GOUT AND DIET

MYTHS AND TRUTHS ABOUT GOUT

WILD SALMON DELIGHT RECIPE

HEALTHY HABITS OVER MEDICATION

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GOUT AND DIET

Most of our readers are well aware of the metabolic syndrome and the five classic diseases comprising it: 1) high blood pressure, 2) type 2 diabetes, 3) coronary heart disease, 4) obesity, and 5) dyslipidemia [increased blood triglycerides, increased small dense LDL cholesterol and decreased HDL cholesterol].

An additional disease that frequently occurs in patients with the metabolic syndrome is gout. Consequently it is sometimes considered to be a disease of insulin resistance that is part of the metabolic syndrome. In this issue I will show you why gout often occurs simultaneously with the classic diseases of insulin resistance. More importantly, I will show you how and why current dietary recommendations to treat gout are largely ineffective and that a better nutritional strategy exists to ameliorate or prevent disease symptoms. This dietary strategy is supported not only by recent empirical data, but also by a long trail of evolutionary and genetic evidence which demonstrates how our genome has effectively skirted gout via certain mutations in the face of a high meat diet.

Figure 1 pretty much sums up what most people know about gout – intense pain and swelling of the big toe joint.

Gout is one of humanity’s oldest diseases on written record, having been identified by the Egyptians in 2640 BC and recognized by Hippocrates in the 5th century BC.

Originally, gout was associated with the wealthy and affluent, such that it has been called a “disease of kings and king of diseases.” Throughout recorded history, gout has rubbed shoulders with the rich and famous, affecting kings (Alexander the Great, Charlemagne, Henry VIII), statesmen (Benjamin Franklin, Alexander Hamilton), artists (Alfred Lord Tennyson and Voltaire), and scientists (Isaac Newton, Charles Darwin, Leonardo da Vinci). Historically, the association of gout with wealth and affluence had been attributed to gluttony and excess consumption of alcohol. As is the case with many diet related diseases, there is intriguing information suggesting that gout was either unknown or rare in indigenous peoples, and as they adopted western diets, the incidence of gout rapidly increased. Gout is no longer considered to be a disease of the wealthy and affluent but rather now is a worldwide disease associated with the adoption of western diets. In the U.S. gout afflicts at least 3.4 million men.

GOUT: THE BASICS

Gout is a painful disease that can occur in any joint or tissue throughout the body but most frequently presents itself in the first metatarsal phalangeal joint of the big toe or in the ankle or knee (see Figure 3). When blood concentrations of uric acid rise too high (>7.0 mg/dl in men and >6.0 mg/dl in women) crystals of uric acid (monosodium urate) may form and settle in the joint spaces causing pain, swelling, inflammation...
and stiffness (11). Continued accumulation of uric acid crystals in a joint forms a large deposit called a tophus which can then erode and damage nearby bones.

Hence, the proximate (nearby or immediate) cause of gout is elevated blood concentrations of uric acid (hyperuricemia). This information has been known since 1859 with the publication of Alfred Garrod's book, “The Nature and Treatment of Gout and Rheumatic Gout” (4). Of more interest to you, our readers, is not necessarily the proximate cause of gout, but rather its ultimate cause. Blood concentrations of uric acid are a lot like a bank account – your account balance is determined by the difference between the amount of money you deposit and the amount you spend. Similarly blood concentrations of uric acid depend upon the difference between the uric acid entering the blood and uric acid leaving the blood. The amount of uric acid entering the blood is determined by how much uric acid is synthesized by the liver and then dumped into the bloodstream. The amount of uric acid leaving the bloodstream is determined by the rate the kidneys excrete it and to a lesser extent by its breakdown by gut bacteria. In more than 90 % of all gout patients, the disease results because they are “underexcretors” – meaning that the kidney can't get rid of blood uric acid fast enough relative to how much is being produced in the liver (11).

Let's first talk about uric acid entering the blood. Uric acid is synthesized in the liver and then enters the blood, but a key element in understanding how gout develops is knowing precisely how the liver makes uric acid. The liver synthesizes uric acid from precursor molecules called purines (GMP and AMP). Purines are the nitrogenous base pairs which form the structural cross rung molecules of both DNA and RNA. As DNA and RNA are broken down within cells, the purines then can be metabolized into uric acid by the liver and a few other tissues within the body. The liver receives purines from two sources: 1) the diet, and 2) the daily breakdown of the body's own tissues. About 2/3 of the daily purine load comes from the body's turnover of cells, while 1/3 comes from the diet (11). When the combined purine load (from both diet and turnover of the body's own cells) exceeds the kidney's ability to excrete it, blood concentrations of uric acid rise, thereby increasing the risk for gout.

The prevailing notion has been that reduction of dietary sources of purines, particularly from meats and seafood could help to ameliorate and prevent gout symptoms (3, 11, 13, 14). Table 1 lists the purine concentrations of various foods and their recommended intake for gout patients. Note that suggested low purine foods include white bread, crackers, sugars, sweets, cake, cookies, rice, cereals, ice cream and milk. As you will soon see, these very same low purine foods may not prevent gout, but may actually represent one of its primary causes. Further, the recommendation to reduce high purine foods such as fish, shellfish, meats, poultry and organ meats may be of dubious therapeutic value (11) because clinical trials of low purine diets only marginally reduce (1-2 mg/ dl) blood uric acid concentrations (15-17). Although high protein, meat based diets contain high amounts of purines and would be expected to promote gout symptoms, protein ingestion actually decreases blood uric acid levels by increasing uric acid excretion (18). This seemingly paradoxical effect occurs because the kidney increases its excretion of uric acid when faced with elevated dietary purines (19).

So, let's put 2 and 2 together. If high protein, meat based diets actually increase uric acid excretion, and 90 % of all gout patients have the disease because they are underexcretors – it makes little sense to implicate meat and high protein diets as a fundamental causes of gout. What we really need to look for are dietary factors which can simultaneously increase uric acid synthesis in the liver and suppress its secretion by the kidneys – Bingo! What might this holy grail of a food look like? For starters – how about the mainstays of the western diet – maybe refined grains and refined sugars? In the typical western diet, these foods comprise nearly 40 % of the daily energy (20).
GOUT: THE REAL DIETARY CAUSES

It has been known for almost 40 years that fructose ingestion or infusions result in hyperuricemia (elevated blood uric acid levels). However, this information has seemingly been buried in the medical literature, since clinical nutrition texts make few or no dietary recommendations for gout patients to reduce dietary sources of fructose. Fructose stimulates synthesis of AMP and GMP which are ultimately converted to uric acid by the liver, thereby elevating plasma uric acid levels. Only fructose causes this effect, as experimental 3,000 kcal day diets consisting entirely of glucose in obese patients did not increase plasma uric acid levels, whereas a high sucrose (table sugar) diet did. Because sucrose is composed of the two simple sugars, glucose and fructose, then the digestion of sucrose in the gut to its two component sugars shows that fructose alone is responsible for inducing hyperuricemia.

In the US diet the two primary sources of fructose are from the digestion of sucrose and from foods containing high fructose corn syrup. Figure 5 shows the total consumption of all refined sugars in the U.S. from 1970 to 2000. Note that total fructose consumption (from both the metabolism of sucrose and high fructose corn syrup) has increased from 51.5 lbs in 1970 to 64.9 lbs in 2000 – an increase of 26%.

Fructose causes hyperuricemia by lowering the inorganic phosphate (Pi) content of the liver. High levels of Pi in the liver normally slow the metabolism of GMP and AMP into uric acid. Fructose is an unusual sugar in that it enters liver metabolism (glycolysis) after the PFK regulatory step, thereby causing unregulated phosphorylation of fructose to fructose 1-P which in turn lowers both liver ATP and Pi. Further, because fructose bypasses the PFK regulatory step, it increases blood lactic acid which is an inhibitor of uric acid excretion by the kidneys. Consequently, fructose ingestion either from high fructose corn syrup or from sucrose enhances uric acid production and also slows it excretion. To add insult to injury, long term ingestion of table sugar (sucrose) and high fructose corn syrup, because they are high glycemic load carbohydrates, will chronically elevate blood insulin concentrations and frequently result in insulin...
resistance. Numerous studies conclusively show that insulin is a potent inhibitor or uric acid excretion by the kidneys. Taken together, these basic and well established biochemical facts indicate that sucrose, high fructose corn syrup and all high glycemic load carbohydrates play a central role in causing gout. Diseases of hyperuricemia are tightly coupled with metabolic syndrome diseases because both categories of diseases result, in part, from chronically elevated insulin.

There is one final dietary key which completes the picture. In addition to fructose, sucrose and high glycemic load carbohydrates, excessive consumption of alcoholic beverages may also promote gout symptoms by simultaneously increasing uric acid production and slowing its excretion. The metabolism of alcohol (ethanol) like that of fructose reduces the liver stores of ATP and Pi by uncoupling oxidation from phosphorylation and thereby increases uric acid synthesis from AMP and GMP. A by product of alcohol metabolism is lactic acid which once again inhibits uric acid excretion in the kidneys by competitively inhibiting uric acid secretion in the proximal tubules.

As you Paleo Diet Newsletter readers are well aware, whenever a complex diet/disease question arises, insight into the problem can almost always be gained by framing the question in an evolutionary perspective. In the case of gout, the recommendation to limit high purine meats is completely contrary to the anthropological evidence showing that animal food was the staple of hunter gatherer diets, typically comprising more than 50% of total daily energy. In ancestral hominins, animal food based diets have an ancient origin dating back at least 2.5 million years, as evidenced by stone tool cut marks present on fossilized bones of prey animals. We can also infer that animal food was the staple of Homo erectus living 1.77 million years ago in what is now the Dmanisi archeological site in the Republic of Georgia. Because of the seasonal scarcity or absence of plant foods at 40 degrees North latitude, these ancestral hominins almost certainly were highly dependent upon animal foods for many months during the year (Figure 7.)

Given our ancient heritage of meat based diets, it is paradoxical that high purine meats would still cause a crippling disease after more than 2 million years of evolutionary experience. A more likely evolutionary scenario would be that natural selection must have been operative in selecting genes to overcome any deleterious

Table 1. Dietary recommendations for gout.

<table>
<thead>
<tr>
<th>Group 1: High Purine Content Foods (100-1,000 mg of Purine Nitrogen per 100g of Food)</th>
<th>Group 2: Moderate Purine Content Foods (9-100 mg of Purine Nitrogen per 100g of Food)</th>
<th>Group 3: Negligible Purine Content Foods included in this group may be used daily.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anchovies, Bouillon, Brains, Broth, Consommé, Goose, Gravy</td>
<td>Heart, Herring, Kidney, Mackerel, Meat Extracts, Mincemeat, Mussels</td>
<td>Bread, white and crackers</td>
</tr>
<tr>
<td>Partidge, Roe, Sardines, Scallops, Sweetbreads, Yeast (supplement)</td>
<td></td>
<td>Butter or margarine*</td>
</tr>
<tr>
<td>Meat and Fish, except those listed in Group 1: Fish, Poultry, Meat, Shellfish</td>
<td>Vegetables: Asparagus, Peas, Beans, Lentils, Mushrooms, Spinach</td>
<td>Cake and Cookies</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Carbonated beverages</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cereal beverage (e.g., Postum)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cereals and Cereal products</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cheese, Chocolate, Coffee, Condiments, Cornbread, Cream*, Custard</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Eggs, Fats*, Vegetables (except those in group 2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fruit, Gelatin Desserts</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Herbs, Ice Cream, Milk</td>
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<tr>
<td></td>
<td></td>
<td>Macaroni noodles, Noodles</td>
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<tr>
<td></td>
<td></td>
<td>Nuts, Oil</td>
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<tr>
<td></td>
<td></td>
<td>Olives, Pickles, Popcorn</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Puddings, Relishes, Rennet Desserts, Rice</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Salt, Sugar and Sweets</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tea, Vinegar, White Sauce</td>
</tr>
</tbody>
</table>

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Given our ancient heritage of meat based diets, it is paradoxical that high purine meats would still cause a crippling disease after more than 2 million years of evolutionary experience. A more likely evolutionary scenario would be that natural selection must have been operative in selecting genes to overcome any deleterious
effects of excessive dietary purine. Let’s take a look at the evidence.

Almost all animals except humans don’t ever get gout because they have an enzyme called uricase which converts uric acid into a substance called allantoin, which is 5-10 times more soluble than uric acid and thus more easily eliminated by the kidneys. Modern humans and great apes cannot synthesize uricase because, over the course of evolution, they have experienced mutations which have inactivated the uricase gene. Chimps and other great apes maintain much higher blood uric acid levels than do other animals capable of synthesizing uricase, however chimps and other great apes apparently do not ever develop gout in the wild, presumably because they consume a near vegetarian diet without additional purines from meat.

As early hominins began to increasingly include more and more purine containing animal foods into their diets, blood concentration of uric acid almost certainly must have been higher than their more vegetarian predecessors, thereby increasing the incidence of gout. Because gout impairs mobility, mortality must have increased in individuals susceptible to gout. Hence, natural selection would have rapidly weeded out individuals who were most susceptible to gout and selected for those who could tolerate a high meat diet without developing gout symptoms. In support of this evolutionary scenario is a metabolic adaptation present in humans which lowers uric acid synthesis despite a high dietary purine intake.

Taking a look at the science of it one more time: as the purine precursors, GMP and AMP, are ultimately converted to uric acid there are a couple of key intermediary steps along the way. AMP is converted to hypoxanthine and then to xanthine and finally to uric acid. GMP is converted to xanthine and then to uric acid. Both the conversion of hypoxanthine to xanthine and xanthine to uric acid are regulated by an enzyme called xanthine oxidase. Humans avoid the overproduction of uric acid in the face of increasing

Figure 7. The earliest evidence of fossilized hominins living outside of Africa at the Dmanisi archaeological site in the Republic of Georgia.
acid concentrations dietary purine intake from meats by decreasing the activity of xanthine oxidase.\textsuperscript{38} Compared to other animals, xanthine oxidase activity is almost 100 times lower in humans.\textsuperscript{39}

This evolutionary adaptation has occurred because the gene coding for xanthine oxidase (more specifically xanthine oxidoreductase) has been repressed.\textsuperscript{40}

So there you have it. The evolutionary model originally predicted that a meat based diet should not increase the risk for gout. Now we have genetic and biochemical evidence supporting the evolutionary model. The final corroborative link would be experimental evidence. If you put gout patients on a meat based, high protein diet, reduce refined sugars and high glycemic load carbohydrates, what do you think will happen.

What might the evolutionary paradigm predict? Let’s take a look.

**THE PROOF IS IN THE PUDDING**  
**A CLINICAL TRIAL**

As is the case with many diet related diseases, the dogma has been so well established that it is difficult to unlearn what was once known to be the absolute truth. Nothing could be a better example of this lesson than the dietary dogma for treating gout. It took until the year 2000 before anyone ever tried putting gout patients on a high protein, low glycemic load diet to see what would happen.\textsuperscript{41} Low and behold this program normalized serum uric acid concentrations in 7 of 12 gout patients and significantly decreased gout attacks. The authors concluded their paper by saying “Current dietary recommendations for gout may need re-evaluation”.

**EPILOGUE:**

Six years have now come and gone since this revolutionary clinical trial has been conducted. You might think that the rheumatology community would jump onto this band wagon as fast as a hot knife through butter. Ah, we should be so lucky – not in our wildest dreams. There has not been a single corroborative or follow up study, and the misconception that a high purine, meat based diet causes gout continues to be spread in prestigious world wide medical journals.\textsuperscript{13}
**WILD SALMON DELIGHT**

- 2 wild salmon filets, 4-6 oz. ea
- 1 Tb. extra virgin olive oil
- 1 t. fresh dill, finely chopped
- 1 t. ground paprika
- 1/2 t. freshly ground black pepper
- 4 oz. white mushrooms, sliced
- 1 large red tomato, diced

Prepare a large saucepan with a steamer basket and 1 inch of water. Bring to a boil. Reduce heat to simmer, place salmon in steamer and cook for fifteen minutes.

Heat oil in a cast iron skillet over medium flame. Add dill, paprika, pepper, and mushrooms and sauté for five minutes. Remove from heat.

Once salmon has finished cooking, remove from pan and top with mushroom and tomato mixture.

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SUCCESS STORY

Hi Loren,

Thanks for your personal response. Your contribution to the ongoing dialog about human nutrition, by so powerfully advancing the scientific arguments in favor of The Paleo diet, is very much appreciated. Your writing has had a profound influence on what I eat everyday, and what I teach to others about nutrition. A number of my patients have made life altering changes in their nutritional patterns because of your writings. Each of them has obtained a copy of one or more of your books. To be sure, I have learned from other nutritionists, but your influence has been the most important because of your lucid articulation of the over-arching theory of the hunter-gatherer diet.

For my own story, I trained and was boarded in General Surgery in the late ‘70s, and then spent a very satisfying twenty plus year career as an emergency physician, a specialty in which I was also boarded. I worked in a big urban hospital emergency department, which included nine years of administration as Assistant Chief and then Chief. I loved the medical practice, but I was caring for others while neglecting myself. I was hypertensive (consistently BP of 144/88), overweight (body fat 34%, BMI 28.7), with abnormal cholesterol (180-190), and a resting pulse in the low 70s. My HDLs were low.

At age 55 I retired, moved to a tiny community in the Sierra mountains with my family, and decided to pay attention to my own health, by actively studying human nutrition and weight loss strategies. I had had a two decade history of yoyo’ing weight, by what I call now the “starvation diet”, trying to eat less of the same calorie dense, high glycemic index processed salty stuff. I thought it was “healthy” food. But I have since learned otherwise; it was in fact endocrinologically poisonous. This starvation diet spells doom for millions of otherwise well intended Americans who know they need to lose weight, and are trying desperately to do so, but are trapped by their own unfortunate and unintended nutritional ignorance.

I read voluminously, including all the major diet books cover to cover Atkins, South Beach, Weil, Ornish, Brand-Miller, Willets, McDougal, Pritikin, and others. I went back and reviewed the basic biochemistry of lipid, protein, and carbohydrate metabolism. My wife invited me to join her at Weight Watchers, and I started counting all my “points”. I was counting points and losing weight, but ravenously hungry all the time… the starvation diet at
work. I realized that counting points was not enough. I realized I could not be hungry all the time for the rest of my life. Two scientific nutritional concepts turned out to be cornerstones in my “cracking” the weight loss nut.

The first was the fundamental importance of glycemic index, and the effect this has on insulin and glucagon levels and resultant wild swings in blood sugar and hunger levels. The second was calorie density: the fact that we eat to satiety based on volume of food eaten, not number of calories. Since only vegetables, and some fruits, are low calorie density foods, each meal must include a generous portion of these food categories.

But the real breakthrough happened when a fellow emergency physician, a colleague and friend, told me of a radio talk show he heard in which Dr. Eaton was interviewed. Knowing of my interest in nutrition, he strongly suggested I look into the paleo approach to nutrition. Further, he said that Dr. Eaton recommended reading the book The Paleo Diet and the articles available online at Dr. Loren Cordain’s website. Reading your book, I quickly realized that all of the apparently disparate concepts I was learning about healthful nutrition fell neatly and logically into place under the overarching theory that the most healthful diet is the one we humans evolved eating. Suddenly calorie density and low glycemic index made sense, because those were the only foods available to us as we evolved. The dramatic diminution of mortality in the prospective, blinded fish oil study on post-myocardial infarction patients made sense once we realize the omega 3/6 ratio of our ancestors and the availability of animal based omega 3 in the wild meat and seafood they ate. In fact, all kinds of apparently disparate nutritional learnings make sense when they are looked at in the light of the theory of evolutionary nutrition. That’s the learning I got directly from you, and I thank you for it.

For my own testimonial, I have gone from a body fat of 34% to 7%, a BMI of 28.7 to 20.6, an abnormal blood pressure of 144/88 to a consistent 104/62 and a high cholesterol of 190 to 132. My HDLs are up. My triglycerides are 35. My resting pulse is now in the high 40s. For the three years before I started eating “paleo”, I had been taking 300 mg of Zantac for G.E.R.D. virtually every single night. In the past two years, I believe I have taken four doses total, and that was always in the context of dietary “indiscretion”. I had been experiencing about five years of D.J.D. inflammation in several of the P.I.P. joints of my fingers with resultant swelling. That has completely quieted down.

The three way combination of eating huntergatherer food, getting my BMI down under 21, and exercising is incredibly healing and powerful medicine; and it beats hands down the medications we give our patients, like anti-hypertensives, lipid lowering agents, and hypoglycemic drugs. Those may provide some benefit for individuals who are unable to change their diet and weight, but they have no effect on the overall root cultural problems of diet, obesity, and sedentary life-style that is endemic in our Western society.

Thanks again for your powerful contribution to my understanding of human nutrition. I’d be happy to post an endorsement to your website. I’ll do the posting with my first name only for privacy purposes.

Warm regards,
Steve L., MD
REFERENCES


