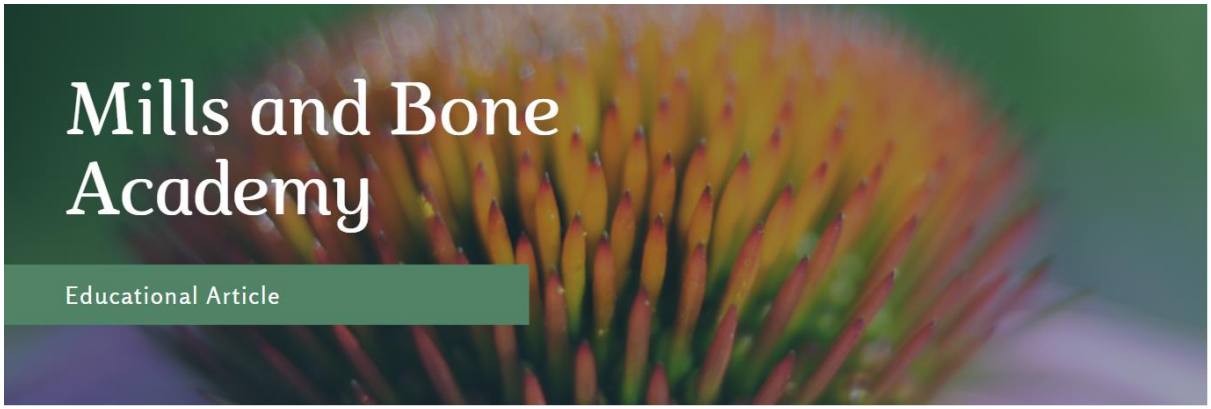

New and Old Insights into Gout – Kerry Bone

Gout is a well-known and common arthritis caused by the deposition of monosodium urate (MSU) crystals within certain joints following chronic high uric levels in the blood (hyperuricemia).[i] It affects between 1 and 2% of adults in developed countries, where it is the most common inflammatory arthritis in men. Population studies suggest its incidence is rising, probably due to the rising incidence of metabolic syndrome (MetS), with which it is intimately connected. In keeping with this connection, gout and hyperuricemia are also associated with hypertension, type 2 diabetes, and renal and cardiovascular diseases.i In fact, gout appears to be a risk for all-cause mortality and cardiovascular mortality and morbidity in addition to the risk conferred by its association with the traditional cardiovascular risk factors.[ii] This is probably due to the fact that a high uric acid level in the blood drives inflammation, even without the deposition of MSU crystals.[iii]

A 2011 review of the risk factors for gout identified 53 relevant studies.[iv] Alcohol consumption, especially beer and spirits, increased the risk of incident gout. Several dietary factors were also implicated, including meat, seafood, sugar-sweetened soft drinks and consumption of foods high in fructose (in keeping with gout's link to MetS, where more than 60% of people with gout also have this disorder[v]). Dairy, folate and coffee intake were each associated with a lower incidence of gout.

Uric acid is normally formed in the body as a by-product of purine metabolism. However, we now understand that a diet high in fructose also leads to higher production of uric acid.[vi] The metabolism of fructose is different to glucose: it is faster and lacks any negative feedback control. So, when we consume a typical sugary drink, a massive flux of fructose arrives in the liver that sends the

cells into metabolic hyperdrive. The first step is the addition of a phosphate entity to the fructose to form fructose-1-phosphate. Because there is no negative feedback control, the liver is obliged to do this for every fructose molecule it encounters. Adenosine triphosphate (ATP) is used to provide this phosphate group, with the resultant production of adenosine diphosphate (ADP). Normally, the ADP would be converted back to ATP by the liver cells, but because all the available phosphate is being taken up dealing with the high flux of fructose, they cannot do this. As a result ATP is depleted, and there is an excessive formation of ADP. (This contrasts with glucose, which has a tightly controlled metabolism via negative feedback, preventing excessive glucose phosphorylation and ATP depletion). The excess ADP is metabolised over several steps to form xanthine, which is then converted to uric acid. Hence, a high fructose load on the liver causes a rise in uric acid production that eventually results in higher levels in the blood.

Hence, one of the key priorities for someone with gout is to ensure that their fructose intake is as low as possible. Cane sugar, honey and corn syrup should all be avoided, and especially in drinks. In addition, dried fruit and fruit juices are best eliminated from the diet. Whole fruit can be consumed, but only those fruits low in fructose, namely stone fruit, berries, tart or sour morello cherries (in preference to normal cherries), banana, pineapple and all the citrus fruits. If a sugar needs to be used to provide extra sweetness, it should be glucose or xylitol (but in moderation). Recent research has further informed the dietary and lifestyle advice for gout. Specifically, moderate intake of purine-rich vegetables (asparagus, mushrooms, peas and so on) or plant protein is not associated with an increased risk of gout.[vii] Hence, these foods can be consumed in moderation. However, the advice regarding avoidance or reduction of red meat, offal, seafood and alcohol has been soundly confirmed.[vii,viii] Low-fat dairy products can be increased, as these appear to be protective,[ix] and the inclusion of cherries in the diet is now supported by reasonable evidence (see below). Weight reduction with daily exercise and a low glycaemic index diet are also important considerations.[x]

The link between cherry consumption and a reduced risk of gout attacks has long been acknowledged. The first attempt to provide objective proof of this relationship was a US study published in 2003. Plasma urate, antioxidant and inflammatory markers were measured in 10 healthy women who consumed sweet cherries.[xi] The women, age

22 to 40 years, consumed two servings (280 g) of cherries after an overnight fast. Blood and urine samples were taken before the cherry intake and at times thereafter. Plasma urate was decreased 5 hours after cherry intake ($p < 0.05$). Urinary urate was increased, indicating better excretion. Plasma C-reactive protein (CRP) and nitric oxide (NO) concentrations had decreased marginally at 3 hours postdose ($p < 0.1$), whereas plasma albumin and tumour necrosis factor-alpha were unchanged.

Much later in 2010, a combined UK/US research team investigated the efficacy of tart cherry juice in aiding recovery and reducing muscle damage, inflammation and oxidative stress.[xii] Twenty recreational marathon runners consumed either cherry juice or placebo for 5 days before, the day of and for 48 hours following a marathon run. Markers of muscle damage (creatine kinase, lactate dehydrogenase, muscle soreness and isometric strength), inflammation (interleukin-6 (IL-6), CRP and uric acid), total antioxidant status (TAS) and oxidative stress (thiobarbituric acid reactive species (TBARS) and protein carbonyls) were examined before and following the run. Isometric strength recovered significantly faster in the cherry juice group. No other damage measures were significantly different. Inflammation was reduced in the cherry juice group and TAS was about 10% greater for all post-supplementation measures ($p < 0.05$). Protein carbonyls were not different; however, TBARS was lower in the cherry juice group than the placebo at 48 hours ($p < 0.05$). Specifically, for the context of this article, uric acid was reduced by around 25% post-race in the tart cherry group compared to the placebo group.

Interesting as these impacts on serum uric acid might be, they did not link cherry consumption to fewer gout attacks. A new US/Australian study published in late 2012 does exactly that. A case-crossover design was used to examine the role of various factors, including cherry consumption, with recurrent gout attacks.[xiii] Individuals with gout were prospectively recruited and followed up online for one year. Participants were asked to provide the following information regarding gout attacks: the onset date of the attack, symptoms and signs, medications (including antigout medications), and exposure to potential risk factors (including daily intake of cherries and cherry extract) during the 2-day period prior to the gout attack. The authors then assessed the same exposure information over four 2-day control periods and estimated the risk of recurrent gout attacks related to cherry intake using conditional logistic regression. The study

included 633 people with gout. Cherry intake over a 2-day period was associated with a 35% lower risk of gout attacks compared to no intake (multivariate odds ratio (OR) 0.65). Cherry extract intake showed a similar inverse association (multivariate OR 0.55).

Herbs have also been traditionally used to help gout sufferers. In fact, arthritic disease caused by accumulation of urate crystals in joints provides a particular indication for herbal remedies. There are a number which are claimed to increase elimination of urate from the kidneys, notably celery (*Apium graveolens*), stinging nettles (*Urtica species*) and birch (*Betula alba*). Use of such herbs appears to ease the symptoms and even help to prevent recurrence. Other herbs traditionally indicated include sarsaparilla (*Smilax species*) and dandelion leaf (*Taraxacum officinale*). A recent survey of 142 herbal practitioners in the UK found that celery, nettles and dandelion leaf were commonly chosen for their reputation for helping the excretion of uric acid, while birch and turmeric (*Curcuma longa)* were high among those chosen to reduce inflammation.[xiv]

Clinical trials are also emerging that suggest certain herbs can lower serum uric acid. The traditional Chinese medicine combination of licorice (*Glycyrrhiza species*) and white peony (*Paeonia lactiflora*) is one such example.[xv] Study participants were male Buddhist vegetarians with asymptomatic hyperuricaemia enrolled at Fu Yuan Buddhist College, Taipei, Taiwan. The control group comprised normal, non-vegetarian healthy men. Both groups received a combination of the two herbs as a decoction 3 times a day for 4 weeks. While there was a small non-significant decrease in serum uric acid in the healthy control group, the average level in the hyperuricaemic participants fell by 19.4% ($p < 0.01$ compared to baseline). Changes in blood pressure were minimal; indicating the dose of licorice used had not significantly influenced this outcome.

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