

# Gout, Diet, and the Insulin Resistance Syndrome



Gout, one of the oldest known forms of arthritis, is characterized by chronic hyperuricemia (serum urate > 450  $\mu\text{mol/l}$  or 7.0 mg/dl in men; and > 350  $\mu\text{mol/l}$  or 6.0 mg/dl in women), recurrent attacks of acute arthritis provoked by the release of monosodium urate crystals into synovial spaces, and eventual development in some patients of urate tophi and chronic tophaceous gouty arthritis. Uric acid is the end product of purine metabolism<sup>1-3</sup>. About one-third of the human daily purine load is from diet, while two-thirds is generated endogenously. In the majority of patients with primary gout, hyperuricemia results from relative renal urate underexcretion (“relative urate underexcretors”), while in about 10% of subjects, hyperuricemia is due to endogenous overproduction of uric acid (“urate overproducers”)<sup>2,3</sup>. Although gout is one of the better understood of the rheumatic diseases, and certainly one of the most gratifying to treat, a number of management issues, including the role of dietary measures, remain uncertain<sup>4</sup>.

## DIETARY FACTORS IN THE PATHOGENESIS OF HYPERURICEMIA AND GOUT

Being a metabolic disorder, gout is significantly influenced by dietary factors that include overeating, obesity, alcohol abuse, dyslipidemia, and insulin resistance syndrome<sup>1,5-8</sup>. The connection of gout with gluttony, overindulgence in food and alcohol, and obesity dates from ancient times. In the 5th century BC, Hippocrates attributed gout to excessive intake of food and wine<sup>9</sup>. For treatment, he recommended dietary restriction and reduction of alcoholic beverages, and for acute attacks, the best medicine was large doses of white hellebore — a powerful purgative. The “status” of gout as a disease of the wealthy has survived over the centuries — if not in fact, in myth. Nearly all accounts of gout emphasize the role of overeating and of excessive consumption of alcohol in the causation of the disease; the “grog-blossom” nose is sometimes considered a marker of gout. In 1713, John Martin wrote in *The Attila of the Gout*: “as to the first and remote, or procatactic causes of gout, there has been little wrangling among the physicians. The general opinion is that *drunkenness & gluttony* are the father & mother of this distemper, and that a moist air, too much sleep, want of exercise and sloth, are necessary causes. They likewise

agree that excess of *venery* has no small hand in the production of it...”<sup>10</sup>. Several epidemiological studies have demonstrated a strong correlation between obesity and hyperuricemia<sup>1,5-7,10-12</sup>. Thus, 3.4% of subjects with a relative weight below the 20th percentile are hyperuricemic, compared with 11.4% of those above the 80th percentile<sup>6,11</sup>. Obesity is associated with both increased production and decreased renal excretion of urate<sup>13</sup>.

A diet rich in purines (Table 1) will produce only a small and transient rise of serum urate by about 60–120  $\mu\text{mol/l}$  (1–2 mg/dl). Conversely, an isocaloric purine-free diet for 7–10 days will slightly lower serum urate by about 60–120  $\mu\text{mol/l}$  (1–2 mg/dl)<sup>13,14</sup>. Habitual intake of a purine-rich diet may also uncover an underlying renal genetic defect that can lead to hyperuricemia. Mean serum urate levels are higher and the incidence of gout is greater among Filipinos living in the USA compared to individuals of identical racial background living in the Philippines. This is explained by the limited ability by some of these people to increase their renal excretion of urate when exposed to the high purine North American diet<sup>15</sup>.

Alcohol consumption has long been closely associated with hyperuricemia and gout<sup>1,5-7,9-12,16-19</sup>. In 1876, Alfred Garrod wrote: “the use of fermented liquors is the most powerful of all the predisposing causes of gout, nay so powerful that it may be a question whether gout would ever have been known to mankind had such beverage not been indulged in”<sup>16,17</sup>. The exact incidence of alcohol induced

Table 1. The purine content of certain foods and beverages.

High purine foods and beverages
• All meats, including organ meats and meat extracts
• Seafood
• Yeast and yeast extracts
• Vegetables: peas, beans, lentils, asparagus, spinach, mushrooms
• Beverages: beer and alcoholic drinks
Low purine foods and beverages
• Dairy products: milk, cheese, butter, eggs
• Grains/cereals and products: bread, pasta, cakes
• Vegetables, fruits, nuts: except peas, beans, lentils, asparagus, spinach
• Sugars, sweets, and gelatin
• Beverages: water, juices, carbonated beverages, tea, coffee and cocoa

gouty arthritis is not known, but it is estimated that half the gout sufferers drink excessively<sup>17</sup>. In a case control study of drinking behavior of 24 patients with gout and 24 age, sex, and weight matched control subjects, the average weekly alcohol intake of gout sufferers was twice that of the control group ( $p < 0.02$ )<sup>17</sup>. A statistically significant relationship between alcohol abuse and acute gout ( $p < 0.05$ ) was also described. Hyperuricemia was also found to be a significant correlate of alcohol abuse in an unselected group of male patients admitted to a general hospital<sup>18</sup>. A dietary study of 61 men with gout and 52 healthy men showed that although the average daily intake of most nutrients, including total purine nitrogen, was similar in both gout sufferers and control subjects, the group with gout drank significantly more alcohol than the controls<sup>19</sup>. The quantity of purine nitrogen derived from alcoholic drinks (mainly beer) was greater in gout sufferers. Alcohol intake, whether alone or with a purine-rich meal, produces greater effects on serum urate levels than a high purine diet. Many patients are aware that feasts containing purine-rich foods and liberal amounts of alcoholic drinks tend to provoke attacks of gout<sup>20</sup>. Such “aldermanic gout” is brought on by rapid changes in serum urate levels resulting from a combination of feasting and excessive alcohol consumption<sup>20</sup>. Similarly, 8 out of 9 patients with gout given whisky while fasting — a circumstance not uncommon in real life — experienced one or more episodes of acute gout<sup>21</sup>. Acetoacetic and beta-hydroxybutyric acidemia associated with fasting results in inhibition of renal urate excretion and a sharp rise of serum urate<sup>21</sup>. Although alcoholic and nonalcoholic patients with gout have comparable interval serum urate levels ( $9.7 \pm 2.1$  vs  $9.5 \pm 2.1$  mg/dl, respectively), during acute attacks of gout, alcoholic patients tend to have significantly lower serum urate levels than nonalcoholics ( $7.7 \pm 1.3$  vs  $10.1 \pm 1.3$  mg/dl, respectively)<sup>22</sup>. This is explained by the frequent coexistence in alcoholics of other provocative factors, such as concurrent trauma and hypothermia of the lower extremities<sup>22</sup>.

A number of mechanisms have been implicated in the pathogenesis of ethanol induced hyperuricemia<sup>17-30</sup>. These include: (1) Acute alcoholic excesses causing temporary lactic acidemia, reduced renal urate excretion, and exacerbation of hyperuricemia<sup>17,18,20-23</sup>. (2) Chronic alcohol ingestion stimulating purine production by accelerating the degradation of adenosine triphosphate to adenosine monophosphate via the conversion of acetate to acetyl CoA in the metabolism of ethanol<sup>24,25</sup>. (3) The purine content of beer, including the readily absorbed guanosine, producing a greater effect on uric acid production<sup>23,26</sup>. (4) Consumption of lead contaminated port wine, moonshine whisky, and other alcoholic beverages causing reduction in renal urate excretion and hyperuricemia (“saturnine gout”)<sup>27-29</sup>. Also, persons who binge drink tend to forget to take their urate-lowering medications. A continued high alcohol intake may

also impair the response to allopurinol therapy by inhibiting the conversion of the drug to its active metabolite, oxipurinol<sup>30</sup>. This results in reduced oxipurinol plasma levels, increased urinary excretion of unmetabolized allopurinol, and hence reduced urate-lowering effects<sup>30</sup>. It follows that urate-lowering drugs are often less effective in patients with gout who continue to drink<sup>31</sup>.

The presence in gout sufferers of an associated metabolic disorder, such as dyslipidemia and insulin resistance syndrome (IRS), may warrant treatment of its own accord, and often some modification of gout management. Nowhere has this been more true than in patients with both gout and IRS, since treatment of gout with a purine restricted diet that is usually rich in both carbohydrate and saturated fat may negatively influence the management of IRS.

Hyperlipidemia, usually hypertriglyceridemia (type IV hyperlipidemia), has been reported in 25–60% of gout sufferers<sup>6,7,32-34</sup>. The association has been attributed to both genetic and environmental factors (diet, obesity, alcohol consumption)<sup>34</sup>. Among genetic factors, 2 apolipoprotein genes are more common in patients with primary gout and hypertriglyceridemia: an uncommon allelic variant of the apoprotein CIII gene, the S2 allele (CIII is one of the 4 major apoproteins of low density lipoprotein)<sup>32</sup>, and an apolipoprotein E phenotype apo e4 allele<sup>33</sup>.

Recent data indicate that hypertriglyceridemia in patients with primary gout is often due to an underlying IRS, or metabolic syndrome X<sup>6-8,34-37</sup>. This is characterized by overall and abdominal obesity with visceral adiposity (a waist/hip ratio  $> 0.85$ , with a waist circumference  $> 100$  cm)<sup>38</sup>; impaired glucose tolerance with resistance to the effects of insulin and compensatory hyperinsulinemia; and the dyslipidemic combination of hypertriglyceridemia, an increase in levels of apolipoprotein B, low density lipoprotein cholesterol (LDL-C), and atherogenic small dense LDL-C particles, and a decrease in high density lipoprotein cholesterol (HDL-C) levels.

IRS is often associated with hyperuricemia, hypertension, and coronary artery disease (CAD). The basic defect in this metabolic syndrome is insulin resistance, which can be detected years before the onset of type 2 diabetes mellitus. Although the exact pathogenesis of IRS is not fully understood, certain dietary factors, particularly fat and total calorie intake, in combination with decreased physical activity, lead to overall obesity with centripetal deposition of fat<sup>38</sup>. Centripetal obesity, in turn, is a powerful stimulus to increased insulin plasma levels<sup>38</sup>.

Euglycemic hyperinsulinemia, induced by exogenous insulin intravenous infusion, has been shown to reduce the renal excretion of urate and sodium in both healthy subjects and hypertensive patients<sup>39-42</sup>. This is mediated through stimulating renal tubular sodium-hydrogen exchanger, thereby facilitating reabsorption not only of sodium, chloride, and bicarbonate, but also of organic anions, such as

urate<sup>40-42</sup>. This explains the frequent association of hyperinsulinemia and IRS with both hypertension and hyperuricemia. Dietary reduction of triglycerides with a low calorie, weight-reducing diet has been shown to increase renal excretion of urate in these patients<sup>39,43</sup>. Recently, 2 other cardiovascular risk factors, impaired endothelium dependent vasodilatation<sup>44</sup> and reduced fibrinolytic activity with elevated plasminogen activator inhibitor-1 (PAI-1) plasma levels<sup>45</sup>, have been shown to be associated with IRS. Unexplained elevation of total plasma homocysteine levels is another CAD risk factor that has also been reported in gout sufferers<sup>46</sup>.

Since patients with IRS may initially present with hyperuricemia and/or gouty arthritis, it is important to screen these individuals for concomitant impaired glucose intolerance, dyslipidemia, hypertension, obesity, or other cardiovascular risk factors<sup>6-8,47,48</sup>. Hyperinsulinemia and IRS have been estimated to occur in 95% and 76% of gout sufferers, respectively<sup>39</sup>. Thus, even in the absence of clinical signs of gout, hyperuricemia may serve as a surrogate marker of IRS<sup>6-8,47,48</sup>. However, it is unlikely that hyperuricemia per se plays a causal role in the pathogenesis of CAD, and any apparent relationship is likely related to the frequent association of hyperuricemia with IRS, obesity, dyslipidemia, hypertension, and diabetes mellitus<sup>49</sup>. Early recognition of IRS will allow nonpharmacologic management by exercise<sup>50</sup> and a diet that is high in unsaturated fats and dietary fiber<sup>51</sup> and restricted in carbohydrates; and if there is significant impairment of glucose tolerance, management will include the use of drugs to increase insulin sensitivity, such as the thiazolidinediones (e.g., rosiglitazone)<sup>52</sup>.

## DIETARY INTERVENTIONS IN THE TREATMENT OF HYPERURICEMIA AND GOUT

All too often patients enquire about dietary measures in the treatment of gout. There are 2 main approaches: the traditional low purine, low protein, alcohol restricted diet, and more recently, a weight-reducing, purine unlimited, calorie and carbohydrate restricted diet, with increased proportional intake of both protein and unsaturated fats (Table 2).

*Traditional low purine, alcohol restricted diet.* Dietary restriction of purine-rich foods (Table 1), once a mainstay in the management of gout, is of lesser importance now that potent, more effective urate-lowering drugs are available<sup>10,13,53</sup>. An isocaloric diet restricted in purines produces

lowering of the urinary excretion of uric acid by about 200–400 (336 ± 39) mg/day/day (1.2–2.4 mmol/day), and a decrease of mean serum urate level by about 1–2 mg/dl (60–120 μmol/l)<sup>13,14</sup>. Patients are advised to avoid drinks or foods that they know might precipitate an acute gouty attack, such as large servings of meat and heavy beers. However, a rigid purine restricted diet is of dubious therapeutic value and can rarely be sustained for long.

Moderation in dietary purine consumption, rather than a strict low purine diet, may be helpful, particularly in patients with large tophi experiencing difficulty controlling the hyperuricemia, despite urate-lowering drug therapy<sup>13,53</sup>. Although high protein diets contain large quantities of purines and are associated with an increased rate of endogenous purine production, such diets often increase urinary urate excretion, and may even lower serum urate levels<sup>19,54</sup>. Tofu (soybean curd) is rich in protein, but most of the purines are lost during processing, and ingestion of tofu produces only a small rise of serum urate in both healthy individuals and gout sufferers<sup>55</sup>.

Many patients with gout are overweight, and weight reduction through gradual caloric restriction and exercise, in addition to its beneficial effects on any associated hypertension, dyslipidemia, or IRS, can enhance renal excretion of urate and lowering of serum urate<sup>39,43,56</sup>. “Crash” dieting and sustained fasting are best avoided, as they may induce lactic acidemia, worsening hyperuricemia, and precipitate attacks of gout. Limitation of alcoholic beverages produces a comparatively greater effect on serum urate levels than purine restriction, and may also reduce the requirements for urate-lowering drugs. Although correction of obesity and purine excess and alcohol avoidance will reduce serum urate, there are no longterm studies of the effectiveness of such an approach, and the benefits are often limited by the relatively small percentage reduction in serum urate levels, and the difficulty of maintaining such improvement in the long term.

*Weight-reducing, calorie restricted diet, with moderate carbohydrate restriction and increased proportional intake of protein and unsaturated fats.* Given the strong association between the IRS, hyperuricemia, and gout, a weight-reducing calorie restricted diet with moderate carbohydrate restriction and increased proportional intake of protein and unsaturated fat has recently been advocated in patients with primary gout<sup>39</sup>. Low purine foods are often rich in both carbohydrate and saturated fat. These tend to further decrease insulin sensitivity, leading to higher plasma levels of insulin, glucose, triglycerides, and small, dense LDL-C particles and decreased HDL-C levels, thereby increasing the risk of CAD in these patients<sup>39,57</sup>. By contrast, a low energy, calorie restricted, high protein, high unsaturated fat, low carbohydrate diet improves insulin sensitivity and decreases plasma glucose, insulin, and triglyceride levels, with a reduction in the incidence and mortality of

Table 2. Dietary interventions in the management of gout.

<ul style="list-style-type: none"> <li>• Calorie restriction and weight reduction in obese patients</li> <li>• Limitation of alcoholic beverages</li> <li>• Traditional low purine, protein restricted diet</li> <li>• Weight-reducing, calorie restricted diet with moderate carbohydrate restriction and increased proportional intake of protein and unsaturated fats</li> <li>• ? Experimental fish oil and plant seed oil dietary supplementation</li> </ul>
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CAD<sup>39,57,58</sup>. Recently reported in 13 middle aged men with gout<sup>39</sup> is a study of a calorie restricted (1600 kcal/day or 6690 kJ/day), weight-reducing diet with restriction of carbohydrate (40% of energy/day), increased proportional intake of protein (30% of energy or 120 g/day, compared to 80–90 g/day generally recommended in diets of Western countries), and replacement of saturated by unsaturated fat (30% of energy/day). Unsaturated fats included both monounsaturated (nuts, olive and canola oils) and polyunsaturated fats (fish). Purine-rich foods were not restricted, but patients were encouraged to limit dairy products (milk, cheese, butter) that, although low in purine content, are high in saturated fat<sup>39</sup>. The 16 week trial resulted in a mean weight loss of 5.4 kg, significant reductions in serum urate, triglycerides, LDL-C, and total cholesterol, and a significant decrease in the frequency of gouty attacks. The beneficial effects of the diet are mediated through improving insulin sensitivity, with reduction of insulin plasma levels, an increase in the renal excretion of urate, and lowering of serum urate levels<sup>39</sup>. These preliminary observations, which need to be confirmed in larger, longer term controlled studies, raise concerns about the usefulness of the traditional low purine diet in the management of gout. Such a diet, with its unlimited intake of carbohydrate and saturated fat, will not benefit a patient with both gout and IRS. A weight-reducing diet, with moderate carbohydrate restriction and increased proportional intake of both protein and unsaturated fats, is clearly preferred, but there are no longterm studies of the efficacy of such an approach.

*Experimental fish oil and plant seed oil dietary supplementation.* There is some experimental evidence to indicate that diets enriched in both gamma-linolenic acid (GLA) in plant seed oil (evening primrose oil) and eicosapentaenoic acid (EPA) in fish oil significantly suppress urate crystal induced inflammation in the Sprague-Dawley rat subcutaneous air pouch model<sup>59</sup>. GLA is metabolized into prostaglandin E<sub>1</sub> (PGE<sub>1</sub>, which is antiinflammatory), whereas EPA is metabolized into both PGE<sub>3</sub> (which is less inflammatory than PGE<sub>2</sub>) and leukotriene B<sub>5</sub> (which suppresses both LKB4 production by neutrophils and interleukin 1 generation by macrophages)<sup>59</sup>. The effects on the course of clinical gout of a diet enriched with both fish oil and plant seed oil have not been studied.

## CONCLUSION

While dietary restriction of purines has long been superseded by more effective urate-lowering drugs, recent data suggest that dietary measures may play a much greater role in the treatment of metabolic disorders commonly associated with gout: obesity, IRS, and dyslipidemia. Before commencing lifelong urate-lowering drug therapy, it is important to identify and treat any of these underlying disorders that may be contributing to the hyperuricemia. In light of its clinical and therapeutic implications, it is important to

recognize the strong association of IRS (abdominal obesity, dyslipidemia, raised serum insulin levels, and glucose intolerance) with hyperuricemia and gout. Although the exact frequency of IRS in patients with gout is not known, estimates range between 76% for IRS and 95% for hyperinsulinemia<sup>39</sup>. An elevated serum urate level may serve as a surrogate marker of IRS, and hence an indicator of risk of CAD. Given the prognostic ramifications of IRS in terms of cardiovascular morbidity, dietary intervention is strongly recommended in these patients.

There is growing evidence that a low energy, calorie restricted, low carbohydrate (40% of energy), high protein (120 g/day, or 30% of energy) diet, with unsaturated fat (30% of energy) and high dietary fiber, is more beneficial in terms of lowering serum urate, insulin, LDL-C, and triglyceride levels, and hence reducing CAD risk, than the conventional low purine diet, with its unlimited intake of carbohydrates and saturated fat<sup>8,13,39,57,58</sup>. Restriction of alcoholic beverages is key in the management of gout; a continued high intake of alcohol can result in refractoriness to urate-lowering effects of both allopurinol and uricosurics<sup>31</sup>.

Dieting of any kind is burdensome for most patients, and urging patients to change longstanding, ingrained habits can prove fruitless. Only 20% of patients seeking medical care are ready to change unhealthy behaviors, including hazardous alcohol use and bad eating habits<sup>60</sup>. Sustaining a lifestyle change can also be both difficult and impractical and the relapse rate is high<sup>60</sup>. Given the renewed interest in the importance of dietary measures in the management of gout and its associated metabolic disorders, particularly the IRS, new strategies are needed to motivate patients and improve the physician's effectiveness in counselling patients to initiate and adhere to a lifestyle change, including longterm dietary interventions<sup>60</sup>.

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