotein(a) remained unchanged. CONCLUSION: The hypocholesterolemic action of prickly pear may be partly explained by the fibre (pectin) content, but the hypoglycaemic actions (improvement of insulin sensitivity) in the non-obese, non-diabetic need further investigation to get more insights on the potential advantage of treating the metabolic syndrome.

Wolfram RM, Kritz H, Efthimiou Y, Stomatopoulos J, Sinzinger H.Effect of prickly pear (Opuntia robusta) on glucose- and lipid-metabolism in non-diabetics with hyperlipidemia--a pilot study. Wien Klin Wochenschr. 2002 Oct 31;114(19-20):840-6.

To assess the hypoglycemic effect of the nopal Opuntia streptacantha Lemaire (O.streptacantha Lem.), three groups of patients with non-insulin-dependent diabetes mellitus (NIDDM) were studied. Group one (16 patients) ingested 500 g of broiled nopal stems. Group 2 (10 patients) received only 400 ml of water as a control test. Three tests were performed on group 3 (6 patients): one with nopal, a second with water, and a third with ingestion of 500 g broiled squash. Serum glucose and insulin levels were measured at 0, 60, 120, and 180 min. After the intake of O. streptacantha Lem., serum glucose and serum insulin levels decreased significantly in groups 1 and 3, whereas no similar changes were noticed in group 2. The mean reduction of glucose reached 17.6 +/- 2.2% of basal values at 180 min in group 1 and 16.2 +/- 1.8% in group 3; the reduction of serum insulin at 180 min reached 50.2 +/- 8.0% in group 1 and 40.3 +/- 12.4% in group 3. This study shows that the stems of O. streptacantha Lem. cause a hypoglycemic effect in patients with NIDDM. The mechanism of this effect is unknown, but an increased insulin sensitivity is suggested.

Frati-Munari AC, Gordillo BE, Altamirano P, Ariza CR. Hypoglycemic effect of Opuntia streptacantha Lemaire in NIDDM. Diabetes Care. 1988 Jan;11(1):63-6.

See also:

Frati-Munari AC, Yever-Garces A, Islas-Andrade S, Ariza-Andraca CR, Chavez-Negrete A. Studies on the mechanism of "hypoglycemic" effect of nopal (Opuntia sp.). [Article in English, Spanish] Arch Invest Med (Mex). 1987 Jan-Mar;18(1):7-12.

Frati-Munari AC, Fernandez-Harp JA, Banales-Ham M, Ariza-Andraca CR.Decreased blood glucose and insulin by nopal (Opuntia sp.). [Article in English, Spanish] Arch Invest Med (Mex). 1983;14(3):269-74.