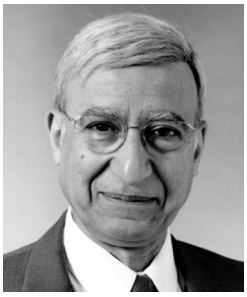
Editorial

Gout: Excess Calories, Purines, and Alcohol Intake and Beyond. Response to a Urate-Lowering Diet



Gout is one of the oldest and better understood of the rheumatic diseases. It is characterized by chronic hyperuricemia (> 450 µmol/l or > 7.0 mg/dl in men, and > 360 µmol/l or > 6.0 mg/dl in women), recurrent attacks of acute arthritis provoked by release of sodium urate crystals into joints, and eventual development in some patients of urate tophi, chronic tophaceous gouty arthritis, and urate nephropathy. Throughout its long history, various diets have featured prominently in the treatment of gout[1-4]. These included: barley water, barley bread, purgatives (hellebore, colchicum), bing cherry[5], a number of natural plant remedies[6,7], and since the mid-20th century, a low-purine diet[8]. About 300 years ago, the philosopher John Locke (1632–1704) proposed a diet low in meat and high in milk, dairy products, and herbs as a means to prevent gout[1,3,4].

In humans, uric acid (UA) is the end-product of purine metabolism. About two-thirds of the daily purine load is generated endogenously from turnover of cells, while one-third is derived from the diet. Purine-rich foods include animal meats (beef, pork, lamb, organ meats, and meat extracts), seafood (fish fillets, tuna, shrimp, lobster, clams, etc.), and plants (yeast extracts, peas, beans, lentils, asparagus, and mushrooms). By contrast, dairy products (milk, cheese, yogurt, ice cream), grains and their products (bread, pasta, cereals), vegetables, fruits, nuts, sugars, and sweets are low in purines.

In most animals, UA is further catalyzed to allantoin by the enzyme urate oxidase or uricase[3,9,10]. Allantoin is 5–10 times more soluble than UA, and is more readily eliminated by the kidneys. Thus, in most lower mammals, serum urate levels are quite low (< 120 µmol/l or < 2.0 mg/dl, usually 30–60 µmol/l or 0.5–1.0 mg/dl). Humans, chimpanzees, orangutans, and gibbons have a nonsense codon inserted into this gene that resulted in the synthesis of a short 10-amino acid fragment devoid of uricase activity[9,10]. As a consequence, unlike in other mammals, higher concentrations of serum urate (> 120 µmol/l or > 2 mg/dl) can occur in humans and higher primates and, when saturation is reached, uric acid can precipitate in articular and other tissues, causing gout. The influence of diet becomes apparent when one compares serum urate levels in great apes to those of humans: 90–180 µmol/l or 1.5–3.0 mg/dl versus 240–330 µmol/l or 4.0–5.5 mg/dl, respectively[3,9]. This is attributed to differences in diet. Apes' diet consists mainly of fruits and vegetations, with only small amounts of animal protein. Uricase is essential in lower mammalian species. Mice in which the uricase gene has been disrupted by homologous recombination in embryonic stem cells ("urate oxidase knockout mice") develop severe hyperuricemia (mean 650 µmol/l or 11 mg/dl), massive uricosuria, rapidly progressive urate nephropathy, and early death, but no urate tophi[11]. Treatment with allopurinol reverses most of these abnormalities.

In the majority of patients with primary gout (> 90%), hyperuricemia is due to reduced renal proximal tubular UA excretion ("relative urate or gouty underexcretors")[12]. These patients excrete < 3.6 mmol/day or < 600 mg/day UA on a low-purine diet for one week. The UA clearance is reduced: < 6 ml/min (normal 6–11 ml/min), with a UA/creatinine ratio of < 6%. The capacity to eliminate a urate (purine) load is reduced, and excretion of normal amounts of UA is accomplished at inappropriately higher serum urate levels. A genetic basis is suggested by the frequent presence of a similar proximal tubular abnormality in first-degree relatives[12]. Whether this urate underexcretor status is related to mutation of a specific human tubular urate anion transporter 1 (URAT1) is unclear[12,13]. URAT1 is a specific proximal renal tubular luminal-border organic (urate) anion transporter protein that regulates UA excretion and hence serum urate[13]. In a minority of patients (< 10%), hyperuricemia results from an increased rate of *de novo* purine biosynthesis ("gouty or urate overproducers/overex-

See Response to a urate-lowering diet according to polymorphisms in the apolipoprotein AI-CIII-AIV cluster, *page 903*

cretors")[12]. These patients excrete excessive amounts of UA (> 3.6 mmol/day or > 600 mg/day on a low-purine diet for 1 week), and their UA clearance is either normal or increased, with a UA/creatinine ratio of > 6%.

Several epidemiological studies have demonstrated a strong association between hyperuricemia/gout and overeating, obesity, excessive purine consumption, alcohol intake, dyslipidemia, diabetes mellitus, and insulin resistance syndrome (IRS)[14-18]. Gluttony, overindulgence in foods, and excess weight have long been closely associated with hyperuricemia and gout[1,14]. Thus, only 3.4% of individuals with a relative weight below the 20th percentile are hyperuricemic, compared with 11.4% of those above the 80th percentile[14]. Dietary changes, and their effects on serum urate levels, have been implicated in the changing worldwide epidemiology of hyperuricemia and gout. Over the past 20 years, the incidence of gout has significantly increased in several countries, coinciding with an overall increasing frequency of obesity, diabetes mellitus, hypertension, IRS, and cardiovascular disease[10,14]. Gout is considered by many as part of the current global epidemic of obesity, diabetes mellitus, and hypertension. Diets that are rich in fruits, vegetables, and low-fat dairy foods, such as Dietary Approaches to Stop Hypertension (DASH diet), may reduce not only blood pressure but also the frequency of hyperuricemia and gout[3].

All too often, patients enquire about the role of diet modification in the prevention and treatment of gout. Although during the past 40 years, the place of diet regulation in the treatment of gout has been superseded by the introduction of potent urate-lowering drugs, recently there has been a surge of renewed interest in dietary intervention and the role of excess purines, alcohol intake, and IRS[14-18]. Short term studies have shown that a purine-rich diet for 1–2 weeks produces a small transient rise in serum urate by 60–120 µmol/l (1–2 mg/dl)[8,14]. Conversely, an isocaloric low-purine diet for 7–10 days will slightly reduce serum urate by about 60–120 µmol/l (1–2 mg/dl)[8,14].

However, habitual longterm intake of a purine-rich diet may uncover in some individuals an underlying renal tubular genetic defect that can lead to hyperuricemia. Thus, the 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[16]. This is thought to be due to the limited capacity of some of these individuals to increase their renal excretion of urate when exposed to the purine-rich North American diet[16]. A recent large 12-year prospective epidemiological study utilizing a 4-yearly "food-frequency questionnaire" showed that habitual higher meat and seafood intake independently increased the risk of incident gout among men, while higher intake of dairy products (milk, yogurt, cheese, and ice cream) was protective against the risk[17]. Further, high intake of animal or vegetable proteins, and consumption of purine-rich vegetables (peas, beans, lentils, asparagus, spinach, and mushrooms) did not increase the risk of incident gout[17]. The investigation supports John Locke's age-old observation that less meat and plenty of milk are beneficial in the prevention and treatment of gout[1,3,4].

Another large study, by the same lead investigators, using data from the Third National Health and Nutrition Examination Survey (NHANES-III) for the years 1988–94, examined the relationship between the intake of purine-rich foods, proteins, and dairy products and serum urate levels[18]. The investigation showed that higher levels of meat and seafood consumption in both men and women are associated with higher serum urate levels, but the total protein intake is not[18]. By contrast, consumption of dairy products was inversely associated with serum urate levels[18]. Consumption of purine-rich foods, especially meats, has also been shown to increase risk of repeat gout attacks[19].

It is of interest to note that meat consumption has also been linked to development of coronary artery disease (CAD), type-2 diabetes mellitus, colon cancer, and more recently inflammatory polyarthritis, including rheumatoid arthritis[20]. By contrast, a Mediterranean-type diet (less red meat, more fish, an abundance of plant foods, olive oil as the main source of fat, and moderate consumption of wine) is associated with a lower incidence of these disorders[20,21]. The effects of a Mediterranean diet on the incidence of hyperuricemia/gout have not been studied. However, there is 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[23]. GLA is metabolized into prostaglandin E_1 (PGE_1, which is antiinflammatory), whereas EPA is metabolized into both PGE_3 (which is less inflammatory than PGE_2) and leukotriene B5, which suppresses both leukotriene B4 production by neutrophils and interleukin generation by macrophages[23]. The effects of a diet enriched by both plant seed oil and fish oil on the clinical course of gout have not been examined.

The connection of gout with excessive alcohol intake dates from ancient times[1-3,14,24,25]. A number of studies have described a significantly higher alcohol intake in patients with gout than in healthy controls. The exact incidence of alcohol-induced gouty arthritis is not known, but it is estimated that half the gout sufferers drink excessively[24]. A recent, large, 12-year, prospective epidemiologic study showed that alcohol intake in men is strongly and independently associated with an increased risk of gout[26]. The risk of incident gout was 2.5 times higher among men who consumed 50 g or more alcohol per day compared with those who abstained from alcohol[26]. The magnitude of the association rose with increasing alcohol intake, and varied according to the type of alcoholic beverage. Thus, 2 or more

beers/day confer a greater risk of incident gout (relative risk 2.6) than 2 or more servings of spirits per day (relative risk 1.6). Moderate wine consumption (2 glasses/day) did not seem to increase the risk of gout[26].

Alcohol induces hyperuricemia by a number of mechanisms[14,25,26]. During acute alcohol excesses, alcohol is converted to lactic acid. This reduces renal UA excretion by competitively inhibiting UA secretion by the proximal tubules. Also, chronic ethanol consumption increases purine and UA production by accelerating the degradation of adenosine triphosphate to adenosine monophosphate, a UA precursor. The process involves the conversion of acetate to acetyl CoA in the metabolism of ethanol. The greater hyperuricemic effects of beer, compared to other alcoholic drinks, are attributed to its large purine content, predominantly guanosine[14,25,26]. In the NHANES-III study, alcohol intake in both men and women was associated with higher serum urate levels[27].

Dyslipidemia, usually type IV hyperlipidemia or hypertriglyceridemia, has been reported in 25–60% of gout sufferers[14,28]. The association has been attributed to both genetic and environmental (diet, obesity, alcohol intake, and lack of exercise) factors[28]. Recent data indicate that hypertriglyceridemia in patients with primary gout is often part of an underlying metabolic syndrome or IRS[14,29-32]. This is characterized by overall and abdominal obesity with visceral adiposity (a waist/hip ratio > 0.85, with a waist circumference > 102 cm in men and > 88 cm in women), impaired glucose tolerance with resistance to the effects of insulin and compensatory hyperinsulinemia, and the dyslipidemic combination of hypertriglyceridemia, increase in levels of apoliprotein 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 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 caloric intake, in combination with decreased physical activity, can lead to overall obesity with centripetal deposition of fat[14,29-32]. Centripetal fat, in turn, is a powerful stimulus to increased insulin plasma levels[30]. Euglycemic hyperinsulinemia has been shown to reduce the renal excretion of both urate and sodium; hence the frequent association of IRS with both hyperuricemia/gout and hypertension[14,32-34]. A 3-week, 1200 cal, weight-reducing diet in these individuals resulted in both a reduction of serum triglyceride levels and an increase of renal UA excretion with reduction of serum urate[35]. However, the effects were reversed when calories were again increased[35].

IRS is estimated to occur in 75–95% of patients with primary gout[14,28,31,36]. Thus, an elevated serum urate level may serve as a surrogate marker for IRS, and hence an indicator of CAD risk. Given the prognostic implications of IRS in terms of cardiovascular morbidity and mortality, exercise and dietary intervention are strongly recommended in these individuals.

There is preliminary evidence that a calorie-restricted (about 1600 cal/day), low-carbohydrate (40% of energy) diet, with a proportionate increased intake of both proteins (120 g/day or 30% of energy) and unsaturated fats (including fish, nuts, and olive and canola oils; 30% of energy) and a high dietary fiber, can be beneficial in these patients[36]. The diet is associated with lowering of serum urate, insulin, LDL-C, and triglyceride levels and hence reduced CAD risk[36]. Restriction of alcohol intake is key in the management of those patients who also have gout. A continued high alcohol consumption can exacerbate hyperuricemia and also result in refractoriness to the urate-lowering effects of both allopurinol and uricosuric drugs[37].

In addition to environmental influences (excess calories, purines, and alcohol), genetic factors play an important but poorly understood role in the development of hyperuricemia and gout[38-40]. A familial occurrence is observed in about 40% (11–80%) of individuals with primary gout, but the exact genetic abnormality, whether renal, metabolic, or both, has not been elucidated[38]. Genetic differences in the regulation of UA synthesis, UA renal excretion, or both may account for some of the racial differences in the susceptibility to gout[38,39]. However, the Mendelian mode of transmission of familial primary gout and the candidate gene or region remain unclear[40]. There is a strong familial tendency for gout to cluster in families among Taiwanese aborigines, in whom the prevalence of gout is particularly high (15.3% in men, 4.8% in women, compared to about 1.0% in men and 0.5% in women in Western countries)[40]. There is recent evidence to indicate an autosomal pattern of inheritance with low penetrance among these individuals, with susceptibility loci (D1S498 > D1S2635) located in the 1q21 region, and the margin of 1q22 on chromosome 1[40].

In contrast, the nature of the genetic defect and the mechanism of hyperuricemia are better defined in certain known familial forms of secondary gout[38-42]. Included among these are a partial or complete deficiency of hypoxanthine guanine phosphoribosyl transferase (HGPRT) enzyme (X-linked), phosphoribosyl pyrophosphate (PRPP) synthetase superactivity (X-linked), glucose-6 phosphatase deficiency (autosomal recessive), and fructose-1-phosphate aldolase deficiency (autosomal recessive)[38]. Autosomal dominant medullary cystic kidney disease (ADMCKD), with a gene on 1q21 region of chromosome 1[41], and autosomal dominant familial juvenile hyperuricemic nephropathy (FJHN), with a gene localized to a candidate interval of –9 cM flanked by the loci D165403 and D165311G on chromosome 16 at 16p12[42], are 2 hereditary renal diseases associated with gout.

In this issue of *The Journal*, F. Cardona and co-investigators from Malaga, Spain, investigated the influence of polymorphism in the apolipoprotein AI-CIII-AIV gene cluster (on chromosome 11q/23-q24) on the response to a 2-week, low-purine diet in patients with gout[43]. Apolipoprotein-AI is the major protein in high density lipoproteins, while apolipoprotein-CIII is an exchangeable component of triglyceride-rich lipoproteins. Apolipoprotein A-IV is incorporated in triglyceride-rich lipoproteins and chylomicrons[44]. Variations in the apo AI-CIII-AIV gene cluster (the S2 allele) and in their genotypes (as determined for the restriction endonuclease enzymes: *XmnI*, *PstI*, *SstI*, *MspI*) are associated with traits in plasma lipids, lipoproteins, and apolipoproteins[14,28,42-46].

The 2-week low-purine diet resulted in reduction of plasma levels of triglycerides, cholesterol, glucose, and urate and a decrease in 24-hour urinary UA excretion[43]. The decrease was mainly due to the diet, except for plasma triglycerides, which were also influenced by the allele *X*2 of *XmnI* polymorphism of apolipoprotein AI gene, suggesting a gene-diet interaction[47]. The *X*2 allele of *XmnI* may thus serve as a genetic marker for greater responsiveness (particularly reduction of triglyceride levels) to dietary intervention[43]. The A allele of *MspI* polymorphism of the apolipoprotein AI gene is associated with higher levels of total cholesterol and LDL-cholesterol[43]. Interaction between *XmnI* and *MspI* polymorphisms of apolipoprotein AI gene is associated with elevated levels of both cholesterol and triglyceride[43].

In this study, patients with *X*2, A, and SI alleles showed the most significant reduction in total cholesterol and triglycerides[43]. Although the study was limited by its uncontrolled design, small sample size, short duration (2 weeks) and the potential influence of confounding factors (such as obesity and insulin resistance syndrome), the investigation highlights the potential influence of genetic factors on the response to a urate-lowering diet in patients with primary gout. However, it is noteworthy that the traditional low-purine diet is not palatable or practical for very long, produces only 10–20% reduction of serum urate levels, and is generally high in both carbohydrates and dairy products rich in saturated fats, hence increasing CAD risk[14,36].

In summary, the study by Cardona and colleagues[43] draws attention to the potential role of genetic influences on the response to dietary intervention in patients with gout, and calls for a larger, longterm, controlled prospective investigation to confirm these initial observations. Dieting of any kind is both burdensome and difficult to sustain for most patients. Urging individuals to change long-standing, "unhealthy" behaviors, such as smoking, poor eating habits, excessive alcohol use, or lack of exercise, often proves unsuccessful[48]. Less than 20% of patients seeking medical advice are prepared to make a sustained lifestyle change[48]. However, in the management of patients with IRS and gout, weight reduction, dietary modification, and exercise are crucially important even though many of these individuals may require additional drug therapy to correct type-2 diabetes mellitus, dyslipidemia, and hypertension, and hence reduce the risk of CAD.

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