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Report

Suppress Deadly After-Meal Blood Sugar Surges

By Daniel Becker

High blood sugar is fast becoming the leading *preventable* killer of maturing individuals in the United States. In addition to the **26 million** Americans with diabetes, the Centers for Disease Control estimate that ***more than a third of the general population is now pre-diabetic***.1

This may be just the tip of the iceberg.

As **Life Extension**® members know, recent data confirm that risk for most degenerative diseases and death rise dramatically when fasting blood glucose exceeds **85 mg/dL**.2

Yet the medical establishment persists in defining readings up to **99 mg/dL** as "safe." By this measure, **virtually *all* of us are vulnerable to diabetic complications**.

Even more alarming is widespread physician ignorance of the stealth danger posed by blood sugar surges after *meals* that can reach diabetic levels and last for hours—or even days.

These ***after-meal glucose "spikes"*** inflict silent damage to cells via multiple mechanisms and have been linked to **cardiovascular disease**, **cancer**, **Alzheimer's disease** , **kidney failure**, and **retinal damage**.3-16

The good news is there are documented ways to suppress deadly after-meal glucose surges.

The most recent is a **green coffee bean extract** shown to *neutralize* a key enzyme that facilitates after-meal glucose surges.

When tested on humans in a placebo-controlled study, this natural extract produced an extraordinary **24% drop** in after-meal blood sugar in just **30 minutes**!17

Silent Epidemic of High Blood Sugar

The percentage of adults suffering from dangerous, chronically high blood sugar has been *vastly* underestimated.

Currently, you aren't considered diabetic unless your fasting blood glucose is higher than **125 mg/dL**. The range from **100-125 mg/dL** is considered "pre-diabetic," while anything lower is defined as normal.

Unfortunately, your risk for age-related disease is far greater at these "normal levels" than has been previously recognized. Optimal fasting glucose should be within the range of **70-85 mg/dL**.

A recent study of **46,000** middle-aged individuals revealed that more than **80%** had fasting blood sugar of **85 mg/dL** or higher.18 A similar epidemiological analysis of **11,000** middle-aged and older people found that more than **85%** had fasting blood sugar of **85 mg/dL** or higher.19

As **Life Extension**®has long warned, a thorough survey of the scientific literature confirms that maturing individuals with blood sugar levels in these ranges—below 100 mg/dL—are nonetheless at *substantially* increased risk of virtually all degenerative diseases, including:

- Cancer4,20-29
- Cardiovascular disease5,9-15,17,30,31
- Alzheimer's disease 17,32,33
- Kidney disease8,34
- Pancreatic dysfunction35
- Diabetic retinopathy (which can lead to blindness)6,36
- Neuropathy (nerve pain and dysfunction)37,38

One team of researchers found that the risk of developing diabetes itself was increased more than **seven-fold** in people with fasting glucose levels of **105-109 mg/dL**, compared with people with fasting glucose levels **less than 85 mg/dL**.19

An analysis of **1,800** maturing individuals revealed that **coronary artery disease** rates over a 10-year period in individuals currently defined as "**pre-diabetic**" were ***nearly identical*** to those with **full-blown diabetes**.39

A similar analysis of **33,230** men found that high glucose within the "normal" range was independently associated with a **38%** increase in deaths from **digestive tract cancers**.40

These results underscore the critical need to **redefine diabetes** as fasting glucose above **85 mg/dL**.

Table 1: Increased Health Risks in People with "Normal" Glucose Levels

CONDITION	GLUCOSE LEVELS (MG/DL)	INCREASED RISK
Developing Type 2 Diabetes	100-104	Up to 283%19
Stomach Cancer	95-105	Up to 130%49
First-time Heart Attack	Above 88	242%47
Need for Coronary Bypass or Stent Procedure	Above 95	73%50

Undetected *Daily* Diabetic Glucose Levels?

Conventional medicine's approach to glucose control goes beyond the problem of ***outdated reference ranges***. Fasting blood glucose concentrations alone do not identify individuals with an increased risk of glucose-related disease onset because ***they do not detect dangerous after-meal glucose spikes***.41,42

The current diagnostic of fasting glucose readings is only a snapshot that does not adequately measure of an aging individual's hour-to-hour glucose status over the course of the entire day.

By definition, fasting blood glucose tests are conducted eight or more hours or more *after* your last meal. This method *fails* to account for a vital risk marker specific to you as an individual: after each meal, your blood sugar rises sharply for at least two hours before returning to normal.

Depending on the number and frequency of meals consumed, *an aging individual may sustain dangerously high blood sugar throughout the day that will not be detected by conventional measures*.

A mounting body of scientific evidence suggests that **after-meal** glucose spikes inflict as much or more damage than high

fasting blood sugar.43-46

For example, in aging individuals with "normal" blood sugar readings and "normal" glucose-tolerance tests, heart attack risk increases by **58%** for a **21 mg/dL** increase in ***after-meal*** blood sugar.47 And for a similar after-meal increase, ***risk of cardiac death*** increases by 26%.48

This means that if your blood sugar surges 63 mg/dL after a meal, your risk of cardiac death increases nearly **twofold**.

One research team found that risk of stroke increased when fasting glucose rose above **83 mg/dL**. And every **18 mg/dL** increase beyond **83 mg/dL** resulted in a **27%** greater risk of dying from stroke!5

This means that an individual with a fasting blood glucose level of **119 mg/dL** has a **54%** higher risk of stroke-related death compared to an individual whose fasting blood glucose is only **83 mg/dL**. If you wonder why stroke continues to disable and kill so many—despite better control of hypertension than ever—look no further than the epidemic of **high blood glucose** plaguing aging humans.

These alarming data underscore the vital importance of *suppressing* **after-meal** glucose surges and controlling **fasting** blood glucose in order to prolong healthy life span.

CONTROL AFTER-MEAL GLUCOSE SURGES

- Elevated blood sugar is a silent danger that increases the risk of cardiovascular disease, cancer, Alzheimer's, kidney disease, neuropathy, and retinal damage.
- More than a third of the American population is estimated to be pre-diabetic.
- Currently, fasting blood sugar levels higher than 125 mg/dL are considered diabetic and levels between 100-125 mg/dL are considered pre-diabetic.
- Life Extension advises that optimal fasting blood glucose levels are in the range of 70-85 mg/dL. A growing body of evidence shows that tissue damage and disease risk increase when fasting blood glucose levels are above 85 mg/dL.
- Coffee consumption has been associated with a decreased risk of developing type 2 diabetes.
- A beneficial compound in coffee called chlorogenic acid has been credited with coffee's glucose-lowering effects.
- In a clinical trial, individuals who received 400 mg of a green coffee berry extract containing 50% chlorogenic acid prior to an oral glucose challenge demonstrated a 32% reduction in blood glucose at 2 hours.

The Little-Known Enzyme Behind Chronic Blood Sugar Overload

Most people think blood sugar levels are determined by the amount of carbohydrates or sugar they eat and how well their pancreas is working.

The truth is more complex.

You won't hear this from most physicians, but your **liver** also plays a key role in regulating blood sugar, one that contributes directly to dangerous blood glucose surges after heavy meals.

Under normal conditions, the liver keeps a certain amount of sugar in storage. If your blood sugar falls too low, it releases this stored sugar in order to boost blood glucose back to healthy levels in a process called ***glycogenolysis***.

If its stores of sugar are depleted, your liver has another means at its disposal to boost blood sugar: *making sugar on its own from other sources, including* **fats** *and* **protein** through a process called ***gluconeogenesis***.

Humans evolved this capability to prevent acute, potentially deadly hypoglycemia (low blood sugar) during near-starvation states.

In young, healthy individuals, both these processes—**sugar release** or ***glycogenolysis*** and blood sugar synthesis or ***gluconeogenesis*** —are naturally suppressed after a meal to prevent blood sugar from getting too high.

As you age, this balancing mechanism may become impaired. Your liver releases stored sugar and makes additional sugar after you finish a meal—*precisely when your body needs additional blood sugar the least.*

At the core of pathologic glycogenolysis (release of stored blood sugar) and gluconeogenesis (synthesis of new sugar) is the enzyme ***glucose-6-phosphatase***. Heavy meals can activate this enzyme, which in turn tells your liver to release its sugar stores and helps it to make more sugar, despite the flood of glucose from the meal you just finished.

It is this age-related ***dysregulation*** of **glucose-6-phosphatase** activity that accounts for the difficulty many maturing individuals face in maintaining optimal glucose levels. The dual processes of ***glycogenolysis*** and ***gluconeogenesis*** triggered by **glucose-6-phosphatase** can keep blood sugar high even with a lower-calorie or low-carbohydrate diet since glucose can *also* be synthesized from proteins and fats. (Note those who practice calorie restriction are usually able to keep their fasting glucose below 86 mg/dL and after-meal glucose surges below 120 mg/dL.)

Suppressing the activity of **glucose-6-phosphatase** is a cornerstone strategy in maintaining control of after-meal blood sugar spikes and limiting their potentially destructive impact.

In the quest to identify compounds that might favorably target the glucose-6-phosphatase enzyme, researchers turned their attention to the fact that heavy coffee drinkers enjoyed dramatically lower risk of diabetes.

HOW MUCH COFFEE TO DRINK OR CHLOROGENIC ACID TO TAKE?

Increased **coffee** consumption results in a substantially reduced risk of diabetes.57-61

The prestigious journal *The Lancet* published a 2002 population study that included over **17,000** people. The researchers found a **50%** lower risk of diabetes among those who consumed **7 cups** of coffee a day compared to those who drank only **2 cups** a day.61

So why not just drink more coffee?

Coffee "beans" are the seeds contained inside the plant's fruit, the coffee berry. They possess a significantly higher proportion of beneficial phenolic acids (**50%**) than the berry (about **35%**).

An analysis of the proprietary green coffee bean extract used in clinical studies cited in this article reveals that just **350 mg** supplies the same amount of chlorogenic acid found in **14 cups** of dark roast coffee. The problem with dark roasted coffees is that the roasting process removes too many beneficial polyphenols such as ***chlorogenic acid***.

Green coffee bean extract also supplies the antioxidant compound **ferulic acid**, shown to exert a therapeutic anti-glucose effect in tandem with chlorogenic acid.61

After analyzing the blood of subjects given this green coffee bean extract, one 2008 study published in the *Journal of Nutrition* confirmed the presence in their blood samples of the same major phenolic compounds—including ***chlorogenic acid*** —provided by drinking roasted, brewed coffee. The researchers added that the compounds in green coffee bean extract were highly absorbable and readily metabolized in humans.76

In addition to their high absorption rate, the compounds in green coffee bean extract are believed to furnish **stronger glucose-lowering protection** than roasted coffee. That's because *roasting destroys much of the coffee bean's beneficial*

content.

Conventional "lightly roasted" coffee provides about **92** milligrams of chlorogenic acid per cup. Heavily roasted coffee provides far less chlorogenic acid. A cup of a new "polyphenol-retaining" coffee (with chlorogenic acid added back in after roasting) provides **172** mg of chlorogenic acid. So drinking one or two cups of this new **polyphenol-retaining** coffee provides **172** to **344** mg of ***chlorogenic acid***, which are in ranges shown to demonstrate therapeutic efficacy.

Green coffee bean extracts are available in new dietary supplements that provide either **200** or **400** mg of ***chlorogenic acid*** per serving. The typical dose for most people is 200 mg of chlorogenic acid before most meals. Those with higher glucose levels should take 400 mg before most or all meals.

Chlorogenic Acid Combats Excess Glucose

An abundance of studies confirms that, in addition to protection against various diseases,5,51-56 increased **coffee** consumption results in a substantially reduced risk of diabetes.56-61

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Coffee's anti-diabetic benefits are dose-dependent. In other words, the more you drink, the greater the benefit. And therein lies the problem: drinking seven cups or more of coffee every day is impractical for most people. This set researchers on a quest to uncover the specific glucose-lowering agents contained in coffee.

SKYROCKETING RATES OF DIABETES

In 2008, there were an estimated 347 million people with diabetes in the world, up from 153 million just 30 years earlier.86 Researchers attributed about 70% of that increase to the global population explosion, but the remaining 30% are related to the rapid rise in overweight and obesity.87

Another reason for the sharp rise is that epidemiologists are finally recognizing that standard definitions of diabetes are inadequate. Simply measuring fasting blood glucose fails to detect up to 70% of people with disturbances in blood glucose regulation.88 An oral glucose tolerance test is required to detect such disturbances, particularly dangerous after-meal sugar spikes.

What this means for you is that you simply cannot assume that you are not diabetic just because your routine fasting blood sugar measurement was normal. Know the facts, and take proper steps to ensure that you protect your tissues from the twin threats of chronically elevated blood glucose and after-meal sugar spikes.

Coffee's contents are complex, containing more than 1,000 discrete compounds. 62

Compelling new data reveal that the ***chlorogenic acid*** content in coffee is primarily responsible for its glucose-lowering effects via several interesting mechanisms.63,64

Chlorogenic acid inhibits the ***glucose-6-phosphatase*** enzyme that stimulates glycogenolysis and gluconeogenesis.65,66 As discussed earlier, excessive activity of this enzyme contributes to dangerous after-meal blood sugar spikes and high blood glucose levels between meals.67

Chlorogenic acid directly inhibits glucose absorption from the intestinal tract. Studies show that coffee with a high

chlorogenic acid content delays intestinal glucose absorption.59

Chlorogenic acid inhibits the intestinal enzyme ***alpha-glucosidase*** that breaks apart complex sugars and enhances their absorption.68 Slowing the breakdown of those common sugars (including sucrose, or table sugar), dramatically limits after-meal glucose spikes.

Chlorogenic acid-rich plant extracts have been shown to reduce fasting blood glucose values by more than **15%** in diabetic patients with poor response to medication.69 A similar effect was seen in healthy volunteers, whose intestinal absorption of glucose was reduced by 7% following a chlorogenic acid-enriched coffee drink.70 And a chlorogenic acid supplement of 1 gram reduced glucose levels by 13 mg/dL, 15 minutes after an oral glucose challenge, demonstrating its ability to ***lower the after-meal spike*** in humans.71

A chlorogenic acid-rich extract of green coffee beans is also effective in animal studies against weight gain, reducing total weight and body fat accumulation by inhibiting fat absorption and preventing new fat production in liver tissue.72,73 Chlorogenic acid reduces liver fat content in animal studies as well, a vital factor in reducing the impact of overweight and obesity.74

DISEASE RISKS OF HIGH-NORMAL BLOOD SUGAR

Cancer: Numerous studies—including one published in the May 17, 2010, online issue of *The Oncologist* that was so large that it included half of all type 2 diabetics in Sweden20 —have found that the risk for cancer increases among diagnosed diabetics.14,23,24 Rising in lock-step with glucose levels as they edged up within the normal range were the risks for cancers of the endometrium, pancreas, colon, and colorectal tumors of a more aggressive nature.21,25,26,28,29

Cardiovascular disease: Subjects showed risks for cardiovascular events, cardiovascular disease, and cardiovascular mortality that increased in direct relation to elevated—but still high-normal—glucose levels.9,11-13,15 One researcher commented that within limits, lower glucose levels, even among those without diabetes, resulted in lower cardiovascular risk. Coronary artery disease risk was twice as high in patients with impaired glucose tolerance, compared with patients with more normal glucose tolerance.77 While diabetes is defined as experiencing regular after-meal glucose levels of **200 mg/dL**, one research team found a risk for stroke that increased as fasting glucose levels rose above **83 mg/dL**. In fact, every **18 mg/dL** increase beyond **83** resulted in a **27%** greater risk of dying from stroke.5

Cognitive impairment: As blood sugar rose—whether within the normal or the diabetic ranges—the risk for this mild cognitive impairment and dementia increased.32,33

Kidney disease: Surges in blood sugar promoted a greater production of fibrous kidney tissue—which causes kidney disease—than a high but constant blood sugar level.8 The study authors suggested it may be fluctuations in glucose—more than the levels themselves—that produce the vascular complications implicated in kidney damage. Another study found a direct increase in chronic kidney disease as levels of hemoglobin A1c (a marker of long-term glucose control) rose.34

Pancreatic dysfunction: Beta cells located in the pancreas produce the insulin that helps control blood sugar. But high glucose levels can make these cells dysfunctional, raising the risk of type 2 diabetes. Researchers discovered that mild beta cell dysfunction was already detectable in those whose glucose levels spiked two hours after eating, despite staying completely within the range considered by the medical establishment to be normal.35

Diabetic retinopathy: High glucose levels precipitate diabetic retinopathy—damage to the retina that can lead to blindness. In one study, retinopathy was diagnosed in **13%** of people who later progressed to diabetes and in **8%** of those who never progressed to diabetes.7

Neuropathy: As expected, patients with nervous system damage (***neuropathy***) whose ***postprandial*** (after-meal) glucose readings were above the diabetic threshold, showed damage to their large nerve fibers. However, neuropathy patients whose glucose readings—although elevated—remained well within the **normal** range still showed damage to their small

nerve fibers. Within any blood sugar range, reported the journal *Neurology* in 2003, the higher the glucose, the greater the involvement of the large nerve fibers.37 Another nerve damage study in 2006 confirmed these results.38

Compelling Confirmatory Data

A team of Japanese researchers recorded a **43%** drop in blood sugar levels after administering **green coffee bean extract** to mice after a heavy meal.75

In a clinical trial presented in 2011, researchers gave different dosages of ***standardized*** green coffee bean extract, each containing **50%** chlorogenic acid, to **56** people. Next, they gave the participants **100 grams** of glucose in an ***oral glucose challenge test***. The oral glucose tolerance test is a standard method of gauging an individual's response to ***after-meal*** sugar exposure.

Blood sugar levels dropped by an increasingly greater amount as the test dosage of green coffee bean extract was raised, from **100 mg** up to **400 mg**. At the **400 mg** dosage, there was a full **32%** decrease in blood sugar—**two hours** after glucose ingestion.17

This means that if you had a dangerous after-meal glucose reading of **160 mg/dL**, the proprietary green coffee bean extract would slash it to **109 mg/dL**.

These findings are in line with supportive data demonstrating green coffee bean extract's numerous glucose-fighting mechanisms of action.

Other models reveal that chlorogenic acid favorably modulates gene expression to enhance the activity of liver cells and increase levels of the hormone ***adiponectin***, which enhances insulin sensitivity and exerts anti-inflammatory, anti-diabetic, and anti-atherogenic effects.76

Summary

Twenty-six million Americans are now considered diabetic, while more than one in three are *pre-diabetic.* Recent data confirm that your risk for degenerative disease and premature death increases substantially when fasting blood glucose exceeds **85 mg/dL**. Yet the medical establishment persists in defining readings up to **99 mg/dL** as "safe."

Also overlooked in the effort to combat today's diabetes epidemic is the insidious process of ***after-meal blood sugar surges***. Regardless of whether your fasting glucose readings are "normal," these surges can cause a diabetic-like state in the body that lasts for hours, inflicting undetected, system-wide damage to healthy tissues.

Driving this danger is the little-known role your liver plays in creating and releasing *additional* glucose into the blood. This process, which regulates blood sugar in the absence of food when you're young, becomes detrimentally stimulated after heavy meals by the enzyme ***glucose-6-phosphatase*** as you age. The result is a dangerous flood of sugar into your bloodstream after every meal.

A breakthrough weapon to control these after-meal blood sugar surges has been identified: **green coffee bean extract**. It contains a compound called ***chlorogenic acid*** shown to target ***glucose-6-phosphatase*** and *blunt* post-consumption blood sugar levels by up to **32%** in human trials.

UNDERSTANDING GLUCONEOGENESIS

The enzyme *glucose-6-phosphatase* (G6P) helps to produce dangerous after-meal blood sugar spikes in two ways. It releases glucose from its storage area in the liver, and it promotes formation of new glucose molecules from non-sugar

sources.78 The latter process is called gluconeogenesis.

Traditionally, scientists have assumed that amino acids from proteins were the only precursors of glucose in gluconeogenesis.79 Recent discoveries, however, suggest that fatty acids are also important precursors of this dangerous source of excess glucose.79,80

Fatty acids contribute to gluconeogenesis by at least three mechanisms. First, excessive fatty acids stimulate gluconeogenesis and provide G6P the energy it needs to convert traditional substrates such as amino acids into glucose.81-84 Second, when triglycerides break down to fatty acids, glycerol is released, and then converted into glucose by gluconeogenesis.85 Finally, advanced computer models have revealed new pathways by which fatty acids are directly converted into glucose; the final steps in those pathways involve G6P.79

These discoveries provide further insight into the causes of the deadly after-meal glucose spikes. They also provide further incentives to block the enzymes that participate in gluconeogenesis, such as G6P. Green coffee extracts are an excellent source of G6P-blocking nutrients.

If you have any questions on the scientific content of this article, please call a **Life Extension**® Health Advisor at 1-866-864-3027.

References

1. Available at http://www.cdc.gov/media/releases/2011/p0126_diabetes.html. Accessed November 3, 2011.

2. Bjornholt JV, Erikssen G, Aaser E, et al. Fasting blood glucose: an underestimated risk factor for cardiovascular death. Results from a 22-year follow-up of healthy nondiabetic men. *Diabetes Care*. 1999 Jan;22(1):45-9.

3. Bardini G, Dicembrini I, Cresci B, Rotella CM. Inflammation markers and metabolic characteristics of subjects with one-hour plasma glucose levels. *Diabetes Care*. 2010 Feb;33(2):411-3.

4. Stattin P, Bjor O, Ferrari P, Lukanova A, et al. Prospective study of hyperglycemia and cancer risk. *Diabetes Care*. 2007 Mar;30(3):561-7.

5. Batty GD, Kivimäki M, Smith GD, Marmot MG, Shipley MJ. Post-challenge blood glucose concentration and stroke mortality rates in non-diabetic men in London: 38-year follow-up of the original Whitehall prospective cohort study. *Diabetologia*. 2008 Jul;51:1123-6.

6. Singleton JR, Smith AG, Bromberg, MB. Increased prevalence of impaired glucose tolerance in patients with painful sensory neuropathy. *Diabetes Care*. 2001;24(8)1448-53.

7. Beckley ET. ADA Scientific Sessions: Retinopathy Found in Pre-Diabetes. *DOC News*. 2005 Aug;2(8):1-10.

8. Polhill TS, Saad S, Poronnik SSP, Fulcher GR, Pollock CA. Short-term peaks in glucose promote renal fibrogenesis independently of total glucose exposure. *Am J Physiol Renal Physiol*. 2004 Aug;287(2):F268-73.

9. Pan WH, Cedres LB, Liu K, et al. Relationships of clinical diabetes and symptomatic hyperglycaemia to risk of coronary heart disease mortality in men and women. *Am J Epidemiol*. 1986 Mar;123(3):504-16.

10. Barrett-Connor EL, Cohn BA, Wingard DL, Edelstein SL. Why is diabetes mellitus a stronger risk factor for fatal ischemic heart disease in women than in men? The Rancho Bernardo Study. *JAMA*.1991 Feb 6;265(5):627-31.

11. Coutinho M, Gerstein H, Poque J, Wang Y, Yusuf S. The relationship between glucose and incident cardiovascular events:

a metaregression analysis of published data from 20 studies of 95,783 individuals followed for 12.4 years. *Diabetes Care.* 1999 Feb;22(2):233-40.

12. Wilson PWF, Cupples LA, Kannel WB. Is hyperglycaemia associated with cardiovascular disease? The Framingham Study. *Am Heart J*. 1991 Feb;121 (2 Pt 1):586-90.

13. de Vegt F, Dekker JM, Ruhe HG, et al. Hyperglycaemia is associated with all-cause and cardiovascular mortality in the Hoorn population: the Hoorn study. *Diabetologia*. 1999 Aug;42(8):926-31.

14. DECODE Study Group 2001, the European Diabetes Epidemiology Group. Glucose tolerance and cardiovascular mortality: comparison of the fasting and the 2-hour diagnostic criteria. *Arch Intern Med.* 2001 Feb 12;161(3):397-404.

15. Saydah SH, Miret M, Sung J, Varas C, Gause D, Brancati FL. Post-challenge hyperglycemia and mortality in a national sample of US adults. *Diabetes Care.* 2001 Aug;24(8):1397-402.

16. Matsuzaki T, Sasaki K, Tanizaki Y, et al. Insulin resistance is associated with the pathology of Alzheimer disease: the Hisayama study. *Neurology*. 2010 Aug 31;75(9):764-70.

17. Nagendran MV. Effect of Green Coffee Bean Extract (GCE), High in Chlorogenic Acids, on Glucose Metabolism. Poster presentation number: 45-LB-P. Obesity 2011, the 29th Annual Scientific Meeting of the Obesity Society. Orlando, Florida. October 1-5, 2011.

18. Nichols GA, Hillier TA, Brown JB. Normal fasting plasma glucose and risk of type 2 diabetes diagnosis. *Am J Med.* 2008 Jun;121(6):519-24.

19. Kato M, Noda M, Suga H, Matsumoto M, Kanazawa Y. Fasting plasma glucose and incidence of diabetes—implication for the threshold for impaired fasting glucose: results from the population-based Omiya MA cohort study. *J Atheroscler Thromb*. 2009;16(6):857-61.

20. Hemminki K, Li X, Sundquist J, Sundquist K. Risk of cancer following hospitalization for type 2 diabetes. *Oncologist*. 2010 May 17;15:548-55.

21. Aleksandrova K, Boeing H, Jenab M, et al. Metabolic syndrome and risks of colon and rectal cancer: the European Prospective Investigation into Cancer and Nutrition Study. *Cancer Prev Res (Phila).* 2011 Jun 22.

22. Czyzyk A, Szczepanik Z. Diabetes mellitus and cancer. *Eur J Intern Med*. 2000 Oct;11(5):245-52.

23. Vigneri P, Frasca F, Sciacca L, Pandini G, Vigneri R. Diabetes and cancer. *Endocr Relat Cancer*. 2009 Dec;16(4):1103-23.

24. Martin-Castillo B, Vazquez-Martin A, Oliveras-Ferraros C, Menendez JA. Metformin and cancer: doses, mechanisms and the dandelion and hormetic phenomena. *Cell Cycle*. 2010 Mar 21;9(6):1057-64.

25. Cust AE, Kaaks R, Friedenreich C, Bonnet F, et al. Metabolic syndrome, plasma lipid, lipoprotein and glucose levels, and endometrial cancer risk in the European Prospective Investigation into Cancer and Nutrition EPIC. *Endocr Relat Cancer*. 2007 Sep;14(3):755-67.

26. Rosato V, Tavani A, Bosetti C, et al. Metabolic syndrome and pancreatic cancer risk: a case-control study in Italy and meta-analysis. *Metabolism*. 2011 May 5.

27. Stocks T, Lukanova A, Bjørge T, et al. Metabolic factors and the risk of colorectal cancer in 580,000 men and women in the metabolic syndrome and cancer project (Me-Can): Metabolic Syndrome Cancer Project (Me-Can) Group. *Cancer*. 2010 Dec 17.

28. Schoen RE, Tangen CM, Kuller LH, et al. Increased blood glucose and insulin, body size, and incident colorectal cancer. *J Natl Cancer Inst*. 1999 Jul 7;91(13):1147-54.

29. Healy L, Howard J, Ryan A, et al. Metabolic syndrome and leptin are associated with adverse pathological features in male colorectal cancer patients. *Colorectal Dis*. 2011 Jan 20.

30. Held C, Gerstein HC, Zhao F, et al. Fasting plasma glucose is an independent predictor of hospitalization for congestive heart failure in high-risk patients. *American Heart Association 2006 Scientific Sessions*. November 13, 2006. Abstract 2562.

31. Lamblin N, Bauters C. Hemoglobin A1c levels are associated with severity and prognosis of systolic chronic heart failure in nondiabetic patients. *American Heart Association 2006 Scientific Sessions*. November 13, 2006. Abstract 2372.

32. Cukierman-Yaffe T, Gerstein HC, Williamson JD. Relationship between baseline glycemic control and cognitive function in individuals with type 2 diabetes and other cardiovascular risk factors: the action to control cardiovascular risk in diabetes-memory in diabetes (ACCORD-MIND) trial. *Diabetes Care*. 2009 Mar;32(2):221-6.

33. Sonnen JA, Larson EB, Brickell K. Different patterns of cerebral injury in dementia with or without diabetes. *Arch Neurol*.2009;66(3):315-22.

34. Bash, LD, Selvin E, Steffes M, Coresh J, Astor BC. Poor glycemic control in diabetes and the risk of incident kidney disease even in the absence of albuminuria and retinopathy: atherosclerosis risk in communities (ARIC) study. *Arch Intern Med*. 2008 Dec 8;168(22):2440-7.

35. Gastaldelli A, Ferrannini E, Miyazaki Y, Matsuda M, De Fronzo RA. Beta-cell dysfunction and glucose intolerance: results from the San Antonio metabolism (SAM) study. *Diabetologia*. 2004 Jan;47(1):31-9.

36. Cheng YJ, Gregg EW, Geiss LS. Association of A1C and fasting plasma glucose levels with diabetic retinopathy prevalence in the US population: implications for diabetes diagnostic thresholds. *Diabetes Care*. 2009 Nov;32(11):2027-32.

37. Sumner CJ, Sheth S, Griffin JW, Cornblath DR, Polydefkis M. The spectrum of neuropathy in diabetes and impaired glucose tolerance. *Neurology*. 2003 Jan 14;60(1):108-11.

38. Hoffman-Snyder C, Smith BE, Ross MA, Hernandez J, Bosch EP. Value of the oral glucose tolerance test in the evaluation of chronic idiopathic axonal polyneuropathy. *Arch Neurol*. 2006 Aug;63(8):1075-9.

39. Li Q, Chen AH, Song XD, et al. Analysis of glucose levels and the risk for coronary heart disease in elderly patients in Guangzhou Haizhu district. *Nan Fang Yi Ke Da Xue Xue Bao*. 2010 Jun;30(6):1275-8.

40. Matthews CE, Sui X, LaMonte MJ, Adams SA, Heebert JR, Blair SN. Metabolic syndrome and risk of death from cancers of the digestive system. *Metabolism*. 2010 Aug;59(8):1231-9.

41. Glucose tolerance and mortality: comparison of WHO and American Diabetes Association diagnostic criteria. The DECODE study group. European Diabetes Epidemiology Group. Diabetes Epidemiology: Collaborative analysis Of Diagnostic criteria in Europe. *Lancet.* 1999 Aug 21;354(9179):617-21.

42. Nakagami T. Hyperglycaemia and mortality from all causes and from cardiovascular disease in five populations of Asian origin. *Diabetologia.* 2004 Mar;47(3):385-94.

43. Miura K, Kitahara Y, Yamagishi S. Combination therapy with nateglinide and vildagliptin improves postprandial metabolic derangements in Zucker fatty rats. *Horm Metab Res.* 2010 Sep;42(10):731-5.

44. Monnier L, Colette C. Glycemic variability: should we and can we prevent it? *Diabetes Care.* 2008 Feb;31 Suppl

2:S150-4.

45. Monnier L, Colette C, Owens DR. Glycemic variability: the third component of the dysglycemia in diabetes. Is it important? How to measure it? *J Diabetes Sci Technol.* 2008 Nov;2(6):1094-100.

46. Triggle CR. The early effects of elevated glucose on endothelial function as a target in the treatment of type 2 diabetes. *Timely Top Med Cardiovasc Dis.* 2008;12:E3.

47. Gerstein HC, Pais P, Pogue J, Yusuf S. Relationship of glucose and insulin levels to the risk of myocardial infarction: a case-control study. *J Am Coll Cardiol.* 1999 Mar;33(3):612-9.

48. Lin HJ, Lee BC, Ho YL, et al. Postprandial glucose improves the risk prediction of cardiovascular death beyond the metabolic syndrome in the nondiabetic population. *Diabetes Care.* 2009 Sep;32(9):1721-6.

49. Yamagata H, Kiyohara Y, Nakamura S, et al. Impact of fasting plasma glucose levels on gastric cancer incidence in a general Japanese population: the Hisayama study. *Diabetes Care.* 2005 Apr;28(4):789-94.

50. Pereg D, Elis A, Neuman Y, Mosseri M, Lishner M, Hermoni D. Cardiovascular risk in patients with fasting blood glucose levels within normal range. *Am J Cardiol.* 2010 Dec 1;106(11):1602-5.

51. Srinivasan M, Sudheer AR, Menon VP. Ferulic acid: therapeutic potential through its antioxidant property. *J Clin Biochem Nutr*. 2007 March;40(2):92-100.

52. Glei M, Kirmse A, Habermann N, Persin C, Pool-Zobel, BL. Bread enriched with green coffee extract has chemoprotective and antigenotoxic activities in human cells. *Nutr Cancer*. 2006;56(2):182-92.

53. Suzuki A, Yamamoto N, Jokura H, et al. Chlorogenic acid attenuates hypertension and improves endothelial function in spontaneously hypertensive rats. *J Hypertens*. 2006 Jun;24(6): 1065-73.

54. Watanabe T, Arai Y, Mitsui Y, et al. The blood pressure-lowering effect and safety of chlorogenic acid from green coffee bean extract in essential hypertension. *Clin Exp Hypertens*. 2006;28:439-49.

55. Ochiai R, Jokura H, Suzuki A, et al. Green coffee bean extract improves human vasoreactivity. *Hypertens Res*. 2004 Oct;27(10):731-7.

56. Onakpoya I, Terry R, Ernst E. The use of green coffee extract as a weight loss supplement: a systematic review and meta-analysis of randomised clinical trials. *Gastroenterol Res Pract.* 2011;2011.

57. Salazar-Martinez E, Willett WC, Ascherio A, et al. Coffee consumption and risk for type 2 diabetes mellitus. *Ann Intern Me*d. 2004 Jan 6;140(1):1-8.

58. Pereira MA, Parker ED, Folsom AR. Coffee consumption and risk of type 2 diabetes mellitus: an 11-year prospective study of 28 812 postmenopausal women. *Arch Intern Med*. 2006 Jun 26;166(12):1311-6.

59. Johnston KL, Clifford MN, Morgan LM. Coffee acutely modifies gastrointestinal hormone secretion and glucose tolerance in humans: glycemic effects of chlorogenic acid and caffeine. *Am J Clin Nutr.* 2003 Oct;78(4):728-33.

60. 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.

61. van Dam RM, Feskens EJM. Coffee consumption and risk of type 2 diabetes mellitus. Lancet. 2002 Nov 9;360(9344):1477-8.

62. Available at: http://www.illy.com/wps/wcm/connect/us/illy/the-world-of-coffee/the-science-of-coffee/. Accessed July 6,

2011.

63. 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.

64. Greenberg JA, Boozer CN, Geliebter A. Coffee, diabetes, and weight control. *Am J Clin Nutr.* 2006 Oct;84(4):682-93.

65. Henry-Vitrac C, Ibarra A, Roller M, Merillon JM, Vitrac X. Contribution of chlorogenic acids to the inhibition of human hepatic glucose-6-phosphatase activity in vitro by Svetol, a standardized decaffeinated green coffee extract. *J Agric Food Chem.* 2010 Apr 14;58(7):4141-4.

66. Andrade-Cetto A, Vazquez RC. Gluconeogenesis inhibition and phytochemical composition of two Cecropia species. *J Ethnopharmacol.* 2010 Jul 6;130(1):93-7.

67. Bassoli BK, Cassolla P, Borba-Murad GR, et al. Chlorogenic acid reduces the plasma glucose peak in the oral glucose tolerance test: effects on hepatic glucose release and glycaemia. *Cell Biochem Funct.* 2008 Apr;26(3):320-8.

68. Ishikawa A, Yamashita H, Hiemori M, et al. Characterization of inhibitors of postprandial hyperglycemia from the leaves of Nerium indicum. *J Nutr Sci Vitaminol (Tokyo).* 2007 Apr;53(2):166-73.

69. Herrera-Arellano A, Aguilar-Santamaria L, Garcia-Hernandez B, Nicasio-Torres P, Tortoriello J. Clinical trial of Cecropia obtusifolia and Marrubium vulgare leaf extracts on blood glucose and serum lipids in type 2 diabetics. *Phytomedicine.* 2004 Nov;11(7-8):561-6.

70. Thom E. The effect of chlorogenic acid enriched coffee on glucose absorption in healthy volunteers and its effect on body mass when used long-term in overweight and obese people. *J Int Med Res.* 2007 Nov-Dec;35(6):900-8.

71. van Dijk AE, Olthof MR, Meeuse JC, Seebus E, Heine RJ, van Dam RM. Acute effects of decaffeinated coffee and the major coffee components chlorogenic acid and trigonelline on glucose tolerance. *Diabetes Care.* 2009 Jun;32(6):1023-5.

72. Shimoda H, Seki E, Aitani M. Inhibitory effect of green coffee bean extract on fat accumulation and body weight gain in mice. *BMC Complement Altern Med.* 2006;6:9.

73. Cho AS, Jeon SM, Kim MJ, et al. Chlorogenic acid exhibits anti-obesity property and improves lipid metabolism in high-fat diet-induced-obese mice. *Food Chem Toxicol.* 2010 Mar;48(3):937-43.

74. Li SY, Chang CQ, Ma FY, Yu CL. Modulating effects of chlorogenic acid on lipids and glucose metabolism and expression of hepatic peroxisome proliferator-activated receptor-alpha in golden hamsters fed on high fat diet. *Biomed Environ Sci.* 2009 Apr;22(2):122-9.

75. Murase T, Misawa K, Minegishi Y, Aoki M, Ominami H, Suzuki Y, Shibuya Y, Hase T. Coffee polyphenols suppress diet-induced body fat accumulation by downregulating SREBP-1c and related molecules in C57BL/6J mice. *Am J Physiol Endocrinol Metab.* 2011 Jan;300(1):E122-33.

76. Zhang LT, Chang CQ, Liu Y, Chen ZM. Effect of chlorogenic acid on disordered glucose and lipid metabolism in db/db mice and its mechanism. *Zhongguo Yi Xue Ke Xue Yuan Xue Bao*. 2011 Jun;33(3):281-6.

77. Donahue RP, Abbott RD, Reed DM, et al: Postchallenge glucose concentration and coronary heart disease in men of Japanese ancestry. Honolulu Heart Program. *Diabetes*. 1987 Jun;36 (6):689-92.

78. Hemmerle H, Burger HJ, Below P, et al. Chlorogenic acid and synthetic chlorogenic acid derivatives: novel inhibitors of hepatic glucose-6-phosphate translocase. *J Med Chem.* 1997 Jan 17;40(2):137-45.

79. Kaleta C, de Figueiredo LF, Werner S, Guthke R, Ristow M, Schuster S. In silico evidence for gluconeogenesis from Fatty acids in humans. *PLoS Comput Biol.* 2011 Jul;7(7):e1002116.

80. Titov VN, Dmitriev LF, Krylin VA. [Methylglyoxal--test for biological dysfunctions of homeostasis and endoecology, low cytosolic glucose level, and gluconeogenesis from fatty acids]. *Ter Arkh.* 2010;82(10):71-7.

81. DeFronzo RA. Dysfunctional fat cells, lipotoxicity and type 2 diabetes. *Int J Clin Pract Suppl.* 2004 Oct (143):9-21.

82. Tonelli J, Kishore P, Lee DE, Hawkins M. The regulation of glucose effectiveness: how glucose modulates its own production. *Curr Opin Clin Nutr Metab Care.* 2005 Jul;8(4):450-6.

83. Mlinar B, Marc J, Janez A, Pfeifer M. Molecular mechanisms of insulin resistance and associated diseases. *Clin Chim Acta.* 2007 Jan;375(1-2):20-35.

84. Goldstein JL, Zhao TJ, Li RL, Sherbet DP, Liang G, Brown MS. Surviving Starvation: Essential Role of the Ghrelin-Growth Hormone Axis. *Cold Spring Harb Symp Quant Biol.* 2011 Jul 22.

85. Finn PF, Dice JF. Proteolytic and lipolytic responses to starvation. *Nutrition.* 2006 Jul-Aug;22(7-8):830-44.

86. Danaei G, Finucane MM, Lu Y, et al. National, regional, and global trends in fasting plasma glucose and diabetes prevalence since 1980: systematic analysis of health examination surveys and epidemiological studies with 370 country-years and 2•7 million participants. *Lancet.* 2011 Jul 2;378(9785):31-40

87. Finucane MM, Stevens GA, Cowan MJ, et al. National, regional, and global trends in body-mass index since 1980: systematic analysis of health examination surveys and epidemiological studies with 960 country-years and 9•1 million participants. *Lancet.* 2011 Feb 12;377(9765):557-67.

88. Cosson E, Hamo-Tchatchouang E, Banu I, et al. A large proportion of prediabetes and diabetes goes undiagnosed when only fasting plasma glucose and/or HbA1c are measured in overweight or obese patients. *Diabetes Metab*. 2010 Sep;36(4):312-8.