Review

Soyfoods, hyperuricemia and gout: A review of the epidemiologic and clinical data

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Soyfoods have long been a part of traditional Asian diets; they provide plentiful amounts of high-quality protein and have a favourable fatty acid profile. In addition, provocative research suggests soyfoods offer health benefits independent of the nutrients they provide. However, there is a widely-held belief among Asian health professionals and the public that soyfoods increase risk of gout and potentially precipitate acute attacks in patients with this disease. To examine the veracity of this belief, this review critically evaluated the relevant clinical and epidemiologic data. In addition, background information on the etiology and prevalence of hyperuricemia and gout in Asia is provided along with the results of a small survey of Asian healthcare professionals about their attitudes toward soyfoods. Among the healthcare professionals who responded to the survey, 95% considered soyfoods to be somewhat or very healthy and nutritious. In contrast, 48% expressed the view that soyfoods are likely to cause gout. However, none of the six epidemiologic studies identified provided any evidence that soy intake was associated with circulating uric acid levels, hyperuricemia or gout. Data from the five human intervention studies evaluated indicate soy protein does elevate serum uric levels, but in response to amounts comparable to Asian intake, the expected rise would almost certainly be clinically irrelevant. Although there is a need for long-term research, on the basis of the existing data there is no reason for individuals with gout or at risk of developing gout to avoid soyfoods.

Key Words: soy, vegetarian, gout, hyperuricemia, uric acid

INTRODUCTION

Within the past 20 years foods made from the soybean have increased in popularity in non-Asian countries because of research suggesting they provide health benefits independent of their nutrient content. There is particular interest in the role that soyfoods may play in reducing risk of coronary heart disease (CHD),[1,2] osteoporosis and certain forms of cancer, especially cancer of the breast and prostate.[3-10] Throughout much of Asia, foods such as tofu, miso, natto, soy drink and tempe have long been a traditional part of the diet being prized in particular for their versatility. These are the types of products consumed by subjects in the epidemiologic studies discussed latter in this review. Soy drink is the liquid expressed from soaked, pureed soybeans whereas tofu is produced by adding a curdling agent to soy drink so that the curd (tofu) can be separated from the liquid or whey. Natto, tempe and miso (soybean paste) undergo an extensive fermentation process. In addition to these traditional soyfoods, in many non-Asian countries, concentrated sources of soy protein are used as a basis for making everything from meat substitutes to breakfast cereals.

The soybean differs from other foods and legumes in several notable ways. For example, among commonly consumed foods, it is essentially unique in providing nutritionally relevant amounts of isoflavones – diphenolic compounds classified as phytoestrogens because they bind to estrogen receptors (ER) and exert estrogen-like effects under certain experimental conditions – that are responsible for much of the interest in the role of soy in reducing chronic disease risk.[11-13] It is notable that isoflavones are also classified as selective estrogen receptor modulators because they preferentially bind to and transactivate estrogen receptor ERβ in comparison to ERα.[13,14]

In addition, the macronutrient composition of the soybean differs markedly from other legumes as it is higher (percent calories) in protein (~33 versus ~27%) and much higher in fat (~40 versus 3%).[15] Further, the quality of soy protein is comparable to animal protein and superior to that of other legume proteins.[16] The fatty acid profile of the soybean is also noteworthy in that approximately 6% of soybean oil is comprised of α-linolenic acid, which makes the soybean one of the few good plant sources of omega-3 fatty acids.[17]

Soyfoods account for approximately 10% of overall dietary protein intake among older adults in Japan,[18] Indonesia,[19] and Shanghai,[18] although there is evidence, at least

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for Japan, that in recent years the adoption of western-style dietary habits has resulted in a decrease in soy intake among younger people.[18] Intake in Hong Kong and Singapore is approximately half that of Japan.[18] Interestingly, despite the popularity of these foods and their centuries-long history of use, a common perception within Asia is that soyfoods increase risk of gout and potentially precipitate acute attacks in patients with this disease.[20,21] Consistent with this belief are the results of a recent survey of health professionals in Singapore, Indonesia and Thailand (see below). This concern is juxtaposed against a recommendation by the British Society for Rheumatology and British Health Professionals in Rheumatology for gout patients to consume soyfoods and other vegetable sources of protein.[22]

Since the prevalences of both hyperuricemia and gout within Asia appear to be increasing, concerns that soyfoods may be involved in the etiology of this disease could hasten the move away from these traditional foods. Such a development would conflict with recommendations from the World Health Organization to maintain traditional eating patterns to further prevent the increase in the incidence of chronic diseases in Asia typically associated with Western dietary patterns.[23] Furthermore, there is evidence that soyfoods may be useful for addressing several diseases, including: hypertension, the metabolic syndrome and cardiovascular disease, which are associated with hyperuricemia, a condition present in most gout patients.[24] Consequently, eliminating soyfoods from the diet may in fact work against the benefit of patients with gout.

Understanding the impact of soy on gout is not an issue of interest only to Asians. The increased popularity and availability of soyfoods in the United States has made this issue relevant to the more than 5 million Americans with gout.[25] Therefore, since no previous review of this subject was identified in the literature, the purpose of this paper is to evaluate the human evidence relevant to the relationship between soy intake and circulating uric acid levels and gout. Before doing so, background information on the etiology of gout and prevalence of hyperuricemia and gout in Asia is provided along with the results of a small survey of Asian healthcare professionals about their attitudes toward soyfoods. Also, the potential impact of soy intake on diseases associated with gout and hyperuricemia is very briefly discussed.

GOUT – BACKGROUND

Identification of monosodium urate crystals (MSU) in joints and in tophi is considered the "gold standard" for the diagnosis of gout.[26] However, because procedures aimed at demonstrating the presence of MSU are not regularly performed, the diagnosis of gout is frequently made according to clinical data and blood tests. Recent recommendations are for the diagnosis of chronic gout to be made when ≥4 of the following data occur currently or are part of patient history: ≥1 attack of acute arthritis, mono or oligoarthritis attacks; rapid onset of pain and swelling, podagra, erythema, or unilateral tarsitis; possible tophi, and hyperuricemia.[27] Definitions of hyperuricemia vary but it is generally defined as a serum urate level of greater than 7 mg/dL in men and 6 mg/dL in women (1 mg/dL=59.48 μmol/L).[28] However, in the United States, the Centers for Disease Control and Prevention classify serum uric acid values exceeding >8.4 mg/dL for men and 7.5 mg/dL for women as hyperuricemic.[29] Urate crystal precipitation occurs in vitro at about 6.8 mg/dL (408 μmol/L) at 37° F although at lower temperatures precipitation can occur at lower urate concentrations.[30,31]

Uric acid is the final enzymatic product in the degradation of purine nucleosides and free bases in humans. During primate evolution the activity of urate oxidase (uricase, an enzyme catalyzing conversion of uric acid to allantoin) was lost in a two-step mutation process.[32,33] In other mammals, the last enzymatic product of the purine degradation chain is allantoin, which is excreted in the urine. As a consequence, humans have to cope with relatively higher levels of uric acid in the blood (200-400 μM) and are prone to hyperuricemia and gout.[34] More than 90% of gout patients are hyperuricemic although 90% of people with hyperuricemia remain asymptomatic.[35,36] The higher the serum uric acid levels the greater the likelihood that gout will develop.[37] One analysis found that the annual risks of developing gout were 0.5% and 4.5% for those with serum uric acid levels between 415 and 530 μmol/L (7 and 8.9 mg/dL) and >535 μmol/L (9 mg/dL), respectively.[38]

Of the total amount of urate in the body, about two-thirds is produced endogenously and about one-third comes from dietary purines.[39] Approximately 70% of the urate produced daily is excreted by the kidneys whereas the remainder is eliminated by the intestines.[39] Hyperuricemia generally occurs as a result of incomplete renal elimination of purines, but increased endogenous uric acid production and increased intake of purine-rich foods can be contributing factors.[24] Uric acid is produced by the conversion of the purine derivative hypoxanthine to xanthine and xanthine to uric acid by xanthine oxidase.

Dietary habits have been linked with gout in the scientific literature for more than a hundred years. According to Nuki and Simkin,[40] in 1876, Garrod[41] was among the first to suggest that hyperuricemia could be controlled by lowering the intake of purine-rich foods. Nevertheless, to some extent, the importance of dietary behavior has taken a back seat to medications[42,43] for both the long-term[44,45] and acute treatment of gout.[44] To this point, a small survey of Australian rheumatologists found that relatively few respondents referred their gout patients for dietetic services.[46] This observation may be attributed to the perceived difficulty of complying with purine-restricted diets. The position of the US American Dietetic Association is that if purine restriction is desired, if possible, days with meals containing purines, should be interspersed with purine-free days.[47]

In any event, proper dietary choices can produce benefits equal to those of drugs and the results come at lower cost and without the side effects common to gout medications.[48] A recent comprehensive review of the literature concluded that all of the commonly used drugs for gout are associated with serious adverse events, especially in the elderly.[49] Specific foods, beverages and individual nutrients both positively and negatively affect serum uric acid levels and gout risk. For example, evidence indicates

meat and seafood and alcoholic beverages increase and vitamin C supplements, low-fat dairy products and coffee consumption decrease, serum uric acid levels and/or risk of gout.[50-55] In some studies fructose has been linked with hyperuricemia although the data are mixed.[56-59] The intake of purine-rich vegetables has however, been shown not to be associated with gout.[54]

Lists of foods grouped according to their purine content are commonly used as a basis for devising low-purine diets gout patients. Soyfoods are generally listed as have a moderate amount of purines, ranging from 50 to 100 mg/100 g. However, such lists do not account for findings showing that purine bases and metabolites involved in the endogenous synthesis of purines affect serum uric acid levels differently.[60] Among the purines, adenine and hypoxanthine are considered far more uricogenic than guanine and xanthine.[61] Furthermore, the relationship between food intake and gout is likely much more complex than can be understood by simply looking at purine content.[62] Moderate protein restriction is sometimes recommended as a proxy for limiting purine intake,[42] however, protein is not a good reflection of the effect of a given food on serum uric acid levels and protein itself may be uricosuric.[63] Furthermore, protein type as well as overall protein intake may affect uric acid levels.[64]

PREVALENCE OF HYPERURICEMIA AND GOUT IN ASIA

The overall prevalence of gout among the populations of Western industrialized countries such as the United States, the United Kingdom and Germany is estimated to be approximately 1 to 2% (among older people it is much higher) although prevalence is thought to have more than doubled within the past 20 years.[65-69] Comparing the prevalence of gout and hyperuricemia among countries is difficult because of the different methodologies (eg, self report versus doctor diagnosis) and disease criteria used in the relevant studies.[70,71] Nevertheless, there is evidence that the incidence of gout and hyperuricemia has increased not just in the West, but also in Asia. Given the aging of the population in Western countries, the international increase in obesity and Westernization of the diet in developing countries, such increases are not surprising.[72]

Until recently in China, gout and hyperuricemia were thought to be extremely rare. According to Fang *et al.*, the first 2 cases of gout were reported in 1948,[73] and only 25 patients were identified in the Chinese literature in the following decade.[74] Even by 1980, a small survey that included 502 Chinese adult men and women in Beijing, Shanghai and Guangzhou, found a prevalence of hyperuricemia of only 1.35%.[75] However, the prevalences of gout and especially hyperuricemia in Asia are now beginning to approach Western levels.[76,77]

In support of this contention is a recent study of 5,003 subjects randomly recruited from 5 coastal cities (Qingdao, Rizhao, Yantai, Weihai, and Dongying) of Shandong province in Eastern China, which found the prevalence of hyperuricemia and gout to be estimated at 13.19% and 1.14%, respectively.[78] Even higher rates were reported in several other Chinese studies. For example, in the Shanghai Men's Health Study, which included 3,978 urban Chinese men 40-74 years of age, the prevalence of hyperuricemia was 25 percent.[79] This figure is similar to the age-standardized prevalence rate (25.3%) reported for in adults in urban Qingdao, China, although the age-standardized prevalence of gout was only 0.36 percent.[80]

In Taiwan, two studies reported the prevalence of hyperuricemia to be 26.1% and 30.6%.[81,82] However, results from the Elderly Nutrition and Health Survey in Taiwan found that the overall prevalence of hyperuricemia (≥7.0 mg/dL) among the elderly was 36% (46% for males and 26% for females).[83] In fact, in some regions (mostly mountain areas) the prevalence of hyperuricemia was even higher, reaching levels in males and females as high as 62% and 51%, respectively.[83] Among the participants in that survey, 4.2% of males and 1.1% of females were taking uric acid-lowering medication. Not only are rates increasing in Taiwan, but there is a trend toward a younger age at onset; 25% of patients now have their first gout attacks before the age of 30.[84]

In Japan, national census data indicate that the number of individuals visiting hospitals with a self-diagnosis of gout has been increasing. The current estimate is that the 20-25% of the males in Japan have hyperuricemia and according to a recent survey conducted in a local area of Wakayama prefecture, the prevalence of gout is 1.1%.[76] Limited data are available for Indonesia, but the prevalence of gout and hyperuricemia reported in a survey of 4683 rural adults in Northern Central Java was 1.7 and 24.3%, respectively.[85] In Thailand, a survey of over 5000 subjects aged 18 to 60 belonging to the Armed Forces Research Institute of Medical Sciences, found that 25% (n=1396) had serum uric acid levels >7.7 mg/dL and that a similar percentage (n=1394) had levels between 6.5 and 7.6 mg/dL.[86] Finally, in a Korean study of 4,779 male workers, 30 to 39 years of age, who did not take medication for dyslipidemia or have a history of any malignancy at study entry, approximately 20% reported having serum uric acid levels ≥6.7 mg/dL.[87]

HEALTHCARE PROFESSIONAL ATTITUDES TOWARD SOY: SELECTED RESULTS

In 2010, a survey of 239 healthcare professionals from three Asian countries was conducted to determine perception of the health attributes of soyfoods (Table 1). The survey was conducted by The Nutrition Place (Singapore) on behalf of the American Soybean Association International Marketing (Singapore Representative Office). It was a self-completed quantitative survey via pre-recruited professionals from various medical or health related fields in Singapore, Indonesia and Thailand.

In Indonesia, 85 questionnaires were provided to dietitians in 13 hospitals in different parts of Jakarta and were distributed to different health professionals. In Thailand, 69 questionnaires were sent to key dietitians and medical doctors in 4 major hospitals in different parts of Bangkok who distributed them to health professionals who were the main targets of the survey. Finally, in Singapore, 85 questionnaires were distributed to key dietitians and health professionals in 11 public and private hospitals and clinics in different parts of the country. Questionnaires were also sent to dietitians working in various national health agencies and to nutrition educators working in academic institutions. In addition, questionnaires were

distributed to physicians, traditional Chinese medicine practitioners and pharmacists from private institutions.

The response rate was approximately 95%. Of the initially distributed surveys, two, three and seven health professionals in Bangkok, Singapore and Indonesia, respectively, declined to participate. The occupational distribution of the 227 healthcare professional responding to the survey is shown in Table 1 and the attitudes toward soyfoods are listed in Table 2. Ninety-five percent of those surveyed considered soyfoods to be somewhat or very healthy and nutritious. Heart disease and menopause were the two health areas that were judged most likely to benefit from soyfood consumption. Conversely, 52 and 48% of those surveyed were of the opinion that soyfoods are likely to cause allergic reactions and gout, respectively. With regard to gout, there was a considerable variation in response among the three countries as 27, 46, and 69% of the health professionals in Thailand, Indonesia, and Singapore, respectively, expressed concern. Interestingly, among the different professions, 59% of the dietitians/nutritionists indicated soyfoods were linked with gout whereas this was the case for only 53% of the nurses and 44% of physicians.

Table 1. Occupations of healthcare professionals responding to the soyfood survey

Occupation	Total n (%)	Singapore n (%)	Indonesia n (%)	Thailand n (%)
Medical doctor	100 (44)	20 (24)	37 (47)	44 (66)
Dietitian/Nutritionist	50 (22)	29 (35)	15 (19)	5 (7)
Nurse	43 (19)	21 (26)	11 (14)	11 (16)
Pharmacist	9 (4)	7 (9)	0 (0)	3 (4)
Other	25 (11)	5 (6)	15 (19)	4 (6)

Table 2. Attitudes of healthcare professionals toward soyfoods[†]

Attributes	All respondents[2] (n=227)	Respondents in Singapore (n=82)	Indonesia (n=78)	Thailand (n=67)
Overall perception				
Very health and nutritious	44	58	51	19
Somewhat healthy and nutritious	51	38	47	70
Neither healthy nor unhealthy	4	2	1	9
Diseases/conditions for which soy is thought to be protective				
Heart disease	72	77	72	66
Menopause	60	60	55	64
Osteoporosis	54	62	51	46
Obesity	50	33	67	49
Cancer	40	37	56	25
Perceived undesirable effects of soyfoods				
Allergies	52	45	44	71
Gout	48	69	46	27
Breast cancer	15	29	5	12
None	14	4	33	2
Feminization of men	13	18	9	11
Disruption of endocrine systems	10	18	3	9

[†]Values represent percentages

SOY INTAKE AND URIC ACID LEVELS

Epidemiology

Relevant clinical and epidemiologic research was identified by searching PubMed using as keywords, soy, soyfoods, gout, uric acid and hyperuricemia. References within papers identified by this search, as well as papers that came to the attention of the authors through other means were also examined for suitability.

Six epidemiologic studies were identified that examined the relationship between soy intake and serum or plasma uric acid levels.[20,88-92] All six were conducted among Chinese populations, four from Taiwan and two from China. Thus, the data are limited to one ethnic group. Further, in only one of these studies were soyfoods a primary food category of concern.[92] Consequently, the assessment of soyfood intake may have been incomplete in some studies although the study by Chang indicates that the intake of several soy products (soy drink, tofu, tofu pudding or other soybean products) was assessed.[91]

The first published epidemiologic study, which was conducted by Lyu *et al.* from the National Taiwan Normal University compared the diets of 92 male gout patients with the diets of 92 coworker controls, aged 20 to 70 y.[20] Logistic regression analyses showed that high alcohol intake and low intakes of fiber, folate, and vitamin C increased gout risk. Animal protein intake tended to be associated with an increased risk [odds ratio (OR) for third intake tertile, 1.18; 95% confidence interval (CI) (0.58, 2.39), p for trend=0.65] and plant protein a decreased risk [OR for third intake tertile, 0.70; 95% CI

(0.34, 1.42), *p* for trend=0.32] of gout, but in neither case were the associations statistically significant. Purine intake, approximately 20% of which was estimated to be derived from the consumption of soyfoods (data not shown), was unrelated to risk [OR for third intake tertile, 0.97; 95% CI (0.48, 1.97), *p* for trend=0.93].

More direct insight into the possible impact of soy intake on gout risk comes from research by Pan *et al.*, who compared plasma uric acid levels of 55 vegetarian male and female Taiwanese Buddhists with 59 non-vegetarian medical students between the ages of 20 and 30 years.[88] The vegetarians consumed on average 3.5 portions of soyfoods daily versus only one for the non-vegetarians. Plasma uric acid levels [μM, mean ± standard deviation (SD)] did not differ between vegetarians (n=23; 369±48) and non-vegetarian (n=20, 357±30) males. However, the plasma uric acid level of female vegetarians (n=32, 226±59) was significantly lower (*p*=0.05) than the non-vegetarian levels (n=38, 258 ±54). Total dietary protein intake was similar between the two female groups whereas male vegetarians consumed less protein than non-vegetarian males (61.3 g/d±12.1 versus 78.1 g/d± 13.8, *p*<0.001).

The results from a study by Yu *et al.*, which included 2176 Taiwanese adults, 987 (45%) men and 1189 (55%) women, also provide no evidence that soyfood intake leads to higher uric acid levels.[89] Mean ± SD serum urate levels were 6.81±1.66 mg/dL (range, 2.5-16.8 mg/dL) and 5.47±1.55 mg/dL (range, 1.4-11.5 mg/dL) for men and women, respectively. Based on intake data obtained via 24 hour recalls, the consumption of protein-rich foods, which included egg and egg products, dairy products and soybean and soybean products, was shown to be inversely related to the prevalence of hyperuricemia (>458.0 μM, 7.7 mg/dL for men and >392.6 μM, 6.6 mg/dl for women) in both men (*p* for trend, 0.001) and women (*p* for trend, 0.052). Data obtained via food frequency questionnaire (FFQ) showed that soy drink intake was unrelated to risk (*p* for trend, 0.786 and 0.345 for men and women, respectively) whereas the intake of beer, as assessed by both 24 hour recalls (men and women, *p*=<0.001 and 0.002, respectively) and FFQ (men and women, *p*=0.007 and 0.020, respectively), was associated with an increased risk of hyperuricemia.

The most recently-published Taiwanese epidemiologic study included 752 men aged ≥65 y who had been part of the Elderly Nutrition and Health Survey.[91] Chang divided subjects into four groups: normouricemic (n=329), hyperuricemic (n=228), treated hyperuricemic (n=44) and chronic kidney disease (CKD) (n=151). Mean (SD) serum uric acid levels (mg/dL) of the four groups were 5.7±0.9, 8.2±1.1, 7.9±2.5 and 8.2±2.2, respectively.[91] The percentage of men in each of the four groups that consumed soy (soy drink, tofu, sweet bean soup) ≥4 x/wk was 59.2, 52.9, 34.1 and 46.7, respectively. When considering soy intake, with the normouricemic men treated as the reference (1.00), the ORs (95% CI) for developing the other three serum uric acid-related conditions (hyperuricemia, treated hyperuricemia and CKD) were 0.92 (0.76, 1.11), 0.53 (0.36, 0.79) and 0.77 (0.61, 0.97), respectively. The *p*-value, which represents the comparison of ORs among the four serum uric acid-related conditions by using polychotomous logit model analysis, was 0.0051. On the basis of these findings, Chang concluded that men who consumed fewer soy products may be at a higher risk of developing hyperuricemia or CKD.[91]

One of the two non-Taiwanese epidemiologic investigations identified, which was conducted by Liu *et al.*, was a cross-sectional study conducted in China that included 183 participants from Beijing with a mean (SD) age of 40.4±12.5 years.[93] No differences in serum uric acid concentrations between low- (n=98, 274.67±99.00 μM) and high- (n=99, 269.01±84.88 μM) consumers were noted. Mean isoflavone intakes in the low and high isoflavone groups were 4.6 mg/d and 23.6 mg/d, respectively. Based on the ratio of isoflavones (mg) to soy protein (g) reported in this study, estimates are that soy protein intakes in the low and high isoflavone groups were 1.4 and 7.2 g/d, respectively.

In the other epidemiologic study from China, Villegas *et al.* investigated associations between high purine-content foods and protein intake with the prevalence of hyperuricemia using data from a cross-sectional study of 3978 men aged 40-74 years living in Shanghai.[92] Mean soyfood intake in the normal (n=2982) and hyperuricemic (n=996) men were 76.3 and 77.7 g/d, respectively. There was a positive association between protein from animal sources and an inverse association between protein from plant sources and prevalence of hyperuricemia; although in mutually adjusted analysis, these associations were not statistically significant. Importantly, an inverse association approaching significance between soyfood consumption and hyperuricemia was observed (ORs: 1.00, 0.92, 0.86, 0.85, and 0.80 for quintiles of intake; *p* for trend: 0.07).

Finally, in addition to those studies discussed above, two small epidemiologic studies are noteworthy, even though neither assessed soy intake. However, because both involved Taiwanese vegetarians, a reasonable assumption is that soy was a substantial part of their diet. In one, mean (SD) serum uric acid level of middle-aged vegetarians (n=19) was significantly lower (4.54±0.75 versus 5.25±0.84 mg/dL, *p*=0.011) than that of non-vegetarians (n=17); however, there were fewer males among the vegetarians (47 versus 59%).[94] In the other, a cross-sectional study that included 102 Buddhist vegetarian nuns and an equal number of a matched control group (omnivores) age 20 to 78 years, no differences in plasma uric acid level were noted between groups (vegetarian, 4.8±1.0 versus 4.8±1.2 mg/dL, *p*=0.92). In addition, the prevalence of hyperuricemia (≥6 mg/dL) did not differ between groups (vegetarians, 9.8% versus omnivores, 11.8%; *p*=0.65).[95]

The epidemiologic data indicate that soyfood intake is not associated with hyperuricemia; however, the available research has several limitations, including the fact that as already noted, all studies involved subjects of Chinese ethnicity and four of the six studies were conducted in one country, Taiwan. Further, in the study by Lyu *et al.*, data on soyfood intake were not presented nor was the relationship between soy intake and gout directly examined.[20] In the vegetarian study by Pan *et al.*, the differences in soy intake between groups was substantial (3.5 versus 1.0 portions per day) but there was incomplete

assessment of overall dietary intake of the two groups.[88] Therefore, non-soy dietary differences between groups could in theory have masked an effect of soyfoods on serum uric acid levels. To this point, vitamin C has a hypouricemic effect[52,53] and although the intake of this vitamin was not reported, generally vegetarian vitamin C intake exceeds that of non-vegetarians.[96]

In the study by Yu *et al.*, although soyfoods were part of a category of foods inversely related to the prevalence of hyperuricemia,[89] this group also included dairy products, which may be hypouricemic.[50,54] Without knowing approximately how much soy and dairy was consumed, it is difficult to draw any meaningful conclusions from the data. On the other hand, the finding that soy drink intake was unrelated to hyperuricemia is notable, although even in this case, the implications of this observation are limited because absolute intake data were not presented. In the Beijing study by Liu *et al.*, even in the high isoflavone group, soy protein intake was relatively low (~7.2 g/d) and likely represented less than 10% of overall protein intake.[93] The strongest data comes from the study by Villigas *et al.*, which suggested soyfood intake was inversely related to risk of hyperuricemia in men, because of the large number of subjects involved and the extensive assessment of soy intake.[92]

Clinical studies

Five human intervention studies were identified that examined the impact of soy intake on plasma or serum uric acid levels.[97-101] In the first study to be published, Breslau *et al.* utilized a crossover design in which 15 (8 women, 7 men) normal weight subjects consumed for 12 days, diets in which the bulk of the protein was provided by animal products (animal), soy plus eggs (ovo-vegetarian), or soyfoods (n=12) (vegetarian).[97] Serum uric acid levels (mean ± SEM) on days 9-12 of the vegetarian, ovo-vegetarian and animal product dietary periods were 300±20, 320±10 and 330±20 μM, respectively, with no significant differences among groups. Urinary uric acid excretion for these three groups (mean ± SEM) was 479±28, 490±18 and 564±26 mg/d, respectively (p<0.02 animal versus ovo-vegetarian). For the first 6 days of each diet, subjects prepared and ate the appropriate instructed diet at home whereas during the final 6 days, the diets were provided by the clinical research center. Soy protein in the vegetarian diets was provided by soy drink and textured vegetable protein. However, although the diets were said to be isocaloric and protein was said to provide 15-20% of calories, the precise number of grams of protein from each type of food was not indicated. The purine content (mean ± SEM) of the vegetarian, ovo-vegetarian and animal diet, which was estimated from food tables, was listed as 1±0, 2±1 and 72±6 mg [animal diet significantly different from the vegetarian and ovo-vegetarian diets (p<0.001)], respectively, which is surprising given that soyfoods contain purines. Nevertheless, this study provides no evidence that incorporation of soy into the diet affects serum uric acid levels.

In the next study, Yamakita *et al.* measured plasma uric acid levels hourly beginning immediately prior to and for 3 hours following the ingestion of tofu (4 g/kg BW) in Japanese male gout patients (n=10) and healthy subjects (n=8) aged 30 to 50 years.[98] Plasma levels (μM) at 0, 1, 2, and 3 hours in healthy subjects and gout patients were 5.56, 5.59, 5.83, and 5.73, respectively and 8.10, 8.21, 8.27, and 8.12, respectively. In healthy subjects, the rise in plasma levels at hours 2 (p<0.05) and 3 (p<0.01) post-ingestion were statistically significant, whereas there were no significant changes in the gout patients overall. However, there was a statistically significant increase at hour 2 (p<0.05) in gout patients with uric acid clearance below, but not above 6 ml/min. The tofu used in this study was reported to contain 13 mg purines and 6.3 g protein per 100 g.

Canadian researchers were the first to directly compare the effects of isolated soy protein (ISP, by definition is ≥90% protein) with other proteins on serum uric acid levels.[99] After an overnight fast, Garrel *et al.*, provided 80 g of casein, lactalbumin, or ISP to ten young healthy men and women.[99] Serum uric acid levels at 0, 1, 2 and 3 hours post ISP ingestion were 283, 307, 319 (p<0.01 versus baseline) and 314 μM (p<0.01 versus baseline), respectively. In contrast, serum uric acid levels declined by about 10% (casein: 295 to 266 μM, p<0.01; lactalbumin: 301 to 267 μM, p<0.01) in response to the other two proteins. Neither casein nor lactalbumin contained purines whereas the soy protein reportedly contained 118 and 187 mg adenine and guanine, respectively. Uric acid clearance increased similarly in all three proteins confirming the uricosuric action of protein. In a second Canadian study, which utilized a three way crossover design, Brule *et al.* compared the effects of meals containing approximately 50 g protein from different sources – haddock, liver, and soybeans – in 18 healthy men aged 20-48 years.[100] The three meals contained similar amounts of purines but the types of purines differed. At 120 min post ingestion, mean serum acid levels increased by 0.34, 0.15, and 0.25 mg/dl (two groups) in response to the haddock, liver and soybean meals, respectively. In one group of men consuming the soybean meal, serum acid levels increased by 0.48 mg/dl. The increase at 120 min was significant (p<0.05) in all three groups of men consuming haddock and in the group of men consuming soybeans that experienced the largest increase. At 240 min post ingestion, levels returned to near their baseline values in all groups. On the basis of the relatively modest increases in serum uric acid levels, the authors of this study concluded that "The exclusion of some foods high in nucleic acids, such as liver and legumes, in a purine-restricted diet seems too restrictive…".[100]

Finally, Dalbeth *et al.* compared the effects of soy protein (Pro-Fam 873; Archer Daniels Midland, Co, Decatur, Illinois, USA) on serum uric acid levels and excretion over a 3 hour period with three different types of dairy milk in 16 healthy Australian males with a median age of 34 years.[101] The dairy milks varied in their content of orotic acid, a uricosuric compound.[102] All four intervention products led to an increase in serum uric acid excretion; however, in response to soy protein, serum uric acid levels increased by about 10% whereas there was a significant reduction (p value not indicated) in response to each of the three dairy milks. The intervention products provided 80 g protein and were administered in an 800 ml

suspension. The soy protein contained 8.8, 7.6, 9.3, and 10.6 mg of adenosine monophosphate, guanosine monophosphate, adenosine and guanosine, respectively.

The results of the five clinical studies discussed above indicate soyfood intake does not markedly affect serum uric acid levels. In the crossover study by Breslau *et al.*, there were no difference in serum uric acid levels among the three types of diets even though soy protein provided the bulk of the protein in the vegetarian diet.[97] In the tofu study by Yamakita *et al.*, the findings from which should be view cautiously because of the lack of a control protein, serum uric acid levels increased in healthy subjects by only about 5% whereas in gout patients overall, there was no increase.[98] Assuming a body weight of 60 kg, subjects consumed approximately 15 g soy protein. The lack of effect in gout patients in this study is notable since some data suggest gout patients are more responsive to the uricogenic effects of purines than healthy subjects.[60] However, uric acid levels did increase somewhat in gout patients with poor renal uric acid clearance.

In the study Garrel *et al.*, 2 hours post ingestion of soy protein serum uric acid levels increased approximately 13 percent.[99] However, this increase occurred in response to 80 g protein – the amount of protein typically consumed by adults throughout an entire day.[103] In the Australian study by Dalbeth *et al.*, there was only a 10% increase in response to the same amount of soy protein.[101] In response to 50 g soy protein, the amount used in the study by Brule *et a.l*, serum uric acid levels increased only about 5%,[100] similar to that observed in the tofu study.[98] It is not clear why there were similar increases in serum uric acid levels in these two studies despite such large differences in protein intake and purine exposure between the two intervention products (tofu, 31 mg; soy protein, 186 mg).

In any event, the results of the studies by Bresleau *et al.*, Yamakita *et al.* and Brule *et al.*, show that that the consumption of soy protein in amounts similar to and as much as three times higher than typical Japanese intake are unlikely to have clinically relevant effects on serum uric acid levels.[18,97,98,100] This conclusion is supported by the results of an Italian cross-over study by Cicero *et al.*, which found that the consumption of 8 g/d ISP over a 40-day period had no effect on plasma uric acid levels in middle-aged Caucasian hypercholesterolemic subjects.[104] This study is not reviewed in detail here because the soy protein was combined with 2 g/d β-sitosterol, which may have influenced the results. Obvious limitations of the clinical data are the relatively short-term intervention periods and the evaluation of soy protein in isolation rather than as part of a meal containing protein from multiple sources as would typically be the case in free-living populations.

SOYFOODS AND DISEASES ASSOCIATED WITH HYPERURICEMIA AND GOUT

There is a strong association between insulin resistance and hyperuricemia and the metabolic syndrome.[105,106] The increase in serum uric acid concentration in those with insulin resistance is due to a decrease in urinary uric acid clearance.[107] Also, several lines of evidence suggest that hyperuricemia is associated with increased risks of a number of chronic diseases. For example, a systematic review and meta-analysis that included 26 studies and 402,997 adults, found that hyperuricemia was associated with an increased risk of CHD (crude risk ratio [RR] 1.34, 95% CI, 1.19-1.49) and mortality (crude RR 1.46, 95% CI, 1.20-1.73).[108] When adjusted for potential confounders, the pooled RR was 1.09 (95% CI 1.03-1.16) for CHD incidence and 1.16 (95% CI 1.01-1.30) for CHD mortality. For each increase of 1 mg/dl in uric acid level, the pooled multivariate RR for CHD mortality was 1.12 (95% CI 1.05-1.19). The increased risk of CHD mortality was much stronger in women than men.[108] A similar analysis conducted by this same group of investigators also found that hyperuricemia increased risk of stroke incidence and mortality.[109] Research suggests hyperuricemia is also strongly associated with CKD[110,111] and hypertension and as already noted, potentially, the metabolic syndrome.[112-114]

Interestingly, in the early 1980s, Ames *et al.* suggested that an increase in circulating levels of uric acid was advantageous because of in vitro research showing that uric acid is a powerful scavenger of singlet oxygen, peroxyl radicals and hydroxyl radicals.[115] Subsequent research has confirmed the antioxidant properties of uric acid.[116] The antioxidant properties appear to clash with the relationship between hyperuricemia and elevated stroke and CHD risk. However, according to Sautin and Johnson, uric acid can function as both an anti- and pro-oxidant and it is the latter attribute that plays a role in the etiology of cardiovascular disease.[117]

It is beyond to scope of this review to comprehensively evaluate the effects of soyfoods on those conditions and diseases associated with hyperuricemia and gout so only a few general comments on soyfoods and cardiovascular disease will be made although there are intriguing data indicating that relative to animal protein, soy protein favorably affects renal function.[118-127] These data are relevant to gout patients given their proclivity for developing CKD.[111] Also, soyfoods may hold advantages for those at risk of developing, and those with, the metabolic syndrome.[128]

There is considerable evidence indicating that soyfoods offer coronary benefits. They provide ample amounts of high-quality protein and are low in saturated fat and high in omega-6 and omega-3 polyunsaturated fatty acids (PUFA).[16,17] Recent evidence indicates that to decrease risk of CHD, high-saturated-fat-foods should be replaced with a mix of omega-6 and omega-3 PUFA.[129] In addition, meta-analyses indicate that soy protein directly reduces low-density-lipoprotein (LDL)-cholesterol levels by approximately 4 percent.[130-136] Furthermore, there is epidemiologic and clinical evidence indicating that independent of effects on cholesterol, soyfoods reduce risk of CHD.[1,2,137,138] Perhaps most relevant to gout patients is the possibility that soyfoods are hypotensive although soybean isoflavones have also been shown to improve endothelial function in postmenopausal women.[2,134]

SUMMARY AND CONCLUSIONS

The commonly-held belief within Asia that soyfoods increase risk of developing gout and/or are contraindicated for gout patients was confirmed by the results of the small

survey of healthcare professionals (Table 2). However, as discussed, neither the epidemiologic nor clinical data justify this concern. In fact, the most important of the epidemiologic studies, because of its size and comprehensive assessment of soy intake, suggests that soyfoods may actually decrease risk. Further, there is evidence that soyfoods may help to reduce the risk of the comorbidities associated with hyperuricemia and gout. Therefore, healthcare practitioners are not justified in advising their gout patients to avoid soyfoods.

This having been said, it is important to recognize the limitations of the existing data. No long term intervention studies have examined the effect of soy intake on circulating uric acid levels and no large scale epidemiologic studies have examined the soy and gout relationship. Therefore, it would be useful for future Asian epidemiologic studies to do so and for long-term soy intervention studies to include serum uric acid levels as an endpoint. Considering the amount of epidemiologic and clinical work involving soy routinely published, the current literature void could be filled within the foreseeable future.

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AUTHOR DISCLOSURES

MM regularly consults for companies that manufacture and/or who sell soyfoods and/or soy extracts. VLM has nothing to declare. PC has nothing to declare.

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Review

Soyfoods, hyperuricemia and gout: A review of the epidemiologic and clinical data

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黄豆食品與高尿酸血症及痛風：流行病學及臨床研究的回顧

黄豆食品长久以来就是亚洲传统饮食的一部分。 它们提供大量的高质量蛋白质及拥有良好的脂肪酸组合。有一些挑戰性的研究更認為，即使不考虑黄豆食品的营养成分，它们本身也可为健康带来好处。但是，一些亚洲的保健人員和大众都广泛地相信，黄豆食品可增加痛风的风险以及会促成痛风病人急性发作的可能。为了考證此观念的真实性，本篇回顧嚴謹地评估了相关的临床及流行病学的资料。此外，亦提供亚洲高尿酸血症和痛风的病因及盛行率的背景资料，同時呈現一份针对亚洲保健從業人員对黄豆食品看法的小型调查报告。在这些保健相關人員当中，有 95% 认为黄豆食品相當或非常健康及有营养。相反地，有 48% 认为黄豆食品有可能导致痛风。然而，在 6 个被确定的流行病学研究中，并没有任何一个有证据显示摄取黄豆与尿酸的水平、高尿酸血症或痛风有关联。从评估的 5 份人群介入研究资料中，虽然显示黄豆蛋白质会提升血液中的尿酸，但基于亚洲人的黄豆摄取量，可预期的尿酸上升程度在临床上几可確定是無意義的。虽然长期的研究仍有必要，但依据目前已有的资料，已患上痛风或有风险患上痛风的人并不需要避免黄豆食品。

關鍵字：黄豆、素食者、痛風、高尿酸血症、尿酸