METFORMIN, VITAMIN B12, PROLACTIN)

From

http://www.lifeextension.com/protocols/cancer/prostate-cancer-prevention/page-01

Metformin was used in England in 1958 but did not make it into the United States until 1995—37 years later (Dowling 2011)! I am familiar with metformin because the FDA tried to have me incarcerated for recommending it as an anti-aging drug long before it was "approved" to treat type II diabetes.

What's been happening over the last ten years is an explosion of published studies that consistently show that metformin reduces the risks of certain tumors and may be an effective cancer treatment (Hirsch 2009; Anisimov 2005; Vazquez-Martin 2011; Tomimoto 2008; Gotlieb 2008; Cantrell 2010; Libby 2009; Memmott 2010).

People ask me all the time, how can an anti-diabetic drug work so well against cancer? The encouraging news is that metformin functions via multiple mechanisms to create a less favorable environment for tumor progression (Evans 2005; Currie 2009; Nagi 1993; Choi 2013; Luo 2010; Ben Sahra 2011; Loubière 2013; Zakikhani 2008; Ben Sahara 2008; Ersoy 2008). We know that insulin (and glucose) increase the risk of many tumors (Parekh 2013). This is of particular concern to obese men with prostate tumors. Metformin lowers blood glucose and insulin levels. The sidebar titled "Anti-Cancer Actions of Metformin" reveals the multiple anti-cancer mechanism of metformin.

There are nutrients that can have similar effects such as standardized green coffee extract (Ong 2013). We nonetheless suggest that a man with an elevated or rising PSA should ask his doctor to consider prescribing metformin. The starting dose can be 500 mg of extended release (Metformin ER) taken with breakfast each day. Under the supervision of the patient's local medical doctor, the dose can be increased to 500 mg ER taken at breakfast and at dinner. (Dose ranges for non-extended release metformin are 250-850 mg taken before no more than three meals a day.) Metformin is an inexpensive generic drug and can be taken along with nutrients (like green coffee extract) that similarly function to reduce glucose/insulin.

Metformin does more than slash tumor-promoting glucose/insulin levels. It also acts directly on cancer cells to induce apoptosis and/or inhibit proliferation (Jalving 2010). Metformin does this conserving the process by which food is converted to energy (Choi 2013; Luo 2010; Ben Sahra 2011; Loubière 2013). Healthy cells react to metformin by adjusting their functions to use less energy. A cancer cell, on the other hand, that is forced to minimize energy consumption is less able to exhibit aggressive metastatic or proliferative behavior (Dunlap 2012). In other scenarios, the energy stress caused by metformin is sufficient to cause cancer cell death.

The National Cancer Institute is sponsoring a clinical study where metformin will be tested to see if it can slow the progression of prostate cancer in men undergoing active surveillance (watchful waiting) with low-grade tumors (Fleshner 2013). We hope the study design includes the measurement of 2-hour post-prandial (2 hours after meals) blood glucose levels as well as glycosylated hemoglobin (HbA1c) to ascertain that optimal dosing of study subjects has been achieved.

Anti-Cancer Actions of Metformin

Numerous studies show the anti-diabetic drug metformin can slow growth of existing cancers and decrease risk of developing new cancers. Some studies show metformin may protect against prostate cancer and aid in treatment. Here are some of its anti-cancer mechanisms:

Metformin reduces levels of glucose, insulin, and insulin-like growth factors that fuel tumor growth (Evans 2005; Currie 2009; Nagi 1993; Choi 2013).

Metformin activates a powerful molecule called AMPK (adenosine monophosphate-activated protein kinase) that subjects cancer cells to unique metabolic stresses not experienced by healthy tissues. (Activated AMPK promotes death [apoptosis] of malignant cells and prevents their development.) (Choi 2013; Luo 2010)

Metformin independently inhibits mTOR (mammalian target of rapamycin) that regulates cell growth, energy metabolism, cell motility, cell survival, and protein synthesis (Ben Sahra 2011; Loubière 2013).

Metformin mimics the benefits of a hormone called adiponectin in activating AMPK-dependent growth inhibition in prostate cancer cells (Zakikhani 2008).

Metformin blocks cancer cell reproductive cycles by decreasing levels of a growth-promoting protein called cyclin D1 (Ben Sahra 2008).

Metformin increases production of a protein (p27) that inhibits the cell division cycle (Ben Sahra 2008).

Metformin suppresses vascular endothelial growth factor (VEGF) thereby cutting off the blood supply to tumors (Ersoy 2008).

At a cancer conference in early 2013, the results of a study were reported of 22 men (median age 64, median PSA 6 ng/mL) with confirmed prostate cancer that were given 500 mg of metformin three times a day 41 days prior to surgery (prostatectomy). In response to metformin the men showed the expected reductions in glucose and insulin growth factor-1 (IGF-1) blood levels, along with abdominal fat loss (Joshua 2012). What got the researchers excited was that compared to biopsied specimens, the surgically removed prostate glands showed a 32% reduction in a marker of cell proliferation (Ki-67) and a favorable alteration in a pathway tumor cells use to proliferate out of control (via mTOR) (Carlson 2012).

Knowledgeable customers point out that curcumin interferes with these tumor growth pathways via similar mechanisms, which we at Life Extension have long been familiar with (Ravindran 2009). My argument for recommending metformin is that it should produce potent additive effects to curcumin. Moreover, we still don't know what the upper dose limits are for metformin and/or curcumin for cancer treatment, so taking both may have some obvious advantages.

Furthermore, because metformin is a drug, it tends to get more attention from researchers, perhaps because it is easier to obtain funding for drug studies. A European study published this year showed that metformin was effective against advanced castration-resistant prostate cancer. The doctors who conducted this study concluded:

To our knowledge, our results are the first clinical data to indicate that metformin use may improve PSA-recurrence free survival, distant metastasis-free survival, prostate cancer specific mortality, overall survival and reduce the development of castration resistant prostate cancer in prostate cancer patients. Further validation of metformin's potential benefits is warranted (Spratt 2013).

Interestingly, men who are on androgen deprivation therapy to treat prostate cancer often show rising insulin levels that can stimulate tumor growth (Currie 2009;

Hvid 2013). By taking metformin, some of the side effects of androgen deprivation therapy can be mitigated, as was shown in this newly published European study.

So while nutrients like curcumin and green coffee extract and others may share functions that are similar to metformin, we cannot ignore the strong data showing specific benefits to low-cost metformin.

Important to be aware when prescribed Metformin:

Metformin can cause thyroid as well as Vitamin B12 issues. Rather than stop Metformin for prostate cancer issues, I would see it more important that while taking Metformin the patient have regular Vitamin B12 level and Thyroid Hormone level regularly checked.

Should Vitamin B12 level be found below appropriate range (anywhere between 200 to 900 pg/ml - and general consensus is values less than 200 pg/mL constitute a B12 deficiency) 500 to 1000mcg, Vitamin B12 should be supplemented daily and periodicaly have the level re-checked while on Metformin.

The range for TSH (Thyroid-stimulating hormone) is from approximately 0.5 to 4.5/5.0. If found below or at low range, it would be advisable to get an appointment with an endocrinologist to prescribe appropriate medication with the TSH level re-checked periodically.

http://tinyurl.com/jh5ckso

PROLACTIN

Another hormone that prostate tumors use to escape eradication is prolactin (Dagvadorj 2007), and this can easily be suppressed by taking 0.25 mg to 0.5 mg of cabergoline (Dosintex®) two to three times weekly (Drugs.com 2013). MY NOTE: Level should be under 5.0ng/ml. See: http://tinyurl.com/7w5omeo