Life Extension Magazine®

Metformin Makes Headline News

Extensive scientific evidence documents the anti-cancer properties of **metformin**. Yet it is illegal for manufacturers to promote metformin to healthy people who want to reduce their risk of cancer, vascular occlusion, or obesity. Unless the current political/legal stranglehold over medical innovation is lifted, needless suffering and death will continue.

Scientifically reviewed by **Dr. Gary Gonzalez**, MD, in October 2024. Written by: William Faloon.

Metformin is the first-line drug of choice in the treatment of **type II diabetes**. It was first approved in Europe in **1958**.[1]

Americans had to wait until **1994** to *legally* obtain metformin.[1]

The holdup in approving metformin goes beyond the **FDA**. It is an indictment of a **political/legal system** that will forever cause needless suffering and death unless substantively changed.

When **Life Extension**® informed Americans about drugs like metformin in the **1980**s, the FDA did everything in its power to incarcerate me and shut down our Foundation.[2] FDA propaganda at the time was that consumers needed to be "protected" against "unproven" therapies.

William Faloon

As history has since proven, the result of the FDA's embargo has been unparalleled human carnage. So called "consumer protection" translated into ailing Americans being denied access to therapies that the FDA now claims are essential to saving lives.

Today's major problem is not drugs available in other countries that Americans can't access. Instead, it is a **political/legal system** that suffocates medical innovation.

Headline news stories earlier this year touted the **anti-cancer** effects of **metformin**, data that Foundation members were alerted to long ago.[3]

The problem is that it is *illegal* for metformin manufacturers to promote this drug to cancer patients or oncologists. It's also illegal to promote metformin to healthy people who want to reduce their risk of cancer, diabetes, vascular occlusion, and obesity.

This fatal departure from reality continues unabated, as our dysfunctional **political/legal system** denies information about **metformin** that could spare countless numbers of lives.

Type II diabetics suffer sharply higher rates of **cancer**[4-7] and **vascular disease**.[8-11] The anti-diabetic drug metformin has been shown in numerous scientific studies to slash the risk of cancer[12-24] and lower markers of vascular disease.[25-28]

Metformin was shown to reduce blood sugar levels in the **1920s**.[28] One reason it fell off the radar screen is that **insulin** quickly became popular because it produced an immediate glucose-lowering effect.

What doctors back then did not realize is that while insulin saved the lives of **type I diabetics** (who produce little or no insulin), those with **type II diabetes** often produce too much insulin as their pancreas tries to offset multiple metabolic imbalances.

One of the metabolic imbalances of type II diabetes is the excess formation of glucose in the liver. To ensure that blood glucose never drops too low, the liver manufactures glucose in a process called *gluconeogenesis*. In type II diabetes, despite an elevated blood glucose level, the liver inappropriately continues to pump out glucose. This *inappropriate* outburst of glucose from the liver in type II diabetes patients is a classic hallmark of the disease. In

fact, scientific data that measures glucose output by the liver shows that the typical type II diabetic produces **three times more glucose** in their liver than *non-diabetics*.[29] And, as previously reported in this publication, even most non-diabetics produce too much glucose in their liver as they age.

Scientific data shows that metformin reduces glucose production and the rate of *gluconeogenesis* by anywhere from **24%** to **36%,** respectively, thus reducing blood glucose levels while lowering the amount of insulin that is chronically secreted.[29] Metformin also enhances insulin sensitivity, thus enabling cells to remove more glucose from the bloodstream, which further lowers glucose and insulin levels.[30-33] In a recent study conducted by a team of researchers in Italy, **500 mg** three times a day of metformin reduced insulin levels by **25%.**[33]

Excess Insulin Is a "Death Hormone"

In response to continuous over-production of glucose by the liver, the pancreas secretes huge amounts of **insulin** to suppress it. This excess amount of insulin damages blood vessel walls[34-36] and promotes tumor growth.[37-41] For a type II diabetic who is over-producing insulin, the use of insulin injections provides a relatively brief respite from high blood glucose levels—with horrific long-term consequences.

Drug companies today are heavily promoting convenient insulin injection devices to physicians and suggesting that many of them have forgotten about insulin's proven glucose-lowering effects. The harsh reality is that for most type II diabetics, excess insulin represents a "death hormone" that causes weight gain,[42-44] cancer,[45-47] and vascular disease.[48-51]

It was not only the discovery of insulin that delayed recognition of **metformin**. Drugs known as **sulfonylureas** promote the **insulin** release from the pancreas. Sulfonylureas were liberally prescribed for decades and are another ill-conceived way of temporarily suppressing blood glucose at the expense of systemic metabolic havoc.

Like insulin, **sulfonylurea drugs** induce weight gain, which is the opposite effect one is seeking when treating most type II diabetics. All **sulfonylureas** carry an FDA-mandated warning about increased risk of cardiovascular death.

In one study lasting more than 10 years, patients who primarily received metformin had a **39%** reduction in the risk of heart attack and a **36%** reduction of death from any cause.[52] The same study showed that metformin did not cause weight gain in overweight patients, while patients prescribed sulfonylureas gained *more than 7 pounds*, and those using insulin injections gained *over 10 pounds*.[53]

For the multi-decade period Americans were denied access to **metformin**, doctors felt they had little choice but to prescribe **sulfonylurea drugs** and **insulin injections**. The needless suffering and death endured by diabetics during this "*dark age*" of American medicine is incalculable.

Why American Doctors Were Afraid of Metformin

For decades, the American medical establishment labored under an egregious misconception about the safety of metformin.

The reason was that drugs in the same class of metformin (biguanides) can cause a potentially fatal condition called **lactic acidosis**, where the body becomes overly acidic in the presence of excess lactic acid. While other biguanide drugs were withdrawn because of lactic acidosis risk, it turned out that metformin did not induce this same side effect in healthier people.[54] As long as one has sufficient kidney, liver, cardiac, and pulmonary function, any excess lactic acid caused by metformin is safely removed by the kidneys.[55-57]

It turned out that only patients with severe kidney, liver, pulmonary, or cardiac impairment had to avoid metformin because of lactic acidosis concerns, and even these worries were overblown.

I'll never forget what a brilliant medical doctor personally told me after a large study came out that dispelled the myth connecting metformin with lactic acidosis. This doctor knew how effective metformin was, but was terrified of creating lactic acidosis in any of his patients. He told me something to the effect of, "*If this study showing lactic acidosis is not a risk for metformin users is true, then the multi-decade oversight that caused doctors to fear metformin represents one of the great blunders in medical history*."

The regrettable fact is that doctors in the United States were taught to avoid drugs in the class of metformin, even

though metformin itself was being safely used throughout the world. If only the medical establishment in the United States had looked across the border as close as Canada, they would have seen metformin being liberally prescribed with nowhere near the incidences of lactic acidosis they feared.

In the early years, when I was taking metformin for anti-aging purposes, most doctors warned me about lactic acidosis risk. I always asked where in the scientific literature does it show a healthy person is at risk for lactic acidosis when taking metformin? They could never cite a reference, so I continued taking my metformin.

ANALYSIS SHOWS METFORMIN DOES NOT CAUSE LACTIC ACIDOSIS

A Cochrane Systematic Review of over *300 trials* evaluated the incidence of lactic acidosis among patients prescribed metformin vs. non-metformin anti-diabetes medications. Of 100,000 people, the incidence of lactic acidosis was **4.3** cases in the metformin group and **5.4** cases in the non-metformin group. The authors concluded that metformin is not associated with an increased risk for lactic acidosis.[58]

How Metformin Functions

Metformin reduces blood glucose levels primarily by suppressing glucose formation in the liver (hepatic **gluconeogenesis**).[59]

More importantly, it activates an enzyme called **AMPK** (*AMP-activated protein kinase*) that plays an important role in insulin signaling, systemic energy balance, and the metabolism of glucose and fats.[60]

Activation of AMPK is one mechanism that may explain why diabetics prescribed metformin have sharply lower cancer rates. For instance, in a controlled study at MD Anderson Cancer Center, the risk of **pancreatic cancer** was **62% lower** in diabetics who had taken metformin compared to those who had never taken it.[61] Diabetics suffer sharply higher incidences of pancreatic cancer than non-diabetics.[61]

Your Nutrients "May" Work As Well As Metformin

Virtually every Life Extension® member takes **curcumin** on a daily basis.

Curcumin activates the same **AMPK** enzyme at a rate that may be higher than **metformin**. Curcumin also increases insulin sensitivity while reducing expression of glucose-producing genes.[80]

Coffee rich in **chlorogenic acid** or **green coffee extract supplements** have demonstrated a profound reduction in **gluconeogenesis**—with a corresponding decrease in post-meal glucose elevations.[81-83]

We know that suppression of gluconeogenesis, enhanced insulin sensitivity, and activation of AMPK are some of the mechanisms behind metformin's broad-spectrum benefits.

It is not possible at this time, however, to know for sure if aging humans can derive identical benefits from nutrients like **curcumin** and **chlorogenic acid** as are provided by **metformin**.

With my understanding of the beneficial mechanisms of **curcumin** and **chlorogenic acid**, I personally take these nutrients *plus* a high dose **(850 mg)** of **metformin** two to three times a day.

HOW METFORMIN MAY INCREASE HEART ATTACK RISK

Metformin reduces **triglycerides**,[62-64] **glucose**,[32,65,66] **insulin**,[67-69] and **hemoglobin A1C** (a marker of long term glucose control).[32,70] These blood markers are all proven heart attack risk factors. Yet not all studies show metformin reduces heart attack incidence.

One study found that when metformin was added to a group of non-overweight patients taking **sulfonylurea drugs**, there was a significant increase in overall mortality.[71] This suggests that metformin should not be combined with sulfonylureas.

Furthermore, not all studies show that metformin reduces cardiovascular risk or

improves overall survival in type II diabetic patients. There are several reasons to explain these discrepancies.

Metformin is known to cause **vitamin B12 deficiency** which translates into higher levels of artery-clogging **homocysteine**.[72-74] The tiny amount of vitamin B12 and other B-vitamins found in commercial supplements is not always sufficient to offset this problem. Those who take metformin should ensure they are taking higher doses of B-vitamins (at least **300 mcg of vitamin B12**) and check their homocysteine levels to make sure it stays in the safer ranges.[75] One study showed that the addition of **5,000 mcg** of folic acid to patients taking metformin reduced their homocysteine from **15.1 µmol/L** to **12.1 µmol/L**.[76] Optimal homocysteine levels are probably under **8 µmol/L**, but any reduction is helpful. Sadly, most diabetics prescribed metformin don't check their homocysteine levels and don't take enough B-vitamins to prevent a deficiency.

Some studies show that metformin reduces **free testosterone** and **total testosterone** levels in men.[77] Testosterone is especially important in male diabetics as it significantly enhances insulin sensitivity.[78] Life Extension has previously published clinical data showing the critical importance of diabetic men to maintain youthful testosterone levels in order to improve glucose utilization.[79]

The greatest challenge in evaluating clinical data on metformin is that it is often prescribed to debilitated patients who have undergone severe arterial attack for many decades. These diabetic patients are at significant risk of cardiovascular disease from a number of underlying causes. They need to take aggressive steps to correct all independent risk factors for vascular disease, something that is never done in clinical studies.

Politicians Overlook Most Important Issue

Billions of dollars are being spent on campaign ads by politicians. Most of the issues raised will not directly affect you in a meaningful way.

Overlooked is a problem that will affect every one of us—the suffocating impact of **antiquated legislation** on medical progress.

Once you or a family member is diagnosed with a disease like **pancreatic cancer**, campaign ads become background clutter. Your only concern is finding a therapy that offers some hope of survival.

The best our current archaic system offers for **pancreatic cancer** is a drug called **gemcitabine**. Compared to another chemo drug, gemcitabine increased average survival by a meager **36 days**, which conventional doctors described as a "significant improvement."[91]

A team of researchers was able to improve on gemcitabine by using instead a toxic combination of chemotherapy drugs (called FOLFIRINOX). Compared to the gemcitabine group, patients able to tolerate the debilitating side effects of FOLFIRINOX lived **4.3 months longer** than the gemcitabine group, but suffered greater toxicity.[92,93]

The fact that pancreatic cancer still quickly kills virtually everyone who contracts it is a stark example of how today's regulatory system *stifles* innovation. Unregulated environments have produced technologies like hand-held computers that perform miraculously and are affordable to mostly everyone. *Life Extension*® for years has provided hard-core scientific documentation about the **anti-cancer** properties of **metformin**. Yet unless the current political/legal *stranglehold* over medical innovation is lifted, the only cancer patients likely to benefit from metformin will be Foundation members who insist their doctors prescribe it.

Recall that metformin was discovered **90 years ago**, yet conventional doctors are still failing to use it in the prevention and treatment of a host of age-related disorders.

SHOULD YOU ASK YOUR DOCTOR ABOUT METFORMIN?

Metformin is a synthetic compound available in low cost generic form. Some members tell me their health insurance plans cover almost **100%** of the cost. Even out of pocket, metformin is remarkably inexpensive.

The challenge some members find is persuading their doctors to prescribe metformin if they are not diabetic. You may recall the many articles we have published showing that any elevation of **fasting glucose** above **85 mg/dL** increases ones risk for contracting classic diabetic

complications like heart attack and stroke.[84-90]

Therefore, those whose glucose levels exceed **85 mg/dL** should consider metformin for its glucose-lowering properties alone, though **chlorogenic acid**-standardized coffee extracts may accomplish a similar effect.

No one should take metformin without having a complete battery of blood tests to show their doctor that it is not contraindicated because of disorders like kidney failure. Those with low blood sugar (hypoglycemia) may not be able to use metformin.

A suggested starting dose of metformin is **250 mg** before a large meal. The dose may be increased after a week to **250 mg** before three meals a day. After a month, you may consider increasing to **500 mg** before meals and eventually go up to **850 mg** before meals, which is the upper limit dose.

If you notice a slight reduction in appetite, use it to cut back on your calorie intake and hopefully shed some fat pounds. By stabilizing blood sugar and insulin levels, metformin can help reduce food cravings.

The Political/Legal System Must Be Changed

Human clinical research has long been oppressed in the United States by a variety of laws that conspire to deny medical progress.

The few new therapies that are approved are mediocre, expensive, and often laden with side effects. The current system represents the worst of all worlds when it comes to the kind of scientific advances that aging people need to significantly extend their healthy life spans.

Your support of **Life Extension**® enables us to continue our relentless campaign to tear down the strangleholds erected by public and private institutions.

The **37-year delay** in approving metformin provides a real world example of how broken our **political/legal systems** are when it comes to finding cures for degenerative disease and the aging process itself.

What You Can Do To Stop Needless Suffering and Death

Scientists have identified novel ways of treating cancer and other illnesses, but too little of this new technology is being used in clinical practice. When new discoveries are made, drug companies spend years seeking a patent, and then more years carrying it through the cumbersome bureaucratic approval process. A major reason so many cancer patients die today is an antiquated regulatory system that causes effective therapies to be delayed (or suppressed altogether).

This system must be changed, if the 1,500 American cancer patients who perish each day are to have a realistic chance of being saved. Our long-standing proposal has been to change the law so that anyone can opt out of the FDA's umbrella of "protection." This approach will allow companies to sell drugs that have demonstrated safety and a reasonable likelihood of effectiveness, which are clearly labeled "**Not Approved by the FDA.**" Patients who wish can still use only FDA-approved drugs, while those willing to take a risk, in consultation with their doctors, will be allowed to try drugs shown to be safe that are still not approved.

We believe that this initiative will result in a renaissance in the practice of medicine similar to the computer technology revolution of the past four decades. In this environment, many lethal diseases will succumb to cures that are less expensive than is presently the case. And greater competition will help eliminate the health care cost crisis that exists today.

Seriously ill people, in consultation with their doctors, should be able to make up their own minds about what drugs they are willing to try.

This is the time when political leaders will at least listen to their constituent's concerns. I encourage each of you to log on to our legislative action website at **www.lifeextension.com/lac** to easily email your representative and two senators a letter demanding they enact legislation that will enable those with serious illness to obtain therapies far enough along in the clinical trials process to be deemed safe, but not yet approved by the FDA.

Take Action Now!

For longer life,

William Faloon

Tell Congress to Change the Law!

There are millions of cancer patients alive right now who face possible or probable death in the next twelve months. If you add their family members and friends, there are tens of millions of Americans who should be outraged by an outdated regulatory system that bans access to potentially life-saving therapies.

The FDA continues to suppress innovative therapies because the public has failed to demand that our elected officials rein in the FDA's arbitrary authority. The first step in changing today's outmoded system is for those who understand the magnitude of this problem to communicate the urgent need for change to Congress.

Those concerned about this serious issue should log on to **www.lifeextension.com/lac** to insist that their Representative and two Senators help enact legislation that will enable cancer patients to obtain therapies far enough along in the clinical trials process to be deemed safe, but not yet approved by the FDA.

Take Action Now!

Those without computer access can photocopy the next page and mail it to their Representative at The US House of Representatives, Washington, DC, 20515 and two Senators at The US Senate, Washington, DC, 20510. We also ask that you phone your Congressional members at 1-202-224-3121 to let them know how disgusted you are that doctors and patients are not allowed to choose drugs that may be effective against an often fatal disease.

The Honorable:

I am writing to ask that you sponsor or co-sponsor legislation to enable cancer patients (and those with other serious diseases) to purchase medications while they are pending final approval by the FDA. This approach will allow companies to sell novel drugs with a label clearly stating that they are "Not Approved by the FDA."

Consumers who wish to rely on the FDA can limit their choices to fully approved drugs only, while those willing to take a risk (in consultation with their doctors) will be allowed to try what they choose. (Companies that make fraudulent claims for products can be prosecuted under the laws that exist today.)

This initiative can result in a renaissance in the practice of medicine, similar to the computer technology revolution that has occurred over the past three decades. In this environment free of regulatory burden, many inexpensive cures will very likely be found for lethal diseases. And greater competition will help eliminate the health care cost crisis that exists today.

I am tired of reading about medical breakthroughs, only to be told that I will have to wait years before the therapy might become available. As 1,500 Americans die of cancer each day, I consider the introduction and passage of such a law an extremely high priority.

Seriously ill people have the fundamental right to make up their own minds about what drugs they are allowed to try, in consultation with their physicians. Please let me know that you will sponsor or co-sponsor such legislation, which will provide us with quicker access to drugs that the FDA has found safe and potentially effective, but have not yet received final approval.

Sincerely,

Name:

Address:

City:

ST:

Zip:

References

1. Available at: http://onlinelibrary.wiley.com/doi/10.1111/j.1464-5491.2011.03469.x/pdf. Accessed August 2, 2012.

2. Available at: https://www.lifeextension.com/magazine. Accessed May 11, 2012.

3. Available at: http://www.cnn.com/2012/04/05/health/diabetes-drug-fights-cancer. Accessed May 11, 2012.

4. Castillo JJ, Mull N, Reagan JL, Nemr S, Mitri J. Increased incidence of non-Hodgkin lymphoma, leukemia, and myeloma in patients with diabetes mellitus type 2: a meta-analysis of observational studies. *Blood*. 2012 May 24;119(21):4845-50.

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

6. Michels KB, Solomon CG, Hu FB, et al. Type II diabetes and subsequent incidence of breast cancer in the Nurses' Health Study. *Diabetes Care*. 2003 Jun;26(6):1752-8.

7. Aschebrook-Kilfoy B, Sabra MM, Brenner A, et al. Diabetes and thyroid cancer risk in the National Institutes of Health-AARP Diet and Health Study. *Thyroid*. 2011 Sep;21(9):957-63.

8. Haffner SM, Miettinen H. Insulin resistance implications for type II diabetes mellitus and coronary heart disease. *Am J Med*. 1997 Aug;103(2):152-62.

9. Mazzone T, Chait A, Plutzky J. Cardiovascular disease risk in type 2 diabetes mellitus: insights from mechanistic studies. *Lancet*. 2008 May 24;371(9626):1800-9.

10. Alexander CM, Landsman PB, Teutsch SM, Haffner SM. Third National Health and Nutrition Examination Survey (NHANES III); National Cholesterol Education Program (NCEP). NCEP-defined metabolic syndrome, diabetes, and prevalence of coronary heart disease among NHANES III participants age 50 years and older. *Diabetes*. 2003 May;52(5): 1210-4.

11. Schurgin S, Rich S, Mazzone T. Increased prevalence of significant coronary artery calcification in patients with diabetes. *Diabetes Care*. 2001 Feb;24(2):335-8.

12. Libby G, Donnelly LA, Donnan PT, Alessi DR, Morris AD, Evans JM. New users of metformin are at low risk of incident cancer: a cohort study among people with type 2 diabetes. *Diabetes Care*. 2009 Sep;32(9):1620-5.

13. Romero IL, McCormick A, McEwen KA, et al. Relationship of type II diabetes and metformin use to ovarian cancer progression, survival, and chemosensitivity. *Obstet Gynecol*. 2012 Jan;119(1):61-7.

14. Li D, Yeung SC, Hassan MM, Konopleva M, Abbruzzese JL. Antidiabetic therapies affect risk of pancreatic cancer. *Gastroenterology*. 2009 Aug;137(2):482-8.

15. Wang LW, Li ZS, Zou DW, Jin ZD, Gao J, Xu GM. Metformin induces apoptosis of pancreatic cancer cells. *World J Gastroenterol*. 2008 Dec 21;14(47):7192-8.

16. Wright JL, Stanford JL. Metformin use and prostate cancer in Caucasian men: results from a population-based case-control study. *Cancer Causes Control*. 2009 Nov;20(9):1617-22.

17. Bodmer M, Meier C, Krahenbuhl S, Jick SS, Meier CR. Long-term metformin use is associated with decreased risk of breast cancer. *Diabetes Care*. 2010 Jun;33(6):1304-8.

18. Cantrell LA, Zhou C, Mendivil A, Malloy KM, Gehrig PA, Bae-Jump VL. Metformin is a potent inhibitor of endometrial cancer cell proliferation–implications for a novel treatment strategy. *Gynecol Oncol*. 2010 Jan;116(1):92-8.

19. Hirsch HA, Iliopoulos D, Tsichlis PN, Struhl K. Metformin selectively targets cancer stem cells, and acts together with chemotherapy to block tumor growth and prolong remission. *Cancer Res*. 2009 Oct 1;69(19):7507-11.

20. Anisimov VN, Egormin PA, Piskunova TS, et al. Metformin extends life span of HER-2/neu transgenic mice and in combination with melatonin inhibits growth of transplantable tumors in vivo. *Cell Cycle*. 2010 Jan 1;9(1):188-97.

21. Evans JM, Donnelly LA, Emslie-Smith AM, Alessi DR, Morris AD. Metformin and reduced risk of cancer in diabetic patients. *BMJ*. 2005 Jun 4;330(7503):1304-5.

22. Hosono K, Endo H, Takahashi H, et al. Metformin suppresses colorectal aberrant crypt foci in a short-term clinical trial. *Cancer Prev Res (Phila)*. 2010 Sep;3(9):1077-83.

23. Onitilo AA, Engel JM, Glurich I, Stankowski RV, Williams GM, Doi SA. Diabetes and cancer II: role of diabetes medications and influence of shared risk factors. *Cancer Causes Control*. 2012 Jul;23(7):991-1008. Epub 2012 Apr 25.

24. Memmott RM, Mercado JR, Maier CR, Kawabata S, Fox SD, Dennis PA. Metformin prevents tobacco carcinogen--induced lung tumorigenesis. *Cancer Prev Res (Phila)*. 2010 Sep;3(9):1066-76.

25. Nagi DK, Yudkin JS. Effects of metformin on insulin resistance, risk factors for cardiovascular disease, and plasminogen activator inhibitor in NIDDM subjects. A study of two ethnic groups. *Diabetes Care*. 1993 16(4):621-29.

26. Evans JM, Ogston SA, Emslie-Smith A, Morris AD. Risk of mortality and adverse cardiovascular outcomes in type 2 diabetes: a comparison of patients treated with sulfonylureas and metformin. *Diabetologia*. 2006 May;49(5):930-6.

27. Brame L, Verma S, Anderson T, Lteif A, Mather K. Insulin resistance as a therapeutic target for improved endothelial function: metformin. *Curr Drug Targets Cardiovasc Haematol Disord*. 2004 Mar;4(1):53-63.

28. Available at: **http://www.idb.hr/diabetologia/10no3-2.pdf**. Accessed August 2, 2012.

29. Hundal RS, Krssak M, Dufour S, et al. Mechanism by which metformin reduces glucose production in type 2 diabetes. *Diabetes*. 2000 Dec;49(12):2063-9.

30. Moon RJ. The addition of metformin in type 1 diabetes improves insulin sensitivity, diabetic control, body composition and patient well-being. *Diabetes Obes Metab*. 2007 Jan;9(1):143-5.

31. Wong AK, Symon R, Alzadjali MA, et al. The effect of metformin on insulin resistance and exercise parameters in patients with heart failure. *Eur J Heart Fail*. 2012 Jun 27. [Epub ahead of print]

32. Boyda HN, Procyshyn RM, Tse L, et al. Differential effects of 3 classes of antidiabetic drugs on olanzapine-induced glucose dysregulation and insulin resistance in female rats. *J Psychiatry Neurosci*. 2012 May 28;37(4):110140. doi: 10.1503/jpn.110140. [Epub ahead of print]

33. Campagnoli C, Pasanisi P, Abbà C, et al. Effect of different doses of metformin on serum testosterone and insulin in non-diabetic women with breast cancer: a randomized study. *Clin Breast Cancer*. 2012 Jun;12(3):175-82.

34. Cersosimo E, DeFronzo RA. Insulin resistance and endothelial dysfunction: the road map to cardiovascular diseases. *Diabetes Metab Res Rev*. 2006 Nov-Dec;22(6):423-36.

35. Eschwège E. The dysmetabolic syndrome, insulin resistance and increased cardiovascular (CV) morbidity and mortality in type 2 diabetes: aetiological factors in the development of CV complications. *Diabetes Metab*. 2003 Sep;29(4 Pt 2):6S19-27.

36. Osei K. Insulin resistance and systemic hypertension. *Am J Cardiol*. 1999 Jul 8;84(1A):33J-36J.

37. Tran TT, Medline A, Bruce WR. Insulin promotion of colon tumors in rats. *Cancer Epidemiol Biomarkers Prev*. 1996 Dec;5(12):1013-5.

38. Parekh N, Lin Y, Hayes RB, Albu JB, Lu-Yao GL. Longitudinal associations of blood markers of insulin and glucose metabolism and cancer mortality in the T hird National Health and Nutrition Examination Survey. *Cancer Causes Control*. 2010 Apr;21(4):631-42.

39. Otani T, Iwasaki M, Sasazuki S, Inoue M, Tsugane S; Japan Public Health Center-based Prospective Study Group. Plasma C-peptide, insulin-like growth factor-I, insulin-like growth factor binding proteins and risk of colorectal cancer in a nested case-control study: the Japan public health center-based prospective study. *Int J Cancer*. 2007 May 1;120(9):2007-12.

40. Ma J, Li H, Giovannucci E, et al. Prediagnostic body-mass index, plasma C-peptide concentration, and prostate

cancer-specific mortality in men with prostate cancer: a long-term survival analysis. *Lancet Oncol*. 2008 Nov;9(11):1039-47.

41. Hirose K, Toyama T, Iwata H, Takezaki T, Hamajima N, Tajima K. Insulin, insulin-like growth factor-I and breast cancer risk in Japanese women. *Asian Pac J Cancer Prev*. 2003 Jul-Sep;4(3):239-46.

42. Sigal RJ, El-Hashimy M, Martin BC, Soeldner JS, Krolewski AS, Warram JH. Acute postchallenge hyperinsulinemia predicts weight gain: a prospective study. *Diabetes*. 1997 Jun;46(6):1025-9.

43. Russell-Jones D, Khan R. Insulin-associated weight gain in diabetes--causes, effects and coping strategies. *Diabetes Obes Metab*. 2007 Nov;9(6):799-812.

44. Johnson MS, Figueroa-Colon R, Huang TT, Dwyer JH, Goran MI. Longitudinal changes in body fat in African-American and caucasian children: influence of fasting insulin and insulin sensitivity. *J Clin Endocrinol Metab*. 2001 Jul;86(7):3182-7.

45. Bowker SL, Majumdar SR, Veugelers P, Johnson JA. Increased cancer-related mortality for patients with type 2 diabetes who use sulfonylureas or insulin. *Diabetes Care* 2006 Feb;29(2):254-8.

46. Kaaks R. Plasma insulin, IGF-I and breast cancer. *Gynecol Obstet Fertil*. 2001 Mar;29(3):185-91.

47. 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.

48. Hegele RA. Premature atherosclerosis associated with monogenic insulin resistance. *Circulation*. 2001 May 8;103(18):2225-9.

49. Chu N, Spiegelman D, Hotamisligil GS, Rifai N, Stampler M, Rimm EB. Plasma insulin, leptin, and soluble TNF receptors levels in relation to obesity-related atherogenic and thrombogenic cardiovascular disease risk factors among men. *Atherosclerosis*. 2001 Aug;157(2):495-503.

50. Lichtenstein MJ, Yarnell JW, Elwood PC, et al. Sex hormones, insulin, lipids, and prevalent ischemic heart disease. *Am J Epidemiol*. 1987 Oct;126(4):647-57.

51. Dekker JM, Girman C, Rhodes T, et al. Metabolic syndrome and 10-year cardio-vascular disease risk in the Hoorn Study. *Circulation*. 2005 Aug 2;112(5):666-73.

52. Available at: **http://www.nejm.org/doi/full/10.1056/nejmoa0806470#t=article**. Accessed July 11, 2012.

53. Available at: **http://www.bmj.com/content/310/6972/83.full**. Accessed July 11, 2012.

54. Available at: **http://www.medscape.com/viewarticle/714920**. Accessed July 11, 2012.

55. Klow NE, Draganov B, Os I. Metformin and contrast media-increased risk of lactic acidosis. *Tidsskr Nor Laegeforen*. 2001 Jun 10;121(15):1829.

56. Brown JB, Pedula K, Barzilay J, Herson MK, Latare P. Lactic acidosis rates in typeII diabetes. *Diabetes Care*. 1998 Oct;21(10):1659- 63.

57. Misbin RI. The phantom of lactic acidosis due to metformin in patients with diabetes. *Diabetes Care*. 2004 Jul;27(7): 1791-3.

58. Salpeter S, Greyber E, Pasternak G, Salpeter E. Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus. *Cochrane Database Syst Rev*. 2010 Apr 14;(4):CD002967.

59. Kirpichnikov D, McFarlane SI, Sowers JR. Metformin: an update. *Ann Intern Med*. 2002 137(1):25–33.

60. Towler MC, Hardie DG. AMP-activated protein kinase in metabolic control and insulin signaling. *Circ Res*. 2007 100(3):328–41.

61. Li D, Yeung SC, Hassan MM, Konopleva M, Abbruzzese JL. Antidiabetic therapies affect risk of pancreatic cancer. *Gastroenterology*. 2009 Aug;137(2):482-8.

62. Emral R, Köseoğlulari O, Tonyukuk V, Uysal AR, Kamel N, Corapçioğlu D. The effect of short-term glycemic regulation with gliclazide and metformin on postprandial lipemia. *Exp Clin Endocrinol Diabetes*. 2005 Feb;113(2):80-4.

63. Mughal MA, Jan M, Maheri WM, Memon MY, Ali M. The effect of metformin on glycemic control, serum lipids and lipoproteins in diet alone and sulfonylurea-treated type 2 diabetic patients with sub-optimal metabolic control. *J Pak Med Assoc*. 2000 Nov;50(11):381-6.

64. Lund SS, Tarnow L, Frandsen M, et al. Impact of metformin versus the prandial insulin secretagogue, repaglinide, on fasting and postprandial glucose and lipid responses in non-obese patients with type 2 diabetes. *Eur J Endocrinol*. 2008 Jan;158(1):35-46.

65. Hundal RS, Krssak M, Dufour S, et al. Mechanism by which metformin reduces glucose production in type 2 diabetes. *Diabetes*. 2000 Dec;49(12):2063-9

66. Bjørnholt 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.

67. Goodwin PJ, Pritchard KI, Ennis M, Clemons M, Graham M, Fantus IG. Insulin-lowering effects of metformin in women with early breast cancer. *Clin Breast Cancer*. 2008 Dec;8(6):501-5.

68. Velazquez EM, Mendosa S, Hamer T, Sosa F, Glucck CJ. Metformin therapy in women with polycystic ovary syndrome reduces hyperinsulinemia, insulin resistance, hyperandrogenemia, and systolic blood pressure, while facilitating menstrual regularity and pregnancy. *Metabolism*. 1994 May;43(5):647-54.

69. MB Davidson, AL Peters. An overview of metformin in the treatment of type 2 diabetes mellitus. *Am J Med*. 1997Jan;102(1):99-110.

70. Avilés-Santa L, Sinding J, Raskin P. Effects of metformin in patients with poorly controlled, insulin-treated type 2 diabetes mellitus. A randomized, double-blind, placebo-controlled trial. *Ann Intern Med*. 1999 Aug 3;131(3):182-8.

71. Olsson J, Lindberg G, Gottsäter M, et al. Increased mortality in Type II diabetic patients using sulphonylurea and metformin in combination: a population-based observational study. *Diabetologia*. 2000 May;43(5):558-60.

72. Mazokopakis EE, Starakis IK. Recommendations for diagnosis and management of metformin-induced vitamin B12 (Cbl)deficiency. *Diabetes Res Clin Pract*. 2012 Jul 7. [Epub ahead of print]

73. Carlsen SM, Følling I, Grill V, Bjerve KS, Schneede J, Refsum H. Metformin increases total serum homocysteine levels in non-diabetic male patients with coronary heart disease. *Scand J Clin Lab Invest*. 1997 Oct;57(6):521-7.

74. de Jager J, Kooy A, Lehert P, et al. Long term treatment with metformin in patients with type 2 diabetes and risk of vitamin B-12 deficiency: randomised placebo controlled trial. *BMJ*. 2010 May 20;340:c2181. doi: 10.1136/bmj.c2181.

75. Langan RC, Zawistoski KJ. Update on vitamin B12 deficiency. *Am Fam Physician*. 2011 Jun 15;83(12):1425-30.

76. Aghamohammadi V, Gargari BP, Aliasgharzadeh A. Effect of folic acid supplementation on homocysteine, serum total antioxidant capacity, and malondialdehyde in patients with type 2 diabetes mellitus. *J Am Coll Nutr*. 2011 Jun;30(3):210-5.

77. Ozata M, Oktenli C, Bingol N, Ozdemir IC. The effects of metformin and diet on plasma testosterone and leptin levels in obese men. *Obes Res*. 2001 Nov;9(11):662-7.

78. Grossmann M, Thomas MC, Panagiotopoulos S, et al. Low testosterone levels are common and associated with insulin resistance in men with diabetes. *J Clin Endocrinol Metab*. 2008 May;93(5): 1834-40.

79. Available at: **https://www.lifeextension.com/magazine**. Accessed July 9, 2012.

80. Kim T, Davis J, Zhang AJ, He X, Mathews ST. Curcumin activates AMPK and suppresses gluconeogenic gene expression in hepatoma cells. *Biochem Biophys Res Commun*. 2009 Oct 16;388(2):377-82.

81. 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.

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

83. 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.

84. Available at: https://www.lifeextension.com/magazine/mag2012/feb2012_Doctors-Overlook-Leading-Cause-Premature-Death_01.htm. Accessed July 11,2012.

85. Available at: https://www.lifeextension.com/magazine/mag2012/feb2012_Suppress-Deadly-After-Meal-Blood-Sugar-Surges_01.htm. Accessed July 11, 2012.

86. Available at: https://www.lifeextension.com/magazine/mag2011/ss2011_Are-We-All-Pre-Diabetic_01.htm. Accessed July 11, 2012.

87. Available at: https://www.lifeextension.com/magazine/mag2011/ss2011_Effective-Approaches-to-Blunt-Blood-Sugar-Surges_01.htm. Accessed July 11, 2012.

88. Available at: https://www.lifeextension.com/magazine/mag2011/jan2011_Glucose-The-Silent-Killer_01.htm. Accessed July 11, 2012.

89. Available at: https://www.lifeextension.com/magazine/mag2010/ss2010_Protect-Your-Body-from-a-Silent-Killer_01.htm. Accessed July 11, 2012.

90. Available at: https://www.lifeextension.com/magazine. Accessed July 11, 2012.

91. Burris HA III, Moore MJ, Andersen J, et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. *J Clin Oncol*. 1997 Jun;15(6):2403-13.

92. Conroy T, Desseigne F, Ychou M, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N Engl J Med*. 2011 May 12;364(19):1817-25.

93. Lowery MA, O'Reilly EM. Genomics and pharmacogenomics of pancreatic adenocarcinoma. *Pharmacogenomics J*. 2012 Feb;12(1):1-9.

LAB
TESTS

From basic health panels to genetic testing

Learn More ❯

WELLNESS
SPECIALISTS

1-800-226-2370 - **This service is FREE**

7:30 AM - 12 AM (ET) Mon-Fri | 9 AM - 12 AM (ET) Sat-Sun

Learn More ❯

ADVERTISE
IN THE MAGAZINE

Spread the word to Life Extension® customers

Learn More ❯

More Info ⌄

Company ⌄

Resources ⌄

☑☒ **Your Privacy Choices**