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Review

Essentials of dietary habits for prevention and suppression of hyperuricemia

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ABSTRACT

Hyperuricemia is recognized as a lifestyle-related disease. Studies from every part of the world suggest that the incidence of hyperuricemia is increasing. Hyperuricemia is associated with a higher prevalence of comorbidities (e.g., chronic kidney disease, obesity, hypertension, diabetes and cardiovascular disease) compared to subjects with a normal serum uric acid (SUA) level. The objective of this review is to propose the importance of lifestyle in modulating SUA levels based on dietary habits to prevent and suppress hyperuricemia. This review also touches on the association between dietary factors and comorbidities of hyperuricemia. Dietary habits for the prevention and suppression of hyperuricemia are speculated as follows: higher adherence to the Mediterranean diet (The traditional Mediterranean diet); higher adherence to the Dietary Approaches to Stop Hypertension (DASH) diet; encouraged intake of legumes, nuts, fruit, vegetables, fiber-rich foods (e.g., cereals, whole grains, high-fiber bread), dairy products (especially, low-fat or nonfat dairy products), and coffee; limiting the intake of meat, seafood, organ meats high in purine content (e.g., liver, kidney), sugar-sweetened beverages, sugary foods including desserts and sweets, and salt; limiting alcohol consumption; maintenance of good hydration; and weight management including proper calorie intake and adequate exercise. The above dietary habits for the prevention and suppression of hyperuricemia with proper choices of foods may also play a helpful role in the prevention of gout and some of the comorbidities of hyperuricemia. The author wishes to emphasize the importance of recognizing the validity of dietary patterns as a potential method to prevent hyperuricemia and its comorbidities in the general population.

KEYWORDS: cardiovascular disease, chronic kidney disease, DASH diet, food, gout, hypertension, hyperuricemia, Mediterranean diet, obesity, uric acid.

ABBREVIATIONS

ADA	:	The American Diabetes Association
AusDiab	:	Australian Diabetes, Obesity and Lifestyle Study
BMI	:	body mass index
CAD	:	coronary artery disease
CHD	:	coronary heart disease
CKD	:	chronic kidney disease
CVD	:	cardiovascular disease
DASH diet	:	Dietary Approaches to Stop Hypertension diet
DF	:	dietary fiber
NAHSIT	:	The Nutrition and Health Survey in Taiwan
NHANES	:	The U.S. National Health and Nutrition Examination Survey
NO	:	nitric oxide
RNA	:	ribonucleic acid

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SUA : serum uric acid
UA : uric acid
URAT1 : urate transporter 1
UUA : urinary uric acid

1. Introduction

The onset of hyperuricemia is connected deeply with genetic factors and environmental factors [1]. In recent years, the prevalence of hyperuricemia is increasing in many countries around the world and has attracted attention as one of the lifestyle-related diseases [1-9]. For example, in the U.S. National Health and Nutrition Examination Survey (NHANES) (2007-2008), the overall prevalence of hyperuricemia, defined as serum uric acid (SUA) level > 7.0 mg/dL (416.4 μmol/L) in men and > 5.7 mg/dL (339.0 μmol/L) in women, among U.S. adults was 21.4% (total, 43.3 million; men, 20.7 million; women, 22.6 million) [4]. These estimates were higher than those in the NHANES-III (1988-1994) database, representing an increase of 3.2% in the prevalence of hyperuricemia [4].

Hyperuricemia is classified into three types: “overproduction” - an excessive production of uric acid (UA); “underexcretion” - an impairment of urinary uric acid (UUA) excretion; and “mixed,” which is caused by both factors [1]. In the U.S., hyperuricemia results from the overproduction of UA (10%), underexcretion of UA (90%), or often a combination of the two [10]. Regardless of the disease type classification, renal underexcretion of UA is considered to be the most frequent mechanism for the development of hyperuricemia [11, 12].

Hyperuricemia is considered the precursor of gout [10, 13-16]. Hyperuricemia is a major risk factor for gout, kidney dysfunction, and urolithiasis [1]. Hyperuricemia has been related to increased risk of cardiovascular disease (CVD) and metabolic syndrome [17, 18]. Asymptomatic hyperuricemia is a biomarker of both increased risk and presence of vascular disease [e.g., hypertension, coronary artery disease (CAD), renal disease] [19]. Some studies have reported that hyperuricemia has been associated with an increased risk of some diseases related to oxidative stress, such as metabolic syndrome [20], CVD [21] and obesity [22]. Furthermore, recent studies have illuminated the substantial comorbidities of hyperuricemia and gout, particularly metabolic-cardiovascular-renal conditions [23].

This review summarizes the results of clinical research (clinical trials and epidemiological studies) of the association between SUA concentration or hyperuricemia risk and dietary factors. This review also touches on the association between dietary factors and comorbidities of hyperuricemia. In addition, this review proposes healthy dietary patterns for the prevention and suppression of hyperuricemia and the prevention of its comorbidities based on the results mentioned above.

2. Serum uric acid (SUA) concentration

Uric acid (UA) is the end product of purine degradation in humans [24, 25]. Serum uric acid (SUA) concentration reflects the interaction of four major processes: (1) dietary purine intake; (2) endogenous purine metabolism; (3) urinary UA (UUA) excretion; (4) intestinal uricolysis [26]. SUA concentration is determined by the amount of production of UA and efficiency of UUA excretion [27, 28]. Endogenous production of UA from degradation of purine usually contributes about two-thirds of body urate pool, the remainder being dietary in origin [29]. Therefore, elevated SUA levels are caused by increased UA synthesis from food constituents and reduced renal excretion.

UA may function either as an antioxidant (primarily in plasma) or prooxidant (primarily within the cell) [30]. SUA is a major antioxidant in human plasma; but under ischemic conditions, its antioxidant activity is overcome by the prooxidant and proinflammatory effects of reactive oxygen species accumulation [31]. The increase in SUA levels may reflect tissue hypoxia or increased oxygen free radical formation [32]. These effects are the result of the accumulation of oxygen free radicals after xanthine dehydrogenase (EC1.17.1.4) converts to xanthine oxidase (EC1.17.3.2) in parallel with UA production as an effect of adenosine triphosphate degradation [33]. SUA concentration has been assessed as a risk marker for cardiovascular disease (CVD) and renal disease (especially in patients with hypertension,

diabetes, and heart failure) [34]. SUA may be considered as a biomarker for vascular function [35]. The possible explanation could be that UA stimulates oxidative stress through the renin-angiotensin system in vascular endothelial cells as well as vascular smooth muscle cells, and increases nicotinamide adenine dinucleotide phosphate oxidase-derived reactive oxygen species production [36-38]. Furthermore, Jamshed *et al*. [39] have stated that anticipated pathways of UA-induced vascular dysfunction [40] include, but are not limited to, prooxidative effect, whereby UA decomposes and generates free radicals; proinflammatory effect *via* association with biomarkers like interleukins (IL-1, IL-6, IL-10, IL-18), tumor necrosis factor (TNF-α) and C-reactive proteins (CRP); endogenous stimulation of innate immunity; changing expression of endothelin-1; promoting angiotensin-II production; inducing smooth muscle cell proliferation; and direct reaction with, and depletion of nitric oxide (NO). Increased SUA levels are a risk factor for CVD and other disorders where oxidative stress plays an important pathophysiological role [17, 33, 41-44]. In the atherosclerotic prooxidative environmental milieu, the original antioxidant properties of UA paradoxically become prooxidant, thus contributing to the oxidation of lipoproteins within atherosclerotic plaques, regardless of their origins in metabolic syndrome, type 2 diabetes mellitus, accelerated atherosclerosis (atherosclerosis), or non-diabetic vulnerable atherosclerotic plaques [34]. UA can oxidize low-density lipoprotein (LDL) in the presence of copper ions and lipid hydroperoxides, increasing inflammatory status [45]. SUA level is positively associated with several inflammatory markers (e.g., white blood cell count, C-reactive protein, interleukin-6) [46].

3. Association between dietary factors and SUA concentrations or hyperuricemia risk

During human evolution, SUA levels were increasingly according to the usefulness of the diet of high-purine foods for many years [47]. SUA concentration is increased by alcohol consumption, diet, and exercise [48]. The introduction of Western lifestyle to non-Western people has been associated with increases in SUA levels, the incidence of gout or both hyperuricemia and gout [49]. Recent large-scale epidemiological studies have shown that dietary factors affect SUA levels parallel to the direction of risk of hyperuricemia [23]. Therefore, management of SUA concentration is important for the prevention and suppression of hyperuricemia. Dietary habits to reduce SUA concentrations based on proper choices and moderate intakes of foods are essential.

It is important to recognize that current dietary recommendations for the prevention and suppression of hyperuricemia are widely based on results of clinical research (clinical trials and epidemiological studies) looking at association between hyperuricemia and intake of certain foods. Association between hyperuricemia and dietary factors is as follows.

3.1. Energy

In a cross-sectional study performed in the Netherlands within the framework of the Dutch Nutrition Surveillance System (1984-1985), neither energy intake nor energy derived from fats was associated with SUA level among 237 males and 223 females [50]. In both the Australian cohort (the AusDiab Study) and the Norwegian cohort (the Tromsø study), total energy consumed per day was not associated with SUA level in most subject groups [51]. The results from a cross-sectional study by Yu *et al*. [52], which included 2,176 Taiwanese adults, 987 men and 1,189 women, found that total calorie intake was not associated with the prevalence of hyperuricemia. However, Zhu *et al*. [53] reported that excessive intake of energy was a risk factor of hyperuricemia in middle-aged and elderly people in China.

3.2. Dietary fat

In both the AusDiab Study and the Tromsø study cohorts, higher intake of fat was associated with higher SUA levels in most subject groups [51]. In contrast, an epidemiological study conducted by Loenen *et al*. [50] using the Dutch Nutrition Surveillance System (1984-1985) data showed that fat intake was not associated with the SUA level. The U.S. National Health and Nutrition Examination Survey (NHANES) (1999-2004) provided epidemiological evidence that intake of

fat had no significant influence on the risk of hyperuricemia in a representative sample of the U.S. population [9,384 men and women (aged 20-80 years)], without diabetes, cancer, or heart disease [54]. A cross-sectional study in Taiwanese men and women revealed that there was a positive association between intake of fats and oils in men or intake of fat, polyunsaturated fatty acid (PUFA), and total fatty acid in women and the prevalence of hyperuricemia [52]. Zhu *et al*. [53] reported that excessive intake of fat was a risk factor of hyperuricemia in middle-aged and elderly people in China. Animal-based study showed that safflower-seed oil decreased SUA level in hyperuricemia-induced rat [55].

3.3. Protein

Recent epidemiological studies showed that the total protein intake was not associated with the SUA level [50, 51, 56] and hyperuricemia risk [52, 54, 57].

The effect of protein on SUA concentration or hyperuricemia risk varies depending on the protein derived from food. A positive association between protein intake from animal sources and the prevalence of hyperuricemia, as well as an inverse association with protein from plant sources has been revealed [56, 57]. In a cross-sectional study, there was an inverse association between intake of protein-rich foods (egg and egg products, dairy products, soybean, and soybean products) and the prevalence of hyperuricemia [52]. Greater consumption of soy protein (6.1 versus 0.5 g/day) was associated with a lower presence of hyperuricemia in women [58].

Administration of 80 grams of casein and lactalbumin significantly reduced SUA concentration after a 3-hour period, while that of soy protein increased SUA concentration [59]. The amounts used in those studies were much greater than that routinely consumed in an entire day. Jenkins *et al*. [60] found that high intake of gluten-derived protein (especially, wheat gluten) reduced SUA concentration. Ingestion of 10 g/day of rice endosperm protein for 4 weeks significantly decreased SUA concentration compared with the casein group or the baseline in adult male subjects with risk factors for metabolic syndrome [61]. Soy protein with safflower-seed oil decreased SUA level in hyperuricemia-induced rats [55]. The uricosuric effects of casein and lactalbumin seem to contribute to an acute uric acid-lowering effect. These reports indicate that intake of protein from vegetable sources and milk proteins (casein and lactalbumin) may have a protective effect for hyperuricemia. Further clinical trials and prospective studies are needed to clarify the association between protein intake and hyperuricemia risk.

3.4. Oligopeptide

Tyr-Leu-Asp-Asn-Tyr and Ser-Pro-Pro-Tyr-Trp-Pro-Tyr, which is a peptide in the alcalase digest of shark cartilage, had an effect of lowering SUA levels in oxonate-induced hyperuricemic rats [62]. In a randomized double-blind, placebo-controlled study for 4 weeks in gout-free subjects with insignificantly high SUA level [SUA $\geq$ 7.0 mg/dL], SUA level in the tuna extract containing the imidazole compound (L-histidine, anserine and carnosine) group (477.1 mg/day) tended to decrease at week 2 and 4 and significantly decreased at week 2 after the intervention, compared with the placebo group [63].

3.5. Vitamins

3.5.1. Vitamin A and β-carotene

From the results of the NHANES-III (1988-1994) data, Choi *et al*. [64] found that serum retinol levels were associated with SUA levels and the frequency of hyperuricemia, and serum β-carotene, which is a precursor to vitamin A, was inversely associated with SUA levels and the frequency of hyperuricemia. Ford and Choi [65] found that higher serum levels of vitamin A were associated with increasing SUA levels in both males and females, suggesting that supraphysiological vitamin A supplementation may be contributing to high rates of hyperuricemia and gout in the U.S. In contrast, β-carotene supplementation was reported to lower SUA levels in healthy adult subjects [66]. In the AusDiab cohort, increased intake of retinol showed a tendency to increase SUA levels, and increased intake of β-carotene did not lower SUA levels [51].

3.5.2. Vitamin B1 (thiamin) and B2 (riboflavin)

A cross-sectional survey using Australian Diabetes, Obesity and Lifestyle Study (AusDiab) data (1999/00)

collected for 9,734 subjects [4,295 males and 5,439 females (aged ≥ 25 years)] showed that higher consumption of vitamin B1 (thiamin) was associated with lower SUA levels [51]. In both the AusDiab Study and the Tromsø study cohorts, higher consumption of vitamin B2 (riboflavin) was associated with lower SUA levels in most subject groups [51]. Results from these studies showed that the average reduction of SUA level was significant when vitamin B2 intakes were above 2 mg per day [51].

3.5.3. Vitamin B9 (folate)

In the Australian cohort (the AusDiab Study), vitamin B9 (folate) consumption was invesely associated with SUA level [51]. Large amounts of supplemental folate (up to 80 mg/day) reduced SUA levels. The mechanism is presumed to be mediated through the inhibition of xanthine oxidase [67]. However, one intervention study showed that folate supplementation failed to lower blood UA concentrations in individuals with hyperuricemia [68].

3.5.4. Vitamin C

Vitamin C intake has been found to reduce SUA levels in clinical trials [69-73] and epidemiological study [74] and has recently been linked to a reduced future risk of hyperuricemia [52, 74]. For example, the metabolic experiments revealed that ingestion of daily 3 g or more of vitamin C in humans reduced SUA concentration [69-71]. Huang *et al*. [72] found that supplementation with 500 mg/day of vitamin C for 2 months reduced SUA concentration by increasing the estimated glomerular filtration rate (eGFR) in a randomized controlled trial. In the Health Professional Follow-up Study, Gao *et al*. [74] showed that total vitamin C intake of 500 mg/day or higher was associated with a ~ 0.6-0.7 mg/dL lower level of SUA and was over 42% less likely to be hyperuricemia relative to those with intake < 90 mg/day.

Vitamin C possesses uricosuric properties [71, 73, 75]. Vitamin C likely modulates SUA concentration *via* its uricosuric effects. Choi *et al*. [74, 76] proposed that the uricosuric effects of vitamin C could be attributed to the following: (1) vitamin C and UA are reabsorbed through anion-exchange transport in the proximal tubule [72]. Increased vitamin C concentration in the filtrate may competitively inhibit UA reabsorption *via* an anion-exchange transport system at the proximal tubule [71, 72, 75]; (2) the uricosuric effect may be through cis-inhibition of URAT1 (urate transporter 1, the key target of typical uricosurics), Na^+-dependent anion cotransporter (e.g., SLC5A8/A12), or both in the proximal tubule [74, 76]; and (3) greater vitamin C intake may possibly improve renal function and increase the glomerular filtration rate [72, 77], providing another potential mechanism for the uricosuric effect of vitamin C intake [74, 76]. Both human and animal studies have demonstrated that administration of vitamin C increases renal plasma flow and glomerular filtration rate and attenuates the increases in arterial pressure [77, 78]. It is also possible that vitamin C increases glomerular filtration rate, thereby increasing UA excretion. Furthermore, vitamin C inhibits the prooxidant actions of UA during copper-mediated low-density lipoprotein cholesterol (LDL-cholesterol) oxidation, and could reduce oxidative stress and inflammation, and may, therefore, be related to lower UA production [34]. It is speculated that UA-lowering effect of vitamin C is associated with both uricosuric properties and lower UA production.

Juraschek *et al*. [73] studied vitamin C supplementation by pooling the findings from published randomized controlled trials in children and adults not on hemodialysis and found significantly lower SUA levels. Vitamin C supplementation (intravenous 250 mg of vitamin C three times a week for 12 weeks) showed a significant reduction in SUA levels in children with end-stage renal disease on maintenance hemodialysis [79]. Since vitamin C is partly metabolized to oxalate, which can accumulate in renal failure patients, many clinicians recommend a dose of only 60-100 mg/day, which may not be optimal [80]. The upper limit of vitamin C ingestion per day has been stated by the U.S. Food & Drug Administration to be below 2.0 g/day in adults (age > 19 years), as gastrointestinal effects such as diarrhea have been reported with doses over 1000 mg/day. However, it is unclear whether the ingestion of large amounts of vitamin C is what influences individuals with hyperuricemia. Terkeltaub and Edwards [81] have stated that

it is not known if combined effects on urine pH, oxalate generation, and uricosuria of high vitamin C intake can promote urolithiasis.

3.6. Dietary fiber (DF)

We [82-89] found that dietary fiber (DF) suppressed both the overproduction-type and the underexcretion-type hyperuricemia induced by dietary purine in rats. The mechanism is presumed to be mediated by suppression of the digestion and/or absorption of dietary purine by DF [82-87, 89]. In case of agarose, the suppressive mechanism of agarose on hyperuricemia induced by dietary RNA is presumed to be due to suppression of digestion and/or absorption of RNA and an increase in the renal excretion efficiency of UA [88]. Recently, Lin *et al*. [90] observed that inulin suppressed the elevation of SUA concentration in quails fed a purine-rich diet. This result shows the same tendency as the results that we have obtained [82-89]. Recently, clinical trials have revealed that DF intake lowers SUA concentrations in healthy subjects [91] and individuals with hyperuricemia [92]. Epidemiological studies found that increased DF intake was associated with decreased SUA concentrations [51, 54, 93] and reduced hyperuricemia risk [52, 54]. It seems that the basic research results of our series concerning the suppressive effect of DF on hyperuricemia stimulated subsequent clinical research into this matter. The mechanisms by which DF lowers SUA concentrations are fully unknown and must be clarified in further studies. The recommended intake of DF is 14 g/1000 kcal, which is based on protection against cardiovascular disease (CVD) in prospective cohort studies [94], and the recommended acceptable intake of DF for adults is 28 g/day for women and 36 g/day for men in the U.S. [95, 96]. Whereas, an adequate intake recommendation for total DF intake is 38 g/day for men (aged 14-50 years) and 25 g/day for women (aged 19-50 years), while for adults over 50 years of age, the recommendation is 30 g/day for men and 21 g/day for women [97]. Ministry of Health, Labour and Welfare in Japan has recommended that daily DF intake must be 20 g or more for men (aged 18-70 years) and 18 g or more for women (aged 18-70 years), while for adults over 70 years of age, the recommendation daily DF intake is 18 g or more for men and 17 g or more for women [98].

3.7. Minerals

Three cross-sectional studies showed that calcium intake was inversely associated with SUA level [51, 99] and the prevalence of hyperuricemia [52]. The minimal intake associated with SUA reduction was at a level of approximately 1000 mg of calcium per day for men and 650 mg per day for women [51]. Consumption of iron above 11 g per day was inversely associated with SUA level (10-30 μmol/L) in the Australian cohort [51]. In a cross-sectional study of middle-aged and older males in 2,697 participants (aged $\geq$ 40 years) in China, Xie *et al*. [100] found that dietary zinc intake was inversely associated with the prevalence of hyperuricemia. Acting as an antioxidant and anti-inflammatory agent in humans, zinc may be associated with the SUA level, which may function as a prooxidant and proinflammatory factor under certain circumstances [30, 101]. A cross-sectional study indicated that magnesium intake was inversely associated with SUA concentration and the prevalence of hyperuricemia in Chinese male population [102]. A study of 27 men showed that increasing sodium intake from 20 mmoles/day to 200 mmoles/day decreased UA levels by 1 mg/dL ($P < 0.001$) [103]. In a crossover trial of 147 non-obese, normotensive adults, it was found that 7 days of low versus high sodium intake (20 mmoles/day versus 300 mmoles/day) significantly increased serum UA by ~1 mg/dL [104]. A randomized trial analysis also found that high sodium intake lowered SUA concentration [105].

3.8. Flavonoids

Flavonoids from a traditional herb [106] and onion [107] have been demonstrated as a hypouricemic substance by animal studies. Grape seed procyanidins [108], quercetin [109], kaempferol [109], and puerarin [109] lowered SUA levels in oxonate-induced hyperuricemic mice. In fructose-induced hyperuricemic rats, rutin and quercetin significantly reduced SUA levels equivalent to healthy control rats [110]. The mechanism is presumed to be mediated through the inhibition of xanthine oxidase, which oxidized hypoxanthine and xanthine to UA in the purine catabolic pathway [108, 109]. Olive leaf constituents [111], apigenin [111], quercetin [109, 112, 113],

myricetin [113, 114], luteolin [111, 112, 114], and genistein [113] have the ability to inhibit xanthine oxidase *in vitro*. The exact mechanism remains unclear and must be clarified in further studies.

In a randomised, double-blinded, placebo-controlled, cross-over trial, 22 healthy males (19-60 years) ingested quercetin at a dose level of 500 mg per day for 4 weeks [115]. Quercetin significantly reduced plasma UA concentration (approximately 8%) compared with baseline (before ingestion of quercetin) [115]. The consumption of isoflavones was inversely associated with the presence of hyperuricemia in women [58].

3.9. Fuructose and sugar-sweetened beverages

3.9.1. Sucrose

Consumption of added sugar, which are fructose-containing sugars, sucrose and high fructose corn syrup, was associated with the prevalence of hyperuricemia [116].

From an analysis of the NHANES data (1999-2004), Sun *et al*. estimated that the mean intakes of total sugar, total sucrose, and total fructose in the U.S. adults (age 20-80 y) are 135.91 g/day, 36.06 g/day, and 43.1 g/day, respectively. Sucrose is commonly known as table sugar, and is naturally contained in fruit and vegetables. When sucrose is consumed, the enzyme beta-fructosidase separates sucrose into its individual sugar units of glucose and fructose. Oral administration of sucrose at 1.5 g/kg of body weight in healthy male volunteers increased plasma UA concentration and oxypurines (hypoxanthine and xanthine), suggesting that increased plasma UA concentration is attributed to enhanced purine degradation [117].

3.9.2. Glucose versus fuructose

Intake of acute fructose diet for 2 weeks raised SUA concentration compared to glucose diet, irrespective of isocaloric or hypercaloric status [118]. Emmerson [119] indicated that intake of fructose (250-290 g/day) increased SUA concentration by 8-41% compared to glucose in three healthy men. These results suggest that an increasing effect of fructose on SUA concentration is greater than that of glucose. The metabolism of glucose and fructose in humans was reviewed in detail by Sun and Empie [120].

3.9.3. Fructose

Acute oral or intravenous administration of fructose resulted in a rapid increase in SUA levels through accentuated degradation of purine nucleotides in humans [121-123] and increased purine synthesis *de novo* [124, 125]. A 10% fructose given intravenously (0.5 g/kg/hour) for 2 hours increased blood lactate concentration, which may be attributable to the decrease in urinary UA (UUA) excretion *via* urate transporter 1 (URAT1/SLC22A12) [126, 127]. The glucose and fructose in soft drinks facilitate glucose transporter 9 (GLUT9/SLC2A9) (a key protein in urate reabsorption)-mediated urate transport. Therefore, fructose intake has been shown to increase SUA level *via* both decreased UUA excretion and increased UA production [127].

Choi *et al*. [128] reported that increased fructose intake was associated with increased SUA levels and hyperuricemia risk. But, the report of Sun *et al*. [54] did not show the association between them. Thus, the epidemiological study results on the association between fructose intake and SUA concentration or hyperuricemia risk obtained by Choi *et al*. [128] were inconsistent with those of Sun *et al*. [54]. In subjects receiving a low-fructose diet after ingestion of high-fructose diet, fasting plasma UA concentration was increased and urinary UA clearance and fractional UA excretion were lowered, suggesting that decreased urinary UA excretion may contribute to fructose-induced hyperuricemia [129]. It has been reported that higher-than-normal daily intake of fructose may lead to hyperuricemia in humans [130, 131]. Wang *et al*. [132] conducted a systematic review and meta-analysis of controlled feeding trials to assess the effects of fructose on SUA concentrations in people with and without diabetes. The results showed that high fructose intake (213-219 g/day) under hypercaloric feeding conditions (+35% excess energy) raised SUA concentrations [132]. Therefore, it is assumed that high fructose intake (213-219 g/day) under hypercaloric feeding conditions (+35% excess energy) leads to increased hyperuricemia risk.

3.9.4. Sugar-sweetened beverages

There has been an enormous rise in high-fructose corn syrup consumption in the U.S. over the

last few decades due to economic factors that favor use of this artificial sweetener rather than cane sugar products [81]. High fructose corn syrup is made by isomerizing D-glucose to D-fructose. Its components are D-glucose (51.79%), D-fructose (42.10%), and oligosaccharides (5.81%) [133]. Sugar-sweetened soft drinks represent the largest single food source in terms of calories in the U.S. diet [134, 135]. Soft drink consumption in the U.S. increased by 61% in adults from 1977 to 1997 [135]. In a cross-national analysis of 75 countries, soft drink intake was estimated to have globally increased from 9.5 to 11.4 gallons per capita per year between 1997 and 2010 [136]. Consumption of sugar-sweetened beverages has risen sharply in recent decades all over the world [135, 136].

Consumption of sugar-sweetened beverages, a major source of fructose, increased SUA level [99, 128, 137-142]. Sugar-sweetened soft drink consumption (squashes, fizzy drinks, sugar-sweetened beverages, fruit juices, soft drinks, sports drinks, reconstituted powders, and sweetened coffee or tea) was associated with SUA level [99, 128, 137-140] and hyperuricemia risk [128, 143-146]. People who drink many sugar-sweetened beverages tended to be hyperuricemic [147]. These expected data showed that intake of sugar-sweetened beverages was strongly associated with increased SUA level and hyperuricemia risk. Whereas, diet soft drink consumption was not associated with SUA level or hyperuricemia risk [128]. These findings from a nationally representative sample of U.S. adults suggest that sugar-sweetened soft drink consumption increases SUA levels parallel to the direction of the risk of hyperuricemia, but diet soft drink consumption dose not [128].

3.9.5. Fruit juice

A population-based case-control study in 2,076 healthy participants in Scotland reported that there was an association between plasma UA concentrations and intake of pure fruit juice [99]. However, Gao *et al*. [148] reported that no association was found between intake of apple juice, pear juice or fruit juice and plasma UA concentration. In a cross-sectional analysis from the Korean Multi-Rural Communities Cohort Study, there was a close association between orange/orange juice intake and SUA level in male subjects but not with apple/apple juice intake and increased consumption of orange/orange juice and apple/apple juice were not associated with increased hyperuricemia risk [145]. An epidemiological study using NHANES (1988-1994) data showed that there was a positive association between orange juice intake and SUA level or the frequency of hyperuricemia [128]. It is speculated that the association between fruit juice intake and SUA level or hyperuricemia risk varies depending on gender, race, and the type of fruit juice.

3.10. Alcohol and alcoholic beverages

3.10.1. Alcohol

Higher alcohol consumption was associated with higher SUA levels [50, 51, 54, 149-152] and increased hyperuricemia risk [8, 53, 54, 57, 146, 149, 150, 152-165].

Ethanol increases UA production resulting from acetate metabolism and enhanced adenosine nucleotide turnover [156, 157, 166]. Heavy alcohol drinking increases lactic acid [166, 167] and keto acids [156, 166] in blood, leading to increased SUA concentration and decreased urinary UA (UUA) excretion. Lactic acid and ketone acids can exchange with UA in the kidneys *via* sodium-dependent monocarboxylate transporters SLC5A8 and SLC5A12, which provide the main source of anions needed for urate transporter 1 (URAT 1) function [127]. URAT1-transduced urate anion reabsorption is stimulated by intracellular organic anions, including lactic acid and keto acids [24, 127]. URAT 1 is considered to be a key player in UA homeostasis and has been estimated to be responsible for 50% of UA reabsorption [127]. Increased lactic acid and ketone acids in the filtrate enhance UA reabsorption *via* an anion-exchange transport system at the proximal tubule, resulting in the decrease in UUA excretion. Therefore, these mechanisms have been implicated in the pathogenesis of alcohol-induced hyperuricemia, including both decreased UUA excretion [158, 166, 168-170] and increased UA production [156, 157, 166]. The effect of ethanol on UA metabolism was reviewed in detail by Yamamoto *et al*. [167].

3.10.2. Alcoholic beverages

It is important to pay attention to the amount of ethanol ingested and type of alcoholic beverage to prevent and treat ethanol-induced hyperuricemia. The effects of individual alcoholic beverages on SUA concentrations vary according to the type of alcoholic beverages. For example, a clinical trial showed that the degree of increase in SUA concentration by the same amount of alcohol intake was beer (15%) > red wine (9%) > spirits (8%) [171]. The amount of purine contained in alcoholic beverages was beer > wine > spirits [1, 172]. Purine contained in alcoholic beverages contributes to an increase in plasma UA concentrations [167]. Beer ingestion causes an increase in the plasma concentrations and the amount of urinary excretion of hypoxanthine, xanthine and UA [173]. Beer has a large guanosine content, which is more readily absorbed than other purine nucleosides or purine nucleotides. These findings indicated that purine in beer increased the production of UA, which resulted in increases in the plasma UA concentration and the amount of UUA excretion. Choi *et al*. [174] and Yamamoto *et al*. [155] have stated that the purine content of beer probably has an increasing effect for SUA concentration, which is independent of alcohol. It is assumed that SUA concentrations are associated with the amounts of purine in alcoholic beverages.

Villegas *et al*. [152] found that higher consumption of alcoholic drinks (wine, beer, and liquor) was associated with higher prevalence of hyperuricemia in Shanghai men and the prevalence of hyperuricemia was beer > wine (grape and rice) > liquor, in the case of consumption of greater than 3 drinks a day [ethanol amount: beer, ≥ 37.8 g; wine, ≥ 36.9 g; liquir, ≥ 38.7 g]. In a study conducted in Taiwan (the Nutrition and Health Survey in Taiwan), increased beer intake was associated with increased hyperuricemia risk [52]. In a cross-sectional and prospective analysis in 4,449 elderly participants at high cardiovascular risk from the PREvención con DIeta MEDiterránea (PREDIMED) study in Spain, consumption of greater than or equal to 7 glasses a week of wine was associated with a 21% increased risk of hyperuricemia [175]. All forms of alcohol promote hyperuricemia [81].

Choi *et al*. [151] found that SUA levels significantly increased with increasing beer or liquor intake, but not with wine intake, and SUA levels decreased with increasing wine intake except for the top category (≥ 1 serving per day) [151]. Zykova *et al*. [51] observed that the highest consumers of beer or spirits had significantly higher SUA levels compared to the lowest consumers of beer or spirits in both the AusDiab Study and the Tromsø study cohorts and the highest consumers of wine in the AusDiab Study cohort had significantly lower SUA levels (> 10 g alcohol per day versus non-drinkers). In the case of men who consumed 10 g alcohol a day, increase in SUA concentration was higher for beer than wine [150]. Wine drinkers had lower SUA levels (in fact, SUA levels comparable to nondrinkers) than did drinkers of other forms of alcoholic beverages [176]. In case of moderate wine consumption, polyphenols in wine confer a protective effect against hyperuricemia, apart from its antioxidant effect.

Chrysohoou *et al*. [177] reported that the most beneficial values of biochemical and clinical parameters were found in alcohol intake of 100-200 mL (12% alcohol), even after adjustment for various potential cofounders. High alcohol consumption is especially more than 30 g/day alcohol or 2 drinks/day [155]. Yamanaka [1] has recommended that consumption of beer, spirits, wine, and rice wine per one drink should be limited to 500 mL, 60-90 mL, 200 mL, and 180 mL, respectively. Sensible moderate drinking for overall health benefits is 1-2 drinks/day for men and ≤1 drink/day for women [178, 179]. Terkeltaub and Edwards [81] have stated that an ideal amount of alcohol intake for patients with hyperuricemia and gout should be one drink per day and ≤ 2 servings in a 24-hour period.

3.11. Purine and purine-rich foods

3.11.1. Purine

Purine plays fundamental roles in the replication of genetic material, gene transcription, protein synthesis, and cellular metabolism. Increased dietary purine intake stimulates higher production of UA [24]. Increased SUA concentrations by an addition of dietary purine (RNA, adenine, adenosine, or adenosine-5’-monophosphate) to the

fiber-free diet caused experimental hyperuricemia in rats [82, 83, 85-88, 180-186]. Excessive intake of dietary RNA has been reported to increase SUA concentrations and the amount of urinary UA (UUA) excretion in humans [187-192]. Oral doses (0.1 mmoles/kg body weight) of adenosine-5'-monophosphate (5'-AMP), guanosine-5'-monophosphate (5'-GMP), inosine-5'-monophosphate (5'-IMP), hypoxanthine, and adenine administered to individuals without hyperuricemia and gout increased SUA level by 1.0-2.0 mg/dL (59-118 μmol/L) within 24-hour period and caused hyperuricemia [193]. From these reports, it is assumed that excessive intake of foods rich in purine [e.g., ribonucleic acid (RNA), 5'-AMP, 5'-GMP, 5'-IMP, hypoxanthine, and adenine] in humans may increase SUA concentration and cause hyperuricemia. Schlesinger [25] has stated that the variation in hyperuricemia with different purine-rich foods may be explained by the variation in the amounts and types of purine content and their bioavailability for purine-to-uric acid metabolism. Therefore, it is important to consider the total purine content and each purine content (base, nucleoside, and nucleotide) of food for the prevention and suppression of hyperuriemia.

Purine-rich foods theoretically predispose to hyperuricemia by providing exogenous substrate for purine metabolism, end-product of which is UA in humans. Purine-rich foods include animal meat (i.e., beef, pork, lamb, organ meats, and meat extracts), seafood (i.e., fish fillets, tuna, shrimp, lobster, clams, etc) and plants (i.e., yeast extracts, peas, beans, lentils, asparagus, and mushrooms) [172]. By contrast, dairy products (i.e., milk, cheese, yogurt, ice cream), grains and their products (i.e., bread, pasta, cereals), vegetables, fruit, nuts, sugars and sweets are low in purine [172]. As management policy in patients with hyperuricemia, Neogi [194] has stated that individuals with hyperuricemia should reduce the uptake of exogenous purine to reduce UA content contributing for the total UA pool of the body. Yamanaka [1] has recommended that a daily intake of purine should be less than 400 mg.

3.11.2. Meat

Higher meat intake was associated with higher SUA levels [50, 51, 56, 99, 137, 150, 195, 196] and increased hyperuricemia risk [53, 56, 146, 175, 197]. The PREDIMED study in elderly participants at high cardiovascular risk in Spain revealed that consumption of less than 1 serving a day of red meat or processed meat compared with higher intake was associated with a 23% reduced risk of hyperuricemia [175]. The two Nutrition and Health Surveys in Taiwan (NAHSIT) (1993-1996 and 2005-2008) demonstrated that there was a positive association between SUA concentration and intake frequency of organ meats in men [140] and there was a positive association between the prevalence of hyperuricemia and intake frequency of organ meat other than liver, raw meat, and smoked meat in men [52]. Though there was no association between poultry intake and the prevalence of hyperuricemia in the Shanghai Men's Health Study [57], an increased risk of hyperuricemia was related to an increased intake of poultry in the elderly Taiwanese men [144] and in Chinese middle-aged and elderly people [53]. The difference in the results for the frequency of hyperuricemia may be due to the type and location of meat, and the content of nutrients contained in meat (especially, fatty acids and purine). Drinking meat soup increased the risk of hyperuricemia [198].

Yamanaka [1] has recommended that intake of meat (beef, pork, chicken, sheep meat) and giblets per one serving should be 80 g and 40 g, respectively. Terkeltaub and Edwards [81] have recommended that meat (beef, pork, and lamb) consumption for hyperuricemia and gout patients should be ≤6 oz (170.10 g) per day as a starting point.

3.11.3. Seafood

Epidemiological studies found that increased seafood intake was associated with increased SUA concentrations [50, 56, 195, 196] and increased hyperuricemia risk [56, 57, 146, 175, 197, 198]. In the Elderly Nutrition and Health Survey (1999-2000) in Taiwan, a cross-sectional study revealed that increased intake of shellfish was associated with increased hyperuricemia risk [144]. A population-based 3-year follow-up study showed that consumption of raw or roasted fish, but not boiled or fried fish, was related with a higher risk of hyperuricemia in Japanese adults [199]. Purine content increased slightly during

roasting because of moisture and fat loss from the tissues [200]. In contrast, the decreasing purine content is transformed into water or oil after boiling and frying [201]. Therefore, it is speculated that the risk of hyperuricemia is associated with the amounts of purine in cooked fish.

Yamanaka [1] has recommended that intake of fish, shellfish, prawn and shrimp, and crab per one serving should be 80 g, ≤60 g, ≤50 g, and 100 g, respectively. Terkeltaub and Edwards [81] have recommended that seafood (especially, shellfish and crustaceans) consumption for hyperuricemia and gout patients should be ≤6 oz (170.10 g) per day as a starting point.

Fish is rich in the eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) [202]. Choi [23] has stated that the use of plant-derived n-3 fatty acids or supplements of EPA and DHA could be considered in the place of fish consumption among patients with gout or hyperuricemia.

Consumption of fish can reduce the risk of coronary heart disease (CHD) [203], type 2 diabetes [204], and hypertension [205], which are comorbidities of hyperuricemia, and mortality [206].

3.11.4. Purine-rich vegetables

In women, intake of spinach (294 g) juice increased SUA concentration [207]. Serum urate area-under-curve (AUC) increased by 30% during the 4-hour period after the spinach drink (294 g), and 14% after the drink containing strawberries (240 g) [207].

The NAHSIT (1993-1996) demonstrated that there was an inverse association between the prevalence of hyperuricemia and intake frequency of mushrooms in women [52]. The NAHSIT (1993-1996 and 2005-2008) showed that SUA level was positively associated with intake frequency of bamboo shoots in women, whereas SUA level was inversely associated with intake frequency of carrots, and mushrooms in men and women [140].

Intake of purine-rich vegetables (peas, beans, lentils, cauliflower, and spinach was not associated with plasma UA concentration in a population-based case-control study conducted in Scotland (1999-2006) [99]. There was no association between intake of purine-rich vegetables (peas, beans, lentils, spinach, mushrooms, and cauliflower) and hyperuricemia risk [56, 57]. This phenomenon can probably explain that increased intake of vegetable protein and dietary fiber (DF) protect against the risk of hyperuricemia [54, 57].

Yamanaka [1] has recommended that intake of cauliflower, bamboo shoots, spinach and mushroom per one serving should be 50 g, 50 g, 40 g, and 50 g, respectively.

3.12. Legumes and soy products

3.12.1. Legumes

Legumes are rich in proteins, complex carbohydrates, dietary fiber (DF), folate, flavonoids, and various micronutrients (e.g., phytochemicals) [208]. The association between consumption of legumes and SUA level has been investigated in Athens in the ATTICA study [137]. It is speculated that legumes lower SUA levels through both the suppression of purine absorption by DF [83-85] and the inhibition of xanthine oxidase by genistein [113]. Intake of legumes was inversely associated with inflammation [209]. Intake of legumes has beneficial effects for SUA concentrations through anti-inflammation effect. The PREDIMED study conducted in Spain revealed that intake of greater than 3 servings a week of legumes compared with higher intake was associated with a 30% reduced risk of hyperuricemia and there was an inverse association between consumption of legumes and the prevalence of hyperuricemia [175].

3.12.2. Soy products

In a cross-sectional study in Taiwan, intake frequency of soy products was inversely associated with SUA concentration [140]. In a review by Messina *et al*. [210], clinical trials showed that soy food did not markedly affect SUA levels and data of epidemiological studies indicated that soy food intake was not associated with the prevalence of hyperuricemia. While, two cross-sectional studies showed that intake of soy products was inversely associated with the prevalence of hyperuricemia [57, 144].

Intake of soybean [195, 211, 212] and tofu [212] increased postprandial SUA concentrations. SUA concentrations increased by approximately 10%

over a 3-hour period after ingestion of soybean [212]. A clinical trial found that intake of tofu did not result in an increase in SUA concentrations [212]. For a person who ingested soybean or tofu of 80 g of protein, the degree of increase in SUA concentration can be inferred as soybean > tofu. Tofu loses most of the protein and purine contained in soybean during their manufacturing process. Intake of soybean protein raised SUA concentration after a 3-hour period [59]. Therefore, it is presumed that the difference of effect of soybean and tofu on SUA concentration is largely influenced by the content of protein and purine. In a pooled analysis from two 6-month randomized controlled trials, Liu *et al*. [213] found that soy intake did not increase SUA levels among Chinese postmenopausal women with prediabetes or prehypertension. Greater soy consumption was associated with a lower presence of hyperuricemia in women in the community-based cross-sectional study in China [58].

Yamanaka [1] has recommended that intake of dried soybeans, dried adzuki beans, green soybeans, fermented soybeans, broad beans, tofu, soybean fiber, and soybean milk per one serving should be 35 g, 40 g, 40 g, 40 g, 50 g, 100 g, 100 g, and 200 g, respectively. As legumes are purine-rich foods, it is necessary to elucidate the association between intake of legumes and SUA concentration or hyperuricemia risk by means of many large-scale prospective cohort studies and long term randomized controlled trials in the future.

3.13. Nuts

Nuts are rich in unsaturated fatty acids, plant protein, dietary fiber (DF), antioxidant vitamins (e.g., folate, vitamin E), minerals (e.g., magnesium and potassium), and phytochemicals (e.g., flavonoids) [208].

The consumption of 20% flaxseed in rats significantly decreased body weight gain and serum low-density lipoprotein cholesterol (LDL-cholesterol) (22%), glucose (78%) and UA (64%) levels and significantly increased serum high-density lipoprotein cholesterol (HDL-cholesterol) (47%), compared with control group [214]. Flaxseed suppressed the elevation of serum urea nitrogen, creatinine and UA concentrations in rats with renal dysfunction induced by glycerol [215]. These reports suggest that flaxseed intake would play an effective role in the prevention and/or suppression of hyperuricemia and mitigates the renal dysfunction in humans.

In a cross-sectional study, consumption of nuts was inversely associated with lower concentrations of circulating inflammatory molecules and higher plasma adiponectin, a potent anti-inflammatory adipokine [216]. Intake of nuts has beneficial effects for SUA concentrations from a point of view of anti-inflammation effect.

Yamanaka [1] has recommended that intake of peanuts and almonds per one serving should be 20 g and 15 g, respectively. The serving of almonds for human is 30 g/person/day [217]. Choi [23] has expressed the view that intake of nuts should be 1-3 times per day (13-15 g per once). The recent healthy eating pyramid created by Saag and Choi recommends 1-3 times daily consumption of nuts and legumes among patients with gout and hyperuricemia [15].

3.14. Fruit and vegetables

Fruit and vegetables are flavonoid-rich foods and contain significant levels of dietary fiber (DF). Saura-Calixto and Goñi have stated that intake of antioxidant (polyphenols and carotenoids) and nonantioxidant (phytosterols) bioactive compounds and DF is strongly linked with high consumption of fruit and vegetables and may have a significant role in health [218].

Intake frequency of fruit and vegetables was inversely associated with SUA concentration [140]. Schlesinger [25] has stated that fruit and vegetables are associated with decreasing SUA levels. Consuming a fruit and vegetable-based diet alkalinizes urine, increasing UA excretion [219]. A cross-sectional study of 7,403 inhabitants in Foshan areas in China revealed that increased consumption of fruit and fresh vegetables were associated with decreased hyperuricemia risk [198]. Moderate intake of fruit and vegetables were protective factors of hyperuricemia in middle-aged and elderly people in China [53]. In a cross-sectional study, greater variety in fruit and vegetable intake was associated with lower inflammation (serum C-reactive protein concentration) in Puerto Rican adults [220].

Intake of fruit and vegetables has beneficial effects for SUA concentrations from a point of view of anti-inflammation effect.

The dietary guidelines in the U.S. call for 5 to 13 servings of fruit and vegetables a day, depending on an individual's caloric intake [221]. The recommendations in the Dietary Guidelines for Americans distinguish between fruit and vegetables, recommending 2 to 4 servings per day for fruit and 3 to 5 servings per day for vegetables [222].

3.14.1. Fruit

Cherries and cherry products have urate-lowering properties [223-225]. Tart cherry (*Prunus cerasus*) juice (5 mL/kg) treatment in hyperuricemic rats inhibited hepatic xanthine oxidase (EC 1.17.3.2)/ dehydrogenase (EC1.17.1.4) activity and reduced SUA levels [223]. When 10 participants (38.1 ± 12.5 years old; BMI 32.2 ± 4.6; 5 obese, 5 overweight) consumed 8 oz/day (236.6 g/day) of 100% tart cherry juice for 4 weeks, SUA level reduced by 70% [224]. Plasma UA concentration in ten healthy females who consumed 2 servings (280 g) of Bing sweet cherries, grapes or strawberries decreased by 14.5%, 6.5% or 8.4% at 5 hours postdose, as compared with the predose baseline [226]. This result reveals that lowering effect of cherries on plasma UA concentration is stronger than that of grapes or strawberries. This report suggests that cherries exert their urate-lowering effect by increasing the rate of renal glomerular filtration and/or reducing tubular reabsorption [226]. Healthy adults who ate 280 grams of Bing cherries each day for 1 month had a significant reduction in blood levels of substances associated with inflammation and immune cell activity [circulating concentrations of C-reactive protein, regulated upon activation, normal T-cell expressed, and secreted (RANTES), and NO]; the anti-inflammatory effects of substances in cherries may be beneficial for the management and prevention of hyperuricemia [227]. Because cherries have antioxidant and anti-inflammatory properties, it may play an important role in decreasing SUA levels.

Usharani *et al*. [228] evaluated the efficacy and tolerability of standardized aqueous extracts of *Terminalia chebula* and *Terminalia bellerica* in a randomized, double-blind, placebo-, and positive-controlled clinical pilot study in subjects with hyperuricemia for 24 weeks. *Terminalia chebula* 500 mg group, *Terminalia bellerica* 500 mg group, and *Terminalia bellerica* 250 mg group significantly reduced SUA levels compared to placebo group and SUA levels decreased by 16.02%, 27.59%, and 14.05% compared to the respective baseline [228]. *Terminalia chebula* and *Terminalia bellerica* have antioxidant property and the probable mechanism of action of the antioxidant property is inhibition of xanthine oxidase [229, 230]. Quercetin, which helps in reducing the production of UA by inhibiting xanthine oxidase [109, 112, 113], is an important compound found in *Terminalia chebula.* Furthermore, *Terminalia chebula* was shown to be an excellent scavenger of 2,2-diphenyl-1-picrylhydrazyl (DPPH) radicals [231].

Epidemiological studies showed that fruit intake was inversely associated with SUA concentration [137, 150]. Higher consumption of fresh fruit appeared to be associated with lower SUA concentrations in the participants in the Australian cohort and in the obese females in the Norwegian cohort [51].

The methanol extract of a fruit has been demonstrated as a hypouricemic substance in mice [232]. In the PREDIMED study involving elderly participants at high cardiovascular risk in Spain, intake of greater than 3 servings a day of fruit (including natural fruit juices) compared with higher intake was associated with a 7% reduced risk of hyperuricemia and no association was shown between fruit intake and the prevalence of hyperuricemia [175].

Dietary guidelines for Japanese (The Japanese food guide spinning top) has recommended that daily consumption of fruit must be 2-3 servings (approximately 200-300 g), depending on an individual's caloric intake [233]. The recent healthy eating pyramid created by Saag and Choi recommends 2-3 servings daily consumption of fruit among patients with gout and hyperuricemia [15].

3.14.2. Vegetables

Vegetables contain many nutrients, including folate, antioxidants, and dietary fiber (DF), which

contribute to reducing the risk of chronic disease [234].

Ulbricht and Southgate [235] observed that omega-6 polyunsaturated fatty acids (PUFAs) were mostly found in vegetables. Red blood cell omega-6 PUFA was independently associated with SUA concentration [25]. The ATTICA study, a cross-sectional study, showed that intake of vegetables was not associated with SUA level [137].

The NAHSIT (1993-1996) demonstrated that there was an inverse association between the prevalence of hyperuricemia and intake of vegetables in men [52]. In the PREDIMED study involving elderly participants at high cardiovascular risk in Spain, consumption of greater than 2 servings a day of vegetables compared with higher intake was associated with a 10% reduced risk of hyperuricemia, and consumption of greater than 2 servings a week of sofrito sauce, which was made with tomato, onion, spices, garlic, and simmered with olive oil, compared with higher intake was associated with a 19% reduced risk of hyperuricemia, and an inverse association was found between consumption of sofrito sauce and hyperuricemia risk [175].

Ministry of Health, Labour and Welfare in Japan has recommended that daily consumption of vegetables must be 350 g or more (green-yellow vegetables, 120 g or more) [98].

3.15. Bread, margarine, cereals, eggs, seaweeds, fried foods

An epidemiological study showed that consumption of bread and margarine (including low-fat margarine, i.e., 40% fat) was inversely associated with SUA level in women [50]. Higher consumption of high-fiber bread was associated with lower SUA levels in non-obese men and obese women in the AusDib cohort and in non-obese men in the Tromsø cohort [51]. In the AusDib cohort, cereal intake had an inverse relationship with SUA level in all groups [51]. The NAHSIT (1993-1996 and 2005-2008) showed that there was an inverse relationship between SUA concentration and intake frequency of seaweeds or eggs in women [140]. The Elderly Nutrition and Health Survey (1999-2000) in Taiwan (Elderly NAHSIT) demonstrated that an increased risk of hyperuricemia was related to an increased intake of fried foods and a reduced risk of hyperuricemia was related to an increased intake of eggs [144].

Dietary guidelines for Japanese (The Japanese food guide spinning top) has recommended that daily total consumption of vegetables, mushrooms, potatoes and seaweeds must be 5-7 servings (approximately 350-490 g), depending on an individual's caloric intake [233].

3.16. Fermented foods

DM-2918-A, which is a lactic acid bacteria isolated from Chinese sauerkraut, has the ability to degrade nucleosides (inosine and guanosine) *in vitro* and oral administration of DM-2918-A reduced SUA levels in hyperuricemic rats [236]. This report found that certain probiotic strains, specifically from the lactobacillus genus, could degrade inosine and guanosine [236]. Probiotic bacteria of the *Lactobacillus* and *Bifidobacterium* genera reduced inflammation and hyperuricemia in murine models [236-238]. The mechanism by which probiotics reduce hyperuricemia is still being studied, and not completely understood. A total of 111 subjects with SUA levels of 6.0-7.9 mg/dL were provided 2 g per day of fermented barley extract for 12 weeks in a randomized placebo-controlled, parallel-group, double-blinded study [239]. Ingestion of fermented barley extract lowered SUA levels compared with placebo group or baseline [239]. In a randomized controlled trial, supplementation of 6 g of a fermented papaya preparation for 14 weeks to diabetic patients improved SUA levels [240].

3.17. Dairy products

Dairy products are recognized as important dietary factors for reducing SUA concentration. In some clinical trials [91, 211, 241, 242] and epidemiological studies [50, 51, 56, 99, 137, 140, 243], consumption of dairy products (milk, skim milk, low fat dairy, yogurt, low-fat dairy products) was inversely associated with SUA level. In a randomized controlled trial, ingestion of a dairy-free diet for 4 weeks markedly increased SUA concentration [241].

Higher milk consumption was associated with considerably lower SUA level in obese women

and non-obese men from the Tromsø cohort study and in all the groups from AusDiab cohort [51]. Intake frequency of milk was shown to be inversely associated with SUA level in the NNAHSIT (1993-1996 and 2005-2008) [140]. Casein, lactoalbumin, and orotic acid, which are ingredients contained in milk, may exert their uricosuric effects [59, 211, 241, 244].

The cross-sectional and short-term intervention studies of healthy subjects have demonstrated that intake of low-fat dairy products has a moderate urate-lowering effect [243]. Lowering effect of dairy products on SUA concentration in overweight subjects was greater than that in healthy subjects [56].

Decreased hyperuricemia risk was associated with increased intake of dairy products [56, 245] and milk [56]. The NAHSIT (1993-1996) found that there was an inverse association between intake frequency of dairy products or full-cream milk and the prevalence of hyperuricemia [52].

Terkeltaub and Edwards [81] recommend consuming 2 servings per day of nonfat or low-fat yogurt or milk. Choi [23] recommends consuming skim milk or other low-fat dairy products up to two servings daily. Ministry of Health, Labour and Welfare in Japan has recommended that daily consumption of dairy products must be 130 g or more [98]. Dietary guidelines for Japanese (The Japanese food guide spinning top) has recommended that daily consumption of milk and milk products must be 2-3 servings (milk: approximately 100 g/serving; yogurt: approximately 83 g/serving; cheese: approximately 20 g/serving), depending on an individual's caloric intake [233]. The recent healthy eating pyramid created by Saag and Choi recommends that daily supplement of dairy products or calcium should be 1-2 servings among patients with gout and hyperuricemia [15].

3.18. Coffee

Coffee is one of the beverages commonly consumed in Western society [246] and is consumed daily by nearly half of the adults in Japan [247]. Coffee has many different types of antioxidants [248-251] among which the phenol chlorogenic acid is a strong antioxidant [248, 252]. Coffee also contains dietary fiber (DF). The amount of soluble DF contained in instant or soluble coffee (freeze-dried coffee infusion), espresso coffee, and drip brew of coffee are 0.90 g/100 mL, 0.83 g/100 mL, and 0.60 g/100 mL, respectively [253].

Increased intake of coffee and decaffeinated coffee was associated with decreased SUA concentrations [254-257]. Questionnaire-based food frequency studies done in Taiwan as part of the NAHSIT (1993-1996 and 2005-2008) showed an inverse association between intake frequency of coffee and UA concentration [140]. The mean SUA level in individuals consuming ≥5 cups of coffee daily was lower than that in individuals consuming >1 cup by 0.4 mg/dL [256], which was very similar to the results of Choi and Curhan [255]. Corresponding to these results, coffee consumption was inversely associated with SUA level and hyperuricemia risk [245, 254-256]. For example, hyperuricemia risk in individuals with coffee intake of ≥6 cups per day as compared with those with no coffee use was decreased by 43% in a cross-sectional analysis of NHANES-III (1988-1994) [255].

Proposed mechanisms by which higher coffee intake is associated with lower SUA levels and reduced hyperuricemis risk are as follows: (1) high long-term coffee intake was associated with lower insulin levels [258] and increased insulin sensitivity [259]. Antioxidants, such as the phenol chlorogenic acid, may improve insulin sensitivity [260-263] and decrease insulin levels in rats [248, 264] and in turn enhance renal UA excretion [265]. Thus, chlorogenic acid may reduce SUA concentration by alleviating insulin resistance; (2) caffeine (1,3,7-trimethyl xanthine) is a methyl xanthine and may be a competitive inhibitor of xanthine oxidase, as demonstrated in rats [266], although there was no relation between caffeine intake and SUA concentration [255] or hyperuricemia risk [54, 254, 255]; (3) caffeine is known to increase estimated glomerular filtration rate (eGFR) and renal blood flow, and it is possible that caffeine may enhance renal UA excretion [267]; and (4) soluble DF suppresses the digestion and/or absorption of dietary purine in rats [83-85].

Coffee consumption was associated with a lower risk of several specific cancers including prostate

cancer, endometrial cancer, liver cancer, melanoma, non-melanoma skin cancer and neurological conditions, metabolic conditions including type 2 diabetes, metabolic syndrome, gallstone, gout, renal stone and liver conditions including hepatic fibrosis, cirrhosis, cirrhosis mortality, and chronic liver disease [268]. Poole *et al*. [268] have stated that coffee consumption seems generally safe within usual levels of intake, with summary estimates indicating largest risk reduction for various health outcomes at three to four cups a day, and more likely to benefit health than to harm it. However, coffee contains moderate to high amount of oxalate. Therefore, individuals possessing renal stone and/or past stone formers may well limit coffee intake. Choi and Curhan [255] have expressed the view that it is important to note that daily intake of at least 4 cups of coffee was linked with mean SUA level reduction of only 0.18-0.22 mg/dL. From the viewpoint of prevention and suppression of hyperuricemia, drinking 1-4 cups of coffee or decaffeinated coffee per day appear to be beneficial.

3.19. Tea

Tea, which is prepared from the leaf of *Camellia sinensis*, can be divided into six major types of reprocessed basic tea depending on fermentation, such as green tea, blue tea, black tea, yellow tea, white tea and dark tea [269]. Five tea catechins inhibit xanthine oxidase [270].

Intake of green tea in Japanese people is 3.1 cups a day. There was no association between green tea consumption and SUA concentration in middle-aged Japanese males [256, 271]. Intake of 3 cups of green tea per day (200 mL × 3) in men doing weight lifting decreased SUA concentration and suppressed the elevation of plasma xanthine oxidase activity during the 1-minute period after doing weight lifting [271]. Green tea inhibited the xanthine oxidase activity by 13.3% *in vitro* [272]. From these results, it is speculated that the effect of green tea on serum or plasma UA concentration varies depending on the amount of physical activity.

Theaflavin, which is the oxidized derivatives of black tea catechins during fermentation, inhibited the activity of xanthine oxidase [273]. Black tea decreased SUA concentration by 8.5% compared with high UA baseline groups [SUA concentration > 6 mg/dL] in humans susceptible to ischemic heart diseases in a prospective randomized controlled study [274]. In contrast, there was no significant association between consumption of black tea and SUA level [257]. In the Singapore Chinese Health Study cohort, SUA levels significantly increased with increasing frequency of green tea intake and daily drinkers of green tea had a 2-fold increase in the risk of hyperuricemia [SUA level > 356.88 μmol/L (approximately 6 mg/dL)], compared to non-drinkers [257].

In the NHANES-III (1988-1994), although the mean SUA level in women with tea intake ≥4 cups of tea a day was lower by 0.02 mg/dL than in women with no tea intake, tea consumption was not associated with SUA concentration and hyperuricemia risk [255]. This study did not differentiate green tea from black tea and did not indicate the type of tea. In a cross-sectional study in Chinese adults, tea seemed to be the protective factor for hyperuricemia [198, 275]. For example, increased tea intake was associated with decreased hyperuricemia risk [198, 275] and males in the high level of tea intake group was 44% less likely to be hyperuricemic compared to those males in the low level of tea intake group [275]. Torralba *et al*. [276] have stated that the diuretic and antioxidative property of tea may play an important role in the relationship between decreased risk of hyperuricemia and tea consumption. It seems that effect of tea on SUA concentration and hyperuricemia risk varies depending on the type of tea and needs to be evaluated in the future.

4. Association between dietary patterns and SUA concentrations or hyperuricemia risk

4.1. Uric acid-prone pattern versus vegetable and fruit pattern

In a cross-sectional study of 266 ethnic Chinese adults in Taiwan, there was a positive association between the “uric acid-prone (composes of meat, seafood, organ meat, eggs and beverages)” dietary pattern and plasma UA concentration after adjusted for age, gender and body mass index (BMI). Whereas, the “vegetable and fruit (composes of soy products, white vegetables, dark vegetables and fruit)” dietary pattern tended to lower plasma UA concentrations as the quartiles

increased but there was no negative association between them [267].

4.2. Animal products and fried foods pattern versus soybean products and fruit pattern

In a case-control study in Chinese adults, there was a positive association between the "animal products and fried foods (high in pork, eggs, animal giblets, poultry and fried wheat products while low in vegetables and fruits)" dietary pattern and asymptomatic hyperuricemia risk [SUA level > 7.0 mg/ dL (416.4 μmol/L) among men and > 6.0 mg/dL (356.9 μmol/L) among women], and there was a negative association between the "soybean products and fruit (high in soybean products, fruits, vegetables and starchy tubers)" dietary pattern and asymptomatic hyperuricemia risk, independent of blood lipids [277]. Zhang *et al*. [277] found that those in the highest tertiles of "animal products and fried foods" dietary pattern had 120% higher risk of asymptomatic hyperuricemia and those in the highest tertiles of "soybean products and fruit" dietary pattern had 72% lower risk of asymptomatic hyperuricemia, compared to those in the lowest tertiles of each dietary pattern.

4.3. Standard diet recommended by guidelines for hyperuricemia versus fruit and soybean products diet

Zhang *et al*. [278] assessed the effect of the standard diet (the general dietary guidelines for hyperuricemia) and high fruit and soybean products diet interventions on SUA concentration in Chinese asymptomatic hyperuricemia adults for 3 months in an open randomized controlled trial. After 3 months, the standard diet and high fruit and soybean products diet significantly decreased SUA concentration compared with each baseline. However, no differences were observed in SUA concentration between the standard diet and high fruit and soybean products diet. In both the standard diet and high fruit and soybean products diet, compared with the respective baseline, intake of fried wheat products and animal giblets decreased and intake of vegetables, soybean products and fruit increased [278]. However, there were no significant differences in daily food intake between the two groups after a 3-month period dietary intervention [278]. They [278] have stated that high fruit and soybean products dietary intervention could be an effective alternative to a standard diet for achieving clinically important reduction in SUA concentration for asymptomatic hyperuricemia adults. The above open randomized controlled trial results support the report of Chuang *et al*. [140], which showed that an increase in the consumption frequency of soy products, vegetables and fruit decreases SUA concentration.

4.4. The Western diet

The Western diet is characterized by higher intake of red and processed meat, beverages sweetened with sugar, sweets, desserts, French fries, and refined grains, and low intake of fresh fruit and vegetables and low-fat dairy products [279]. The introduction of the Western lifestyle to Japanese people, such as a diet containing greater amounts of meat, has been associated with increase in SUA levels and the incidence of hyperuricemia and gout [49]. The "western (high in beef, lamb, cake, and beverages including juice and alcoholic beverages)" dietary pattern was not associated with the risk of asymptomatic hyperuricemia in a case-control study in China [277]. The Western diet increases SUA levels and the risk of gout, which may explain the increasing prevalence of gout in Western countries [279, 280]. The Western diet also increases the risk of chronic kidney disease (CKD) [281], type 2 diabetes [282], and coronary heart disease (CHD) [283].

4.5. Purine-rich diet versus low-purine, low-protein diet versus purine-free diet versus high-protein diet

Emmerson [153] expressed the view that a purine rich diet will produce a transient elevation in SUA level by 1.0-2.0 mg/dL (59-118 μmol/L). A relatively unpalatable low-purine, low protein and alcohol-restricted diet is expected to decrease SUA concentration by 15% at a maximum [284]. Choi [23] has stated that an isocaloric, low-purine, low-protein diet can reduce SUA concentration by at least 1 mg/dL and up to 15 to 18%, especially if low alcohol consumption is a component. A purine-free diet resulted in an average reduction of plasma UA concentration of 1.0-1.2 mg/dL [285, 286]. An observational study found that a strict purine-free diet reduced SUA level by 15-20% [287]. A strict restriction of protein and

purine can lead to reduction in life quality. Many researchers [25, 81, 154, 288, 289] have stated that traditional low purine diets are generally unpalatable and nutritionally poor, and they are not usually recommended. Schlesinger [25] and Fam [154] have also stated that a rigid purine-free diet can rarely be sustained for a long period of time. However, in the obese, controlled weight management has the potential to lower SUA concentration in a quantitatively similar way to relatively unpalatable "low purine" diet [25]. High-protein diet was associated with increased urinary UA excretion and lowered SUA levels [124, 187, 290-292]. Havlik *et al*. [293] found that protein-rich vegetable-based meat substitutes are more suitable for dietary considerations in a low-purine diet for hyperuricemic subjects.

4.6. The Mediterranean diet

The Mediterranean diet, which is eaten in Cyprus, Croatia, Spain, Greece, Italy, Morocco, and Portugal, has been inscribed in UNESCO's "World Intangible Cultural Heritage" in 2013 [294]. The Mediterranean diet is characterized by nine food and nutrient components: high consumption of vegetables, fruit and nuts, legumes, cereals, and fish; high ratio of monounsaturated fat: saturated fat; low consumption of meat and dairy products; and moderate consumption of alcohol [218, 295, 296]. Briefly, olive oil is a key component of the Mediterranean diet, being the main source of vegetable fat, especially monounsaturated fatty acids; it is high in whole-grain foods and fiber, and rich in fruit, vegetables, legumes, and nuts; small portions of cheese and yogurt are eaten daily; fish is consumed in varying amounts; red meat, poultry, eggs, and sweets are consumed sparingly; modest amounts of red wine complement meals; and regular physical activity is a part of daily life [297]. The Mediterranean dietary pattern can be characterized by the following four essential dietary indicators: (1) monounsaturated to saturated fatty acid ratio (range: 1.6 to 2.0); (2) intake of dietary fiber (DF) (41 to 62 g/person/day); (3) antioxidant capacity of the whole diet (3500 to 5300 trolox equivalent/person/day); and (4) phytosterol intake (370 to 555 mg/person/day) [218]. It is often cited as beneficial for obesity, diabetes, and coronary heart disease (CHD).

4.6.1. Gazpacho

Gazpacho is a typical Mediterranean dish that can be defined as a ready-to-use vegetable soup, containing approximately 80% crude vegetables (tomato, cucumber, pepper), 2-10% olive oil, and other minor components (onion, garlic, wine vinegar, and sea salt), and that is rich in vitamins [298, 299]. Sánchez-Moreno *et al*. [299] assessed the effect of consuming a vegetable-soup "gazpacho" on the concentrations of vitamin C, biomarkers of oxidative stress and inflammation in plasma in a healthy human population for 14 days. Subjects (6 men, 6 women) enrolled in this study consumed 500 mL/d of gazpacho corresponding to an intake of 72 mg of vitamin C. After subjects consumed the vegetable-soup "gazpacho" daily for 14 days, plasma UA concentration was reduced by 13.8% in men and 8.4% in women compared with the respective baseline (before drinking the soup) and there was an inverse association between plasma UA concentration with plasma vitamin C concentration ($r = -0.654$, $P < 0.0001$). A positive correlation was also found between plasma UA and prostaglandin E_2 concentrations ($r = 0.644$, $P = 0.0007$), and monocyte chemotactic protein-1 concentrations ($r = 0.576$, $P = 0.003$). These results indicate the importance of consumption of vitamin C in individuals with high SUA concentration.

4.6.2. Adherence to the Mediterranean diet

In an intervention trial, intake of the Mediterranean diet for 6 months in hyperuricemic patients [Mean SUA concentration 9.12 mg/dL (542.46 µmol/L)] decreased SUA concentration by 20% [6.92 mg/dL (411.60 µmol/L)] on the 1st month, while the mean SUA concentrations on the 2nd to 6th months were maintained at 6.1-6.4 mg/dL (362.83-380.67 µmol/L) [300].

Higher adherence to the Mediterranean diet was associated with lower SUA levels [137, 177, 301] and a lower likelihood of hyperuricemia [137, 177]. Chrysohoou *et al*. [177] found that 1-unit increase in MedDietScore was associated with a 57% lower likelihood of having hyperuricemia, after controlling for age, gender, physical activity status, smoking habits and BMI. Kontogianni *et al*. [137] demonstrated that participants in the highest

quartile of the MedDietScore (32/55 units) had a 70% lower likelihood of having hyperuricemia compared to those in the lowest quartile (19/55 units). In the PREDIMED trial, the findings provide prospective evidence that a greater baseline adherence to the Mediterranean diet was associated with a lower risk of hyperuricemia in elderly Mediterranean participants at high cardiovascular risk [175]. Higher adherence to the Mediterranean dietary pattern was significantly associated with lower levels of renal function indicators (creatinine and UA) [301]. The Mediterranean diet is related to oxidative stress markers [302]. Decrease in serum C-reactive protein levels has also been observed in the Mediterranean diet with olive oil [303]. SUA concentrations have been associated with higher concentrations of several inflammatory markers [46]. Since the Mediterranean diet has antioxidant [302] and anti-inflammatory properties [303], it may play an important role in the decrease in SUA levels [175]. It is speculated that these findings by the above reports support a potential role of the Mediterranean diet for prevention and suppression of hyperuricemia.

The Mediterranean dietary patterns reduced weight gain [304] and decreased the risk of overweight or obesity [305] and cardiovascular disease (CVD) [306]. Adherence to the Mediterranean diet was inversely associated with systolic blood pressure [295] and diastolic blood pressure [295, 301]. Greater adherence to the Mediterranean diet was associated with a lower risk of arterial blood pressure [295], CVD [307-310], cancer [310, 311], Parkinson's disease [311], Alzheimer's disease [311], all-cause mortality [312], cancer mortality [312], and noncontrolled asthma [313]. The Mediterranean diet improved rheumatoid arthritis [314]. The Mediterranean diet with olive oil reduced plasma C-reactive protein levels by 0.54 mg/L compared with a low-fat diet [303].

4.7. The Dietary Approaches to Stop Hypertension (DASH) diet

The Dietary Approaches to Stop Hypertension (DASH) diet emphasizes high intake of fruit, vegetables, nuts and legumes, low-fat dairy products, and whole grains; low intake of sodium, sweets including sweetened beverages, red meat, processed meat, saturated fats, and total fats [105, 315, 316]. The macronutrient composition of the DASH diet are as follows: total fat, 27% of calories; saturated fat, 6% of calories; cholesterol, 150 mg; protein, 18% of calories; carbohydrate, 55% of calories; fiber, 30 g; sodium, 2,300 mg; potassium, 4,700 mg; calcium, 1,250 mg; magnesium, 500 mg [297, 316].

In a randomized, crossover feeding trial in 103 adults with prehypertension or stage 1 hypertension, the DASH diet reduced SUA concentration compared with the control diet (-0.35 mg/dL [95% confidence interval (95%CI [-0.65, -0.05], P = 0.02), and this effect was greater among participants with hyperuricemia (-1.29 mg/dL [95%CI -2.50, -0.08]) [317]. In the DASH diet groups, medium sodium intake (a target of 120 mmoles/day) and high sodium intake (a target of 180 mmoles/day) lowered SUA concentrations compared to low sodium intake (a target of 60 mmoles/day) [317].

The DASH diet has been shown to reduce blood pressure [316] and weight [316, 318]. Adherence to the DASH dietary pattern was inversely associated with waist circumference and diastolic blood pressure [301]. Higher adherence to the DASH-style diet was associated with a lower risk of gout [279], coronary heart disease (CHD) [319], stroke [319], and kidney stones [320]. The DASH eating pattern improved insulin resistance, hyperlipidemia and even overweight/obesity [316].

5. Dietary habits in individuals with hyperuricemia

Many asymptomatic hyperuricemia have developed from inappropriate lifestyle habits such as overeating and/or excessive alcohol consumption [1]. Compared to people who do not have hyperuricemia, diet in individuals with hyperuricemia consisted of higher intake of meat, seafood (fish and shellfish), beer and wine and was lower intake of carbohydrate [6]. The dietary habits in subjects with hyperuricemia in several areas are as follows: diet in individuals living in Gifu prefecture in Japan consisted of high intake of meat, oils, and confectionery and low intake of vegetables [321]; diet in individuals living in Shanghai in China consisted of high intake of

seafood and alcohol [57]; diet in individuals living in Korea consisted of low intake of vitamin A, vitamin C, folate, dietary fiber (DF), calcium, vegetables and dairy products and high intake of alcohol [5]; and diet in individuals living in the Shandong coastal cities of Eastern China consisted of high intake of meat, fish, shellfish, beer and wine, and low intake of carbohydrate [6]. Ichida [322] has stated that people with eating habits, such as excessive purine intake and increased alcohol consumption, are prone to hyperuricemia.

In a cross-sectional study in Chinese adults, consumption of breakfast and midnight snack was associated with hyperuricemia risk [275]. Irregular breakfast intake has been proven to be related to reduced levels of high-density lipoprotein cholesterol (HDL-cholesterol), in which the HDL-cholesterol could be associated with decreased risk of hyperuricemia [323]. Li *et al*. [275] have stated that excessive calorie intake during consumption of midnight snacks could lead to overproduction of metabolic wastes and compared with daytime, decrease urine output substantially at night, resulting in the retention and accumulation of majority of UA in the body and potential high level of SUA consequently.

Sun *et al*. [54] have stated that higher DF intakes are usually associated with healthier diets (higher fruit and vegetables intake) and lifestyle. Schlesinger [25] has stated that subjects whose diet is mainly rich in vegetables will have lower SUA and serum triglyceride levels and higher red blood cell omega-6 polyunsaturated fatty acid (PUFA) levels than those who are preferential meat consumers. Men who ate more dairy products consumed more whole grains [324], vegetables [324, 325], fruit [324, 325], and coffee [325] and consumed less meat [324]. Thus, diet in men consisting of more dairy products leads to increased intake of milk proteins (casein and lactalbumin), vitamin C, folate, dietary fiber (DF), and flavonoids and limited intake of purine and saturated fatty acids. It seems that the composite effect of these components decreases SUA concentration and contributes to decrease in the prevalence of hyperuricemia.

The dietary changes could explain the decrease in the prevalence of hyperuricemia in Taiwan [326]: (1) an increased avoidance of products made from animal fats; (2) increased use of vegetable oil; (3) increase in the intake of fruit and vegetables, soy products, fish, whole grains, nuts and seeds; and (4) decrease in the intake of red meat, carbohydrates and sodium-containing foods.

Gaffo *et al*. [176] have obtained the result that wine drinkers had lower SUA levels than drinkers of other forms of alcoholic beverages. Therefore, they [176] have stated that wine drinkers may do more things correctly for good health than drinkers of other forms of alcoholic beverages. In general, wine drinkers had higher intake of fish [327], fruit [327-329], vegetables [327-329], grain products [328], olive oil [327], DF [328, 329], potassium [328], vitamin E [328], and total carotenoids [328] than consumers of other beverages; wine drinkers had lower intake of red meat [329], meat cooked with oil [329], fried meat [329], total fat [328], cholesterol [328] and saturated fats [329] than consumers of other beverages. In contrast, compared to wine drinkers, beer and liquor drinkers had higher calorie [328] and total fat [328] intake and had lower intake of fruit [328], vegetables [328], and grain products [328]. It has been reported that wine drinkers ate more servings of fruit and vegetables and fewer servings of red or fried meat. Therefore, the diets of wine drinkers contained less cholesterol, saturated fat, and alcohol and more DF. The obvious health benefits of moderate wine intake compared with other alcoholic beverages may be influenced by dietary habits and other lifestyle factors. Compared with all drinkers, those who did not drink alcohol consumed fewer vegetables but more DF [329]. Dietary and lifestyle characteristics may differ for drinkers of specific alcohol beverages and nondrinkers, which would have important implications for studies of alcohol and disease. It must consider the lifestyle factor observed in health differences between drinkers and nondrinkers. It is assumed that differences of health consciousness, lifestyle factors, especially dietary habits, among people drinking alcoholic beverages are associated with hyperuricemia risk. It is necessary to consider that the difference in the investigation time, race, and lifestyle including dietary habits are associated with the frequency of hyperuricemia.

6. Exercise

Yamashita *et al*. [330] investigated 27 overweight subjects who underwent gradual reduction of total calorie intake (1500-800 kcal/day) and exercise therapy (walking, riding, bicycle, ergometer). They [330] found that the UA clearance/creatinine clearance ratio gradually increased to near nomal, while SUA level was reduced during the course of weight reduction. Tsunoda *et al*. [331] treated overweight hypertensive patients with a low-energy diet (3360 KJ/day) for 3 weeks. They [331] found that SUA was decreased along with improvement in insulin resistance. Therefore, it is possible to reduce SUA level in overweight subjects by reducing body weight through dietary modifications and exercise.

Strenuous muscle exercise increases SUA level, whereas moderate exercise dose not have such an effect [332]. In a 6-year longitudinal study of middle-aged Japanese men, an inverse association existed between UA level and physical activity [333]. Exercise (maximum oxygen uptake: VO_2 max 70%) increases adenine nucleotide degradation and lactic acid production in muscles, and induces noradrenaline release, resulting in the increase in plasma concentration and urinary excretion of oxypurines (hypoxanthine, xanthine), and plasma UA concentration, as well as the decrease in urinary UA excretion, along with fractional excretion of UA and xanthine [334]. High lactic acid concentration in blood caused by exercise may inhibit urinary UA excretion. SUA concentration raised by 0.6-0.7 mg/dL in exercise with 60% maximum oxygen uptake (VO_2 max) and slightly raised even with exercise with 40% maximum oxygen uptake (VO_2 max) [335]. Therefore, exercise wherein SUA level does not rise would involve less than 40% maximum oxygen uptake (VO_2 max) [335]. Yamanaka *et al*. [336] showed that muscle exercise not exceeding the anaerobic threshold did not cause adenine nucleotide degradation; thus, aerobic exercise is expected to be beneficial for patients with hyperuricemia. Mineo *et al*. [337] propose to perform aerobic exercise which lasts at least 15 minutes per exercise period at least 3 times a week. Ogino and Hisatome [338] recommend performing isotonic exercise for 30-60 minutes, such as walking, jogging, cycling or swimming, where it is difficult to raise SUA concentrations. Walking or cycling for 30-60 minutes is 2-4 metabolic equivalent tasks (METs-h/day [339]), jogging for 30-60 minutes is 3-6 METs-h/day, and swimming for 30-60 minutes is 4.3-8.6 METs-h/day [337, 340]. Therefore, from the viewpoint of prevention and suppression of hyperuricemia, a physical activity for 30-60 minutes, such as walking, cycling, jogging, or swimming, should be performed three times a week.

7. Dehydration and hydration

Sauna bathing increased plasma concentrations of UA and oxypurines (hypoxanthine, xanthine) and decreased urinary and fractional UA [173]. This result suggests that dehydration causes an increase in plasma UA concentration through enhanced purine degradation and decreased urinary UA (UUA) excretion [173]. Exercise-induced profuse sweating reduced UUA excretion and led to increased SUA concentration [341]. Therefore, dehydration can cause hyperuricemia [342]. For the prevention and suppression of hyperuricemia, it is necessary to drink plenty of water to avoid an increase in SUA level after sauna bathing and exercise that produces heavy sweating. Terkeltaub and Edwards [81] have stated that maintenance of good hydration (five to eight 8-oz servings of water daily: 1183-1893 g) is essential.

8. Weight management

It is possible to decrease SUA level in individuals with overweight and/or obesity by reducing body weight through dietary modifications and moderate exercise [81]. There was a positive correlation between body weight and SUA concentration [50]. The small, open-label, interventional studies showed that weight loss was associated with a decline in plasma or serum UA level [287, 330, 331, 343]. Weight loss likely decreases UA levels by increasing renal UA excretion and in part by decreasing UA production [153, 154].

Total meat consumption was positively associated with weight gain in men and women [344]. Soybean products promoted weight loss as much as skim milk [345]. Average 4-year weight change among 120,877 U.S. women and men in three prospective cohorts [The Nurses' Health Study, The Nurses' Health Study II, Health Professionals

Follow-up Study] was positively associated with intake of butter, potato chips, potatoes (French fried and boiled, baked, or mashed), sugar-sweetened beverages, 100%-fruit juice, sweets or desserts, unprocessed red meat, processed meat, trans fat, and fried foods and was inversely associated with intake of vegetables, whole grains, fruit, nuts, diet soda, yogurt and physical activity [346]. Portion control is essential for weight maintenance [81].

Low-fat, high-fiber (particularly, cereal fiber) diet has a beneficial effect on health and weight control [347]. The percentage of calories from dietary fat has little relationship with weight maintenance, while low consumption of sugary beverages and trans fat and higher intake of fiber appear to be helpful [297]. Holmboe-Ottesen and Wandel [348] have stated that adoption of a low-energy density-high fiber diet could be the most realistic way of maintaining or losing weight in the long term, since such diet is more favorable in terms of quality.

9. Dietary habits for prevention and suppression of hyperuricemia

Recent data from clinical research have revealed association between dietary factors and SUA levels or hyperuricemia risk. Terkeltaub and Edwards [81] have expressed the view that the expected maximal SUA concentration lowering with diet alone is typically 1 mg/dL and up to ~15% if coupled with effective weight loss.

Increased intake of meat [52, 53, 56, 146, 175, 197], seafood (including fish and shellfish) [56, 57, 146, 175, 197-199], alcohol [54, 146, 149, 153, 154, 156-163, 197], alcoholic beverages [52, 57], added sugar which are fructose-containing sugars, sucrose and high fructose corn syrup [116], fructose [128], sugar-sweetened beverages [128, 143, 145, 146], and fried foods [144] was associated with increased hyperuricemia risk. In contrast, increased intake of legumes [175], soy and soy products [52, 57, 58, 198], fruit and vegetables [53], vegetables [52], mushrooms [52], eggs [144], dairy products [52, 56, 245], coffee [56, 245, 254, 255], and tea drunk by Chinese adults [198, 275] was associated with decreased hyperuricemia risk. Higher adherence to the Mediterranean diet (The traditional Mediterranean diet) was associated with lower SUA levels [137, 177, 301] and lower likelihood of hyperuricemia [137, 177]. The DASH diet reduced SUA concentration [317]. Dietary habits for the prevention of hyperuricemia are speculated as follows: limiting the intake of meat, seafood (fish and shellfish), purine-rich foods, high fructose corn syrup-sweetened beverages including serving of naturally sweet fruit juices, sugary foods including desserts and sweets, alcoholic beverages, and salt is important; encouraging the intake of soybean products, legumes, nuts, mushrooms, eggs, fruit, vegetables, fiber-rich foods (e.g., cereals, whole grains, high-fiber bread), dairy products, and coffee may be useful for the reduction of SUA levels; higher adherence to the Mediterranean diet (The traditional Mediterranean diet) and the DASH diet encompasses many of the elements known to be inversely associated with hyperuricemia, such as lower intake of purine content with low intake of meat, higher intake of vitamin C, folate, dietary fiber (DF), and flavonoids with high intake of legumes, nuts, fruit and vegetables; maintenance of good hydration; and weight management including proper calorie intake and adequate exercise.

Recent large-scale epidemiological studies have shown that dietary factors affect SUA levels parallel to the direction of risk of hyperuricemia [23]. Therefore, it is speculated that the above dietary habits contribute not only to the prevention of hyperuricemia, but also to the suppression of hyperuricemia. General health, diet and lifestyle measures for the gout patients recommended by the American College of Rheumatology Guidelines [349] seem to be also fit for individuals with hyperuricemia. The dietary habits summarizing the contents of many research reports for the prevention and suppression of hyperuricemia described in this article are shown in Table 1.

10. Association between dietary factors and gout

Gout is an inflammatory arthritis caused by deposition of monosodium urate crystals in synovial joints. A prolonged rise in SUA $\geq$ 7 mg/dL may lead to the precipitation of urate crystals in and around peripheral joints resulting in gout or gouty conditions [350]. In the Global Burden of Disease

Table 1. Dietary habits for prevention and suppression of hyperuricemia.

Weight management • Weight management including proper calorie intake and adequate exercise. • Optimize weight to be near or at ideal body weight. • Optimizing energy intake and elimination of the obesity [1]. • In overweight patients, sensible diets tailored to weight reduction to achieve ideal body weight (or close to it) and body mass index (BMI) are preferred [81, 349]. • Weight loss for obese patients, to achieve BMI that promotes general health [349]. For example, calorie-restricted, low-carbohydrate, high-protein diet (40% carbohydrate, 30% protein, 30% monounsaturated or polyunsaturated fat) tailored to achievement and maintenance of ideal body weight [343].
Exercise • A physical activity for 30-60 minutes, such as walking, cycling, jogging, or swimming, should be performed three times a week. • Encouraged aerobic exercise [1]. • Isotonic exercise for 30-60 minutes such as walking, jogging, cycling or swimming [338]. • Walking or cycling for 30-60 minutes is 2-4 metabolic equivalent tasks (METs-h/day), jogging for 30-60 minutes is 3-6 METs-h/day, swimming for 30-60 minutes is 4.3-8.6 METs-h/day [337, 340]. • Aerobic exercise which lasts at least 15 minutes per exercise period at least 3 times a week [337]. • Light exercise about 3 times a week with the aim of achieving proper body weight (BMI <25) in individuals with obesity [1].
Meal strategies • It is essential to maintain a moderate amount of one serving, which is composed of staple food, side dishes, main dishes, milk and dairy products, fruit, and vegetables. • Consumption of meals and drinks should be generally about 80% of satiety. • A prevailing principle is that each portion size [25, 81] and overall caloric content should be moderate [81]. • The concept of a smaller dinner plate size (or portions scaled to fit a smaller plate) is valuable for the patient [81]. • Moderation of each portion (e.g., appetizer, main course, dessert) and of serving of alcohol [25, 81]. • Avoid binge eating (“feasting”) and particularly avoid overeating in combination with alcohol excess, particularly on holidays [81]. • Stay well hydrated [1, 349]. • Maintenance of good hydration (five to eight 8-oz servings of water daily: 1183-1893 g) is essential [81]. • Avoid getting rid of stress by overeating in combination with alcohol excess, and live a life without stress.
Purine • Limit intake of meat, seafood (fish and shellfish), and purine-rich foods. • Limit intake of purine is important and daily purine intake should be approximately 400 mg [1].

Table 1 continued..

Meat • Limit intake of meat and organ meat (e.g., sweetbreads, liver, kidney). • Eat one less portion of meat or fish a day [81]. • Intake of meat (beef, pork, chicken, sheep meat) and giblets per one serving should be 80 g and 40 g, respectively [1]. • Meat (beef, pork, and lamb) consumption for hyperuricemia and gout patients should be ≤6 oz (170.10 g) per day as a starting point [81].
Seafood • Limit intake of seafood (fish and shellfish). • Eat one less portion of meat or fish a day [81]. • Intake of fish, shellfish, prawn and shrimp, and crab per one serving should be 80 g, ≤60 g, ≤50 g, and 100g, respectively [1]. • Seafood (especially, shellfish and crustaceans) consumption for hyperuricemia and gout patients should be ≤6 oz (170.10 g) per day as a starting point [81].
Fish oil • Consider fish oil supplements in place of fish [23, 81]. • Consume at least 250 mg/day of long-chain n-3 polyunsaturated fatty acid or at least 2 servings/week of oily fish [515].
Alcohol and alcoholic beverages • Limiting the consumption of alcoholic beverages is important. • Reduce alcohol intake to an ideal amount of one drink per day (no binge drinking; do not consume more than two servings of alcohol in a 24-hour period) [81]. • Sensible moderate drinking for overall health benefits is 1-2 drinks/day for men and ≤1 drink/day for women [178,179]. • The most beneficial values of all these biochemical and clinical parameters were found in alcohol intake of 100-200 mL (12% alcohol) [177]. • Consumption of beer, spirits, wine, and rice wine per one drink should be 500 mL, 60-90 mL, 200 mL, and 180 mL, respectively [1].
Fructose, sugar-sweetened beverages, and sugary foods • Limiting the intake of high fructose corn syrup-sweetened beverages including serving of naturally sweet fruit juices, sugary foods including desserts and sweets is important. • Limit consumption of high fructose corn syrup-sweetened soft drinks and energy drinks, table sugar and sweetened beverages, including serving of naturally sweet fruit juices and desserts [349].
Salt • Limiting the consumption of salt [349].
Legumes and nuts • Encourage intake of soybean products, legumes and nuts. • Ministry of Health, Labour and Welfare in Japan has recommended an intake of legumes of 100 g or more per day [98].

Table 1 continued..

• Intake of dried soybeans, dried adzuki beans, green soybeans, fermented soybeans, broad beans, tofu, soybean fiber, and soybean milk per one serving should be 35 g, 40 g, 40 g, 40 g, 50 g, 100 g, 100 g, and 200 g, respectively [1]. • Intake of nuts 1-3 times per day (13-15 g per once) [23]. • The serving of almonds for human must be 30 g/person/day [217]. • Intake of peanuts and almonds per one serving should be 20 g and 15 g, respectively [1]. • Intake of nuts and legumes should be 1 to 3 servings [15].
Fruit and vegetables • Encourage intake of fruit and vegetables. • Intake of fruit must be 2 to 3 servings among patients with hyperuricemia [15]. • Avoid excess overall intake of foods naturally rich in fructose (e.g., orange, apples) and purine-rich vegetables. • Intake of cauliflower, bamboo shoots, spinach and mushroom, which are purine-rich vegetables, per one serving should be 50 g, 50 g, 40 g, and 50 g, respectively [1]. • Ministry of Health, Labour and Welfare in Japan has recommended that daily consumption of vegetables must be 350 g or more (green-yellow vegetables, 120 g or more) [98]. • Dietary guidelines for Japanese (The Japanese food guide spinning top) has recommended that daily consumption of fruit must be 2-3 servings (approximately 200-300 g) and daily total consumption of vegetables, mushrooms and potatoes and seaweeds must be 5-7 servings (approximately 350-490 g), depending on an individual's caloric intake [233]. • The dietary guideline in the U.S. call for 5 to 13 servings of fruit and vegetables a day, depending on an individual's caloric intake [221]. • The recommendations in the Dietary Guidelines for Americans distinguish between fruit and vegetables, recommending 2 to 4 servings per day for fruit and 3 to 5 servings per day for vegetables [222].
Dairy products • Encourage intake of dairy products (especially, low-fat or nonfat dairy products). • Daily supplement of dairy or calcium supplement must be 1 to 2 servings [15]. • Two servings per day of nonfat or low-fat yogurt or milk [81]. • Drink skim milk or consume other low-fat dairy products up to two servings daily [23]. • Ministry of Health, Labour and Welfare in Japan has recommended that daily consumption of dairy products must be 130 g or more [98]. • Dietary guidelines for Japanese (The Japanese food guide spinning top) has recommended that daily consumption of milk and milk products must be 2-3 servings (milk: approximately 100 g/serving; yogurt: approximately 83 g/serving; cheese: approximately 20 g/serving), depending on an individual's caloric intake [233].
Coffee • Encourage intake of coffee. • Drinking 1-4 cups of coffee or decaffeinated coffee per day appear to be beneficial. • Daily coffee consumption must be three to four cups [268].

Table 1 continued..

• Daily intake of at least 4 cups of coffee was linked with mean SUA level reduction of only 0.18-0.22 mg/dL [255].
Dietary fiber (DF) and fiber-rich foods • Encourage intake of dietary fiber (DF) and fiber-rich foods (e.g., cereals, whole grains, high-fiber bread). • Whole-grain foods at most meals [15]. • Ingesting whole-grain foods once a day. • The recommended intake of DF is 14 g/1000 kcal [94], and the recommended acceptable intake of DF for adults is 28 g/day for women and 36 g/day for men in the U.S. [95, 96]. • An adequate intake recommendation for total DF intake is 38 g/day for men (aged 14-50 years) and 25 g/day for women (aged 19-50 years), while for adults over 50 years of age, the recommendation is 30 g/day for men and 21 g/day for women in the U.S. [97]. • Ministry of Health, Labour and Welfare in Japan has recommended that daily DF intake must be 20 g or more for men (aged 18-70 years) and 18 g or more for women (aged 18-70 years), while for adults over 70 years of age, the recommendation daily DF intake is 18 g or more for men and 17 g or more for women [98].
Vitamin C (ascorbate) • Encourage consumption of vitamin C. • Vitamin C supplementation (500-1,000 mg/day) lowers serum uric acid concentrations. One caution is that it is not known if combined effects on urine pH, oxalate generation, and uricosuria of high ascorbate intake can promote urolithiasis [81].
Diet • Avoid the Western diet. • Encouraged diets are higher adherence to the Mediterranean diet (The traditional Mediterranean diet), the DASH diet, and high fruit and soybean product diet. • The Mediterranean diet [306]: olive oil (50 g/day); tree nuts and peanuts [≥3 servings/week (30 g/day, composed of 15 g of walnuts, 7.5 g of almonds, and 7.5 g of hazelnuts)]; fresh fruits (≥3 servings/day); vegetables (≥2 servings/day); fish (especially, fatty fish), seafood (≥3 servings/week); legumes (≥3 servings/week); sofrito (sofrito is a sauce made with tomato and onion, often including garlic and aromatic herbs, and slowly simmered with olive oil)(≥2 servings/week); white meat (instead of red meat); wine with meals (optionally, only for habitual drinkers) (≥7 glasses/week); soda drinks (<1 drink/day); commercial bakery goods, sweets, and pastries (included cakes, cookies, biscuits, and custard) (<2 servings/week); spread fats (<1 serving/day); red and processed meats (<1 serving/day). • The DASH eating pattern [297, 316]: total fat, 27% of calories; saturated fat, 6% of calories; cholesterol, 150 mg; protein, 18% of calories; carbohydrate, 55% of calories; fiber, 30 g; sodium, 2,300 mg; potassium, 4,700 mg; calcium, 1,250 mg; magnesium, 500 mg. • High fruit and soybean product diet [278]: rice and rice products (150.00 g); wheat and wheat products (100.00 g); other cereals (21.42 g); starchy tubers (8.57 g); fried wheat products (14.29 g); pork (14.28 g); beef/lamb (13.33 g); poultry (14.29 g); animal giblets (7.14 g); aquatic product (21.43 g); milk products (71.43 g); egg (8.33 g); soybean products (100.00 g); dry bean (1.92 g); vegetables (300.00 g); cake (3.33 g); fruit (200.00 g); nuts (0.00 g); beverages (3.33 mL); liquor and alcoholic beverages (5.00 g).

2012 study, the global prevalence of gout was estimated to be 0.08% [351]. The incidence of gout has more than doubled over the past 20 years [352]. SUA level of more than 10 mg/dL may cause progression of hyperuricemia and lead to symptoms of gout [32]. At the time of their first gout flare, patients diagnosed with gout in 2009-2010 had higher prevalence of comorbid conditions compared with 1989-1992, including hypertension (69% versus 54%), diabetes mellitus (25% versus 6%), renal disease (28% versus 11%), hyperlipidemia (61% versus 21%), and morbid obesity [body mass index (BMI) $\geq$ 35 kg/m^2] (29% versus 10%) [352].

Hyperuricemia is considered as the precursor of gout [10, 13-16] and is the most important risk factor of gout [1, 14, 15, 29]. Increased intake of meat [29, 140, 150, 245, 276, 353], seafood [353], fructose [29, 354-356], sugar-sweetened beverages [139, 245, 276, 355], alcohol [150, 174, 276, 357-359], and alcoholic beverages [245] was associated with increased gout risk, whereas higher intake of legumes and nuts [276], fruit [150], less sugary fruit [276], fruit and vegetables [198, 357], whole grains [276], dairy products [29, 245, 353], low-fat dairy products [276], coffee [29, 245, 268, 276, 360-362], vitamin C [29, 76, 276, 357], folate [357], and dietary fiber (DF) [357] was associated with lower gout risk. Purine-rich plant foods like legumes and vegetables did not increase the risk of gout [245]. There was no increased risk of gout associated with increased intake of purine-rich vegetables (peas, beans, lentils, spinach, mushrooms, and cauliflower) [359]. This phenomenon can probably explain that increased intake of vegetable protein and DF protect against the risk of gout [353, 357]. Intake of shrimp and shell, which are purine-rich foods, in hyperuricemic patients was an independent risk factor for gout development from hyperuricemia [363].

Garlic (*Allium sativum*) (raw garlic, dried garlic, garlic oil or a prepared commercial product) has been widely used for gout and rheumatism [364]. There was an inverse association between intake of cherries or its concentrate and the risk of gout attack [365]. Clinical case reports of three patients with gout showed that consumption of 227 g of cherry products daily for 3 days to 3 months reduced plasma UA to normal levels and alleviated attacks of gouty arthritis [225]. From these reports, it is assumed that intake of cherry and cherry products will help prevent hyperuricemia and gout due to decrease in SUA levels.

In an observational study performed by Dessein *et al*. [343], thirteen non-diabetic men with gout (median age 50, range 38-62) ingested calorie-restricted diet (1,600 kcal a day) composed of 40% carbohydrates [replacement of refined carbohydrates (e.g., white flour, white rice) with complex ones (e.g., whole wheat flour, brown rice)], 30% protein, and 30% fat [replacement of saturated fats (e.g., dairy fats, meat fat) with mono- and polyunsaturated ones (e.g., macadamia nuts, almonds, peanuts and peanut butter, olive oil, canola oil, avocados)] for 16 weeks. The mean SUA concentration decreased by 18% in gouty patients after four months of dietary intervention. This was accompanied by a 67% reduction in monthly gouty attack frequency. This pilot study also observed weight reduction and beneficial effects on dyslipidemia in gout. Dessein *et al*. [343] have expressed the view that weight reduction associated with a change in proportional macronutrient intake is beneficial in reducing the SUA levels and dyslipidemia in gout.

The DASH diet was associated with a lower risk of gout, suggesting that its effect of lowering SUA levels in individuals with hyperuricemia translates to a lower risk of gout [279]. In contrast, the Western diet was associated with a higher risk of gout [279]. The Western diet increased SUA levels and the risk of gout, which may explain the increasing prevalence of gout in Western countries [279, 280].

11. Prevalence of comorbidities of hyperuricemia

Many prospective studies have suggested an independent association between SUA levels and the future risk for cardiovascular-metabolic morbidities and mortality [23]. Sattui *et al*. [366] have summarized the results of several experimental studies, epidemiological studies and clinical intervention trials that showed evidence of the association between hyperuricemia and several comorbidities. They [366] took up hypertension, coronary heart disease (CHD), congestive heart failure, stroke, chronic kidney disease (CKD),

insulin resistance and metabolic syndrome, type 2 diabetes mellitus, and neuro-degenerative disorders as comorbidities. Some studies have reported that hyperuricemia is associated with an increased risk of some diseases related to oxidative stress, such as metabolic syndrome [20], cardiovascular disease (CVD) [21] and obesity [22]. *In vitro* and animal models, large epidemiological studies, and small clinical trials suggest that hyperuricemia may contribute to hypertension, chronic kidney disease (CKD), and CVD and more limited hypothesis-generating studies suggest a potential role for diabetes and obesity [367]. Hyperuricemia often precedes the development of obesity, diabetes, and hypertension [368]. The prevalence of comorbidities among individuals with hyperuricemia [SUA level > 7.0 mg/ dL (416.4 μmol/L) among men or postmenopausal women and > 6.0 mg/dL (356.9 μmol/L) among women] in the Shandong coastal cities of Eastern China was 58.6% for overweight and obesity, 45.0% for hypertension, and 10.8% for diabetes [6]. As shown by these reports, the prevalence of comorbidities in the U.S among individuals with hyperuricemia [SUA level > 7.0 mg/ dL (416.4 μmol/L) among men and > 5.7 mg/dL (339.0 μmol/L) among women] was as follows: CKD, stage ≥ 2, 61.4%, 26.6 million and stage ≥ 3, 14.8%, 6.4 million; obesity, 54.4%, 23.1 million; hypertension, 49.7%, 21.5 million; diabetes, 13.5%, 5.8 million; nephrolithiasis, 12.3%, 5.3 million; stroke, 5.7%, 2.4 million; myocardial infarction, 5.1%, 2.2 million; heart failure, 5.1%, 2.2 million [369]. Furthermore, higher levels of hyperuricemia increased the prevalence of its comorbidities [369].

12. Association between comorbidity of hyperuricemia and dietary factors

The comorbidity benefit of any UA-lowering approach is important, as hyperuricemia is associated with cardiovascular-metabolic comorbidities [4, 370] and sequelae (e.g., increased future risk of myocardial infarction and premature death) [370]. Dietary habits for the prevention and suppression of hyperuricemia should be beneficial for the prevention of comorbidities of hyperuricemia. Therefore, considering the prevalence of comorbidities among individuals with hyperuricemia in the Shandong coastal cities of Eastern China [6] and U.S. [369], knowledge of common foods or dietary patterns playing a helpful role in both the prevention and suppression of hyperuricemia and the prevention of its comorbidities is essential. Association between the risk of morbidities of hyperuricemia and dietary factors is as follows.

12.1. Chronic kidney disease (CKD)

SUA concentration is associated with the incidence of chronic kidney disease (CKD) [1, 371-375]. Hyperuricemia is associated with an increased risk of CKD [366, 375]. Hyperuricemia is a risk factor for renal disease progression [32]. Casein with safflower-seed oil was effective in attenuating hyperuricemia-associated renal damage in rats [55].

CKD is considered an inflammatory state [376-378]. A correlation between the risk of developing CKD or the presence of decreased renal function and inflammation has been reported [376]. Renal failure is a prooxidant state, which is characterized by insufficient antioxidant protection and elevated levels of reactive oxygen species. Compared to healthy counterparts, CKD patients exhibited increased serum levels of C-reactive protein, interleukin-6, interferon-γ, and tumor necrosis factor-α, following altered renal cell dynamics and changed plasma flow [379].

In a clinical trial, increased dietary fiber (DF) intake in CKD patients (stage 3, 4 and 5 CKD, but not on dialysis) reduced blood urea nitrogen and serum creatinine levels and improved estimated glomerular filtration rate (eGFR) values [380]. Evidence from a systematic review and meta-analysis conducted by Chiavaroli *et al*. [381] showed that DF had potential effects in the CKD population demonstrating a reduction in serum urea and creatinine concentrations. Xu *et al*. [382] found that high DF intake was associated with better kidney function and lower inflammation in elderly men from Sweden. Higher intake of DF was associated with a lower risk of CKD [383-386]. In a cross-sectional study, DF intake was also associated with CKD progression, but not protein nutritional status, in adults with CKD [387]. Increased DF intake retarded the decrease in the eGFR and reduced the levels of

proinflammatory factors (C-reactive protein, interleukin-6), indoxyl sulfate, and serum cholesterol [387]. Indoxyl sulfate and p-cresyl sulfate are uremic toxins derived solely from colonic bacterial fermentation of protein. A low protein-fiber index (ratio of protein to fiber) was associated with lowering serum indoxyl sulfate and p-cresyl sulfate concentrations in CKD patients [388]. This result suggests that DF may counteract cardiorenal toxicity by limiting proteolytic bacterial fermentation [388]. A cross-sectional study based on the data of the U.S. NHANES-III (1988-1994) showed that higher DF intake was associated with lower risk of inflammation (elevated serum C-reactive protein levels) in both CKD and non-CKD populations and this association was significantly stronger in those with CKD than those without CKD [378]. Buyken *et al.* [389] found that increased intake of DF (fruit fiber) was associated with decreased risk of inflammatory disease. They [389] have also expressed the view that DF is related to the anti-inflammatory effect.

The Western diet increased the risk of CKD [281]. In contrast, dietary patterns high in fresh fruit and vegetables and low in red meat decreased the risk of CKD [281]. Higher risk of developing CKD was associated with higher intake of shellfish and fewer intake of soy products [144]. Therefore, it is assumed that high intake of DF and/or dietary patterns high in fresh fruit and vegetables and low in red meat has a potential role in the prevention of both hyperuricemia and CKD.

12.2. Urolithiasis

Hyperuricemic patients often have urinary acidification [1]. The most important risk factor for UA stone formation is persistently acidic urine [390, 391], favouring the precipitation of urate [390]. As the amount of urinary UA (UUA) excretion increases, frequency of UA stone formation increases [392]. Excessive intake of purine increases the incidence of urolithiasis [1]. There was a positive correlation between urinary pH and intake of fruit and vegetables [393]. In addition, Kanbara *et al*. [219, 394] reported that the less protein-rich and more vegetable/fruit-rich diet significantly decreased SUA concentration and significantly increased UUA excretion and UA clearance, compared with the protein-rich and less vegetable/fruit diet. These reports suggest that urine alkalization by eating less protein-rich and more vegetable/fruit-rich diet is important and effective for promoting UUA excretion [219, 394]. From these facts, it is assumed that intake of abundant fruit and vegetables to prevent hyperuricemia contributes to the alkalization of urine and leads to the prevention of the incidence of UA stone. Decreased nephrolithiasis risk was associated with increased intake of coffee [395, 396]. Finkielstein and Goldfarb have expressed the view that proper daily fluid intake to prevent nephrolithiasis should be set at 2,500-3,000 mL [397].

12.3. Insulin resistance and diabetes

12.3.1. Insulin resistance

Insulin resistance has been associated with obesity, hypertension, glucose intolerance, coronary artery disease (CAD), increased triglyceride (TG) levels, decreased high-density lipoprotein (HDL) cholesterol (HDL-cholesterol) concentrations, increased total cholesterol/HDL cholesterol ratio, low-density lipoprotein (LDL) cholesterol (LDL-cholesterol), and UA concentrations [398, 399]. Many people with metabolic syndrome had insulin resistance [400].

Insulin is shown to decrease renal UA excretion [265, 352, 401] and estimated glomerular filtration rate (eGFR) levels [265, 352]. Insulin resistance has been shown to lead to elevated SUA levels through both direct and indirect mechanisms, which include increased UA production as well as decreased renal UA excretion. Increased SUA levels may in turn worsen insulin resistance and associated features such as hypertension, dyslipidemia, endothelial dysfunction, non-alcoholic fatty liver disease, and chronic kidney disease (CKD), thus increasing the risk of cardiovascular disease (CVD) [402].

There is a strong positive association between insulin resistance and hyperuricemia [10, 33, 154, 403-406]; approximately 63% of subjects with hyperuricemia had insulin resistance (homeostasis model assessment of insulin resistance: HOMA-IR >2.77) [407]. Li *et al*. [408] have stated that insulin resistance and hyperuricemia shared a

bidirectional causal effect. Close associations have been reported between hyperuricemia and all components of the insulin resistance syndrome, including hyperinsulinemia, hypertension, dyslipidemia, and obesity [404]. Hyperuricemia reduces endothelial nitric oxide (NO) bioavailability [34, 366, 409]. Experimental animal models have shown that hyperuricemia-induced vascular dysfunction, inflammation and increased oxidative stress lead to insulin resistance, which later leads to impaired glucose tolerance and predisposes to the other components of metabolic syndrome, such as obesity, hypertension and increased triglyceride (TG)/HDL-cholesterol ratio [366, 409]. Therefore, Sattui *et al*. [366] have expressed the view that a link between hyperuricemia, insulin resistance and metabolic syndrome may explain the association between two overlapping and increasing diseases.

High intake of plant proteins [60, 410], fish-derived proteins [410], dietary fiber (DF) [411-415], magnesium [416], calcium [416], and coffee [258, 259] increased insulin sensitivity.

In a cross-sectional study, high DF intake, particularly soluble DF, was significantly related to lower levels of insulin resistance (HOMA-IR) in women [411]. In a randomized controlled trial, administration of rye bread (6-20 g/day) [412], whole-grain foods [413] or powdered high-fiber foods (mean 10 g/day) [414] significantly increased insulin sensitivity. In a randomized double-blind, placebo-controlled trial, ingestion of wheat- or corn-derived soluble DF (NUTRIOSE) (34 g/day) for 12 weeks in overweight men reduced insulin resistance [415]. In the Framingham Offspring Cohort, intake of cereal fiber, fruit fiber and whole grains was inversely associated with the level of insulin resistance (HOMA-IR) [417]. The benefits of increased DF intake in the prevention and treatment of metabolic syndrome derived mainly from soluble DF, which comes mainly from fruit and vegetables [418]. These benefits are the result of high viscosity of soluble DF that increases the viscosity of diets and slows down gastric emptying and the digestion and the absorption of macronutrients [419]. Short-chain fatty acids, a product of soluble DF fermentation in the gut, stimulate satiety and improve insulin sensitivity [420]. In a single-blind, randomized, parallel nutritional intervention study in subjects with metabolic syndrome, resistant starch consumption improved insulin sensitivity compared with the placebo group [421]. The portfolio of cholesterol-lowering foods, such as oats, barley, psyllium, okra, eggplant, all of which are rich in soluble DF, soy protein, whole almonds, margarine enriched with plant sterol, reduced the mean LDL-cholesterol values by 29% and LDL-cholesterol/HDL-cholesterol ratio by 26.5% [422]. It seems that the above-mentioned cholesterol-lowering foods prevent hyperuricemia.

Replacing fats from red meat and butter with oils or margarine, which is rich in monounsaturated fatty acids or polyunsaturated fatty acids, improved insulin sensitivity and reduced serum LDL-cholesterol/HDL-cholesterol ratio and triglyceride (TG) concentration [423]. Unsaturated dietary fats reduced total cholesterol and LDL-cholesterol [424]. Partly replacing meat with soy in a moderately high-protein diet had clear advantages regarding insulin sensitivity and total-cholesterol and LDL-cholesterol [425]. Soy protein can bind to phytoestrogen compounds to stimulate metabolism by lowering total cholesterol, TG, LDL-cholesterol and reducing insulin resistance, resulting in a better blood profile [426, 427]. A controlled randomized trial found that high intake of plant protein (specifically, wheat gluten) reduced oxidized LDL, serum concentrations of triacylglycerol, creatinine and UA compared with the control [60]. Plant protein-based diets lowered plasma total cholesterol and LDL-cholesterol levels and increased plasma HDL-cholesterol level, resulting in a more favorable blood lipid levels in adolescents [428, 429]. A low-energy, high-protein diet [430], a low-energy, calorie-restricted, low carbohydrate, high protein with unsaturated fat diet [343], high-protein diet [431] and high-monounsaturated fatty acid/low- carbohydrate diet [432] and the DASH diet [316] improved insulin resistance.

Red meat, which is the main source of saturated fatty acids, was positively associated with insulin resistance [433, 434] and reduced renal UA excretion [265, 343, 352, 435]. Fructose intake was linked to increased insulin resistance [248, 436]. Fructose-rich sugar-sweetened beverage intake was associated with elevated levels of

insulin resistance, and this association may be partially mediated by central adiposity and SUA concentrations in adolescents in Taiwan [141, 437]. In contrast, coffee intake increased insulin sensitivity [259] and decreased SUA concentration [254-257]. Factors (e.g., adiposity, dairy intake, coffee intake, fructose intake) that affect insulin resistance and the renal UA excretion can affect SUA levels [265, 352, 401].

The Chinese omnivores had higher SUA levels than Chinese vegetarians [438, 439]. The Chinese vegetarians were more insulin sensitive than their omnivore counterparts [438]. Kuo *et al*. [438] have stated that the degree of insulin sensitivity appeared to correlate with years on a vegetarian diet.

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), the DASH diet and high intake of plant proteins (specifically, wheat gluten), dietary fiber (DF), magnesium, calcium, and coffee which improve insulin resistance, are more beneficial in terms of lowering SUA level, and hence reducing hyperuricemia risk. It is speculated that dietary patterns high in vegetables, nuts, legumes, fruit (less sugary ones), whole grains, and coffee and choices of their foods may also help prevent hyperuricemia by reducing insulin resistance.

12.3.2. Diabetes

Hyperuricemia is likely a risk factor for the development of diabetes mellitus [6]. Type 2 diabetes mellitus, the final expression of insulin resistance, has been associated with increasing SUA concentrations [440, 441] and incidence of hyperuricemia in epidemiological studies [406]. However, Sattui *et al*. [366] have expressed the view that epidemiological data causality is still controversial.

No association was found between intake of red meat [442, 443], poultry [443] and the risk of type 2 diabetes. Whereas, intake of red meat and processed meat [444-446], processed meat [442, 443, 446], white potatoes (fried or baked/boiled) [447], added sugar which are fructose-containing sugars, sucrose and high fructose corn syrup [116], fructose [448, 449], and sugar-sweetened beverages [448, 450, 451] was positively associated with type 2 diabetes risk. In contrast, intake of dietary fiber (DF) [95, 452-456], whole grains [457], legumes [444], nuts [423, 458], fruit and vegetables [459], vegetables [460], dairy products [461], low-fat dairy products [325, 462], coffee [268, 405, 463-465], and tea [310] was inversely associated with type 2 diabetes risk. A meta-analysis has demonstrated that an intervention involving DF supplementation for type 2 diabetes mellitus reduced fasting blood glucose and glycosylated hemoglobin (HbA1c) [466].

A systematic review conducted by Afshin *et al*. [467] demonstrated that consumption of nuts was inversely associated with diabetes [467]. Legumes produce lower glycemic responses, which may protect against diabetes [468].

Green leafy and cruciferous vegetables have been found to have a particularly beneficial effect on diabetes risk and should be included in the recommendation of vegetable intake [348]. Increased intake of green leafy vegetables, which belong to Brassicaceae, was associated with decreased type 2 diabetes risk [469]. Giammarioli *et al*. [470] reported a dietary treatment designed to ensure a daily intake of 700-1000 g of fruit and vegetables with a diet recommended by the EASD (European Association for the Study of Diabetes) to type 2 onset diabetes for 3 months. A high intake of fruit and vegetables by diabetic patients decreased plasma cholesterol and UA concentrations [470]. It seems that decrease in plasma cholesterol and UA concentrations could be attributed to a significant increase in the intake of fiber and vitamin C.

Dietary pattern characterized by higher consumption of red meat, processed meat, French fries, high-fat dairy products, refined grains, and sweets and desserts [282] or that of tomatoes, beans, refined grains, high-fat dairy, and red meat [471] was associated with increased type 2 diabetes risk. In contrast, dietary pattern characterized by high intake of whole grains, fruit, nuts/seeds, green leafy vegetables, and low-fat dairy was associated with decreased type 2 diabetes risk [471]. The Mediterranean diet with olive oil group or the Mediterranean diet with nuts group decreased plasma glucose levels compared with a low-fat diet group (olive oil: -0.39 mmol/L;

nuts: -0.30 mmol/L) [303]. The Mediterranean-style eating patterns achieved improvements in glycemic control [472-475]. Adherence to the DASH dietary pattern was inversely associated with the risk of type 2 diabetes [316, 476, 477]. Furthermore, the DASH eating pattern was shown to improve type 2 diabetes [316]. Campbell [316] has stated that the DASH eating plan is an acceptable eating pattern for people who have diabetes. The Mediterranean-style diet [472, 474, 475, 478, 479], the DASH diet [316, 472, 477-479], and plant-based diet [472, 478-481] are healthy eating patterns that have shown positive results for the management of diabetes.

The American Diabetes Association (ADA) position statement "Nutrition Therapy Recommendations for the Management of Adults with Diabetes" has discussed nutrition therapy for the management of individuals with diabetes in detail [478].

12.4. Hypertension

SUA concentration can be regarded as an independent predictor of hypertension development in the future [1]. Sattui *et al*. [366] have expressed the view that several population studies have proven an independent association between SUA concentration and development of hypertension.

Hyperuricemia is common in patients with essential hypertension. Hypertension is associated with a higher prevalence of hyperuricemia [197]. Approximately 25% of hypertensive subjects appear to have hyperuricemia, and this figure increases to 75% among those with malignant hypertension [40]. Results from a systematic review and meta-analysis conducted by Grayson *et al*. [482] have shown that hyperuricemia is associated with an increased risk for incident hypertension, independent of traditional hypertension risk factor. Potential mechanisms behind the link between hyperuricemia and development of hypertension include nitric oxide (NO) and renin-angiotensin pathways [40]. Hayden and Tyagi [34] have reviewed in detail the potential mechanisms involved with the association of hyperuricemia and hypertension.

Decreased hypertension risk was associated with increased intake of dietary fiber (DF) [95, 383, 454, 483], dairy products [461], and low-fat dairy products [484]. Intake of potassium and consumption of fruit and vegetables play an important role in regulating blood pressure [485]. A recent meta-analysis of 8 controlled feeding trials showed that consumption of pulses lowered systolic blood pressure (-2.25 mm Hg: 95% CI: -4.22, -0.28 mm Hg) and mean arterial blood pressure (-0.75 mm Hg: 95% CI: -1.44, -0.06 mm Hg) [486]. In a meta-analysis of 15 randomized controlled trials, Santesso *et al*. [487] found that higher-protein diets significantly reduced systolic blood pressure and diastolic blood pressure compared to lower-protein diets. The Mediterranean diet with olive oil group or the Mediterranean diet with nuts group decreased systolic blood pressure compared with a low-fat diet group (olive oil: -5.9 mm Hg; nuts: -7.1 mm Hg) [303]. Adherence to the Mediterranean diet was inversely associated with systolic blood pressure [295] and diastolic blood pressure [295, 301]. Furthermore, intake of olive oil, fruit, and vegetables was inversely associated with arterial blood pressure, whereas intake of cereals, meat and meat products, and ethanol was positively associated with arterial blood pressure [295]. The DASH diet has been shown to substantially lower blood pressure [105, 316, 488]. Adherence to the DASH dietary pattern was inversely associated with diastolic blood pressure [301]. The Optimal Macronutrient Intake Trial to Prevent Heart Disease (OmniHeart) suggests that substituting protein or unsaturated fat for some of the carbohydrates in an already healthy diet can further lower blood pressure, improve lipid levels, and reduce estimated cardiovascular risk [489]. A diet with much less salt and increased potassium through an increase in consumption of fruit and vegetables, a reduction in fat intake with substitution of saturated by monounsaturated fat, and a reduction in meat and dairy products with an increase in fish consumption have huge effects on blood pressure [485]. The DASH diet [105, 488, 490] and the OmniHeart diet [489, 490] are dietary patterns to prevent and control hypertension.

The mean daily consumption of dairy products, fruit, and vegetables that contribute to the Mediterranean diet score, which is inversely associated with both systolic and diastolic blood pressure are 196.7 g, 549.9 g and 362.5 g in men, respectively, and 191.1 g, 499.6 g and 356.3 g in women, respectively [295].

12.5. Metabolic syndrome

Obesity (visceral fat type obesity) and insulin resistance are at the core of metabolic syndrome; both promote hyperuricemia principally by impairing renal UA excretion [491]. In a cross-sectional analysis, higher SUA concentrations have been found to be positively correlated with metabolic syndrome [492-494]. The prevalence of metabolic syndrome increased substantially with increasing levels of SUA, from 19% for SUA levels less than 6 mg/dL to 71% for levels of 10 mg/dL or greater (SUA level: <6 mg/dL, 18.9%; 6-6.9 mg/dL, 36.0%; 7-7.9 mg/dL, 40.8%; 8-8.9 mg/dL, 59.7%; 9-9.9 mg/dL, 62.0%; ≥10 mg/dL, 70.7%) [18].

Hyperuricemia is strongly recognized as one of the key components of metabolic syndrome which develops impaired glucose tolerance, diabetes mellitus, dyslipidemia, and hypertension as a common background of visceral fat type obesity and insulin resistance [18, 29]. Results from animal experiments suggest that hyperuricemia may play a part in the development of metabolic syndrome [368].

In the population-based prospective study based on the Tehran Lipid and Glucose Study with 3 years of follow up, fruit fiber intake was inversely associated with the incidence of metabolic syndrome and with a 21% lower risk in the highest tertile of intake compared to the lowest tertile [495]. Fiber from fruit and vegetables reduced proinflammatory plasma concentrations of C-reactive protein, homocysteine, and tumour necrosis factor (TNF)-α and decreased mRNA levels of TNF-α, nuclear factor kappa B-1, and intercellular adhesion molecule-1, all of which may prevent or delay the development of metabolic syndrome [496].

Increased protein intake derived from animal sources was associated with increased risk of metabolic syndrome [497]. Increased metabolic syndrome risk was associated with increased intake of fructose [450, 451]. Whereas, decreased metabolic syndrome risk was associated with increased intake of whole grain [417], fruit fiber [495], fruit and vegetables [428], dairy products [324], regular fat dairy products [498], and coffee [268].

In people who consume avocado, the intake of fruit, vegetables, total lipids, monounsaturated fatty acids, polyunsaturated fatty acids (PUFAs), dietary fiber (DF), vitamin E, vitamin K, magnesium, and potassium was found to be higher while the intake of added sugars was found to be lower [499]. Compared to those who did not consume avocado, people who consumed avocado showed a decrease in body weight, body mass index (BMI) and waist circumference and showed an increase in serum HDL-cholesterol concentration and reduced frequency of metabolic syndrome by 50% [499]. Therefore, avocado consumption was associated with improved overall diet quality and reduced risk of metabolic syndrome [499]. It is assumed that dietary habits of people who consume avocado have a beneficial effect on the prevention of metabolic syndrome.

12.6. Obesity

Tsushima *et al*. [500] have found that adipose tissue produced and secreted UA through xanthine oxidoreductase [xanthine oxidase (EC 1.1.3.22) + xanthine dehydrogenase (EC 1.1.3.204)] and that the production was enhanced in obese mice. Thus, they [500] have stated that high xanthine oxidoreductase activity and UA production by adipose tissue may relate to active lipid metabolism. An Australian study involving 354 women aged 51-62 years old, reported that greater consumption of soy isoflavones was associated with both lower body mass index (BMI) and waist circumference [501]. Greater soy consumption was also associated with lower abdominal obesity in men and women in the community-based cross-sectional study in China [58]. A meta-analysis showed that higher-protein diets led to greater weight loss, and loss in BMI and waist circumference than lower-protein diets [487]. In a prospective study, fruit fiber was inversely associated with waist circumference [418]. Aiello *et al*. [502] performed a single arm longitudinal intervention study in 42 healthy volunteers, administrating 500 g per week of pasta with 3% of Opuntia Ficus Indica (OFI) cladode extracts for 30 days. Functional pasta intake resulted in significant reduction in abdominal waist and concentrations of SUA (5%) and blood glucose (4%) compared with the respective baseline (before administrating the pasta). UA, which is a

prooxidant and proinflammatory factor, significantly decreased, likely due to the increase in dietary fiber (DF) intake contained in experimental pasta, suggesting its possible anti-inflammatory properties.

Skerret and Willett [297] have stated as follows: The higher the BMI (> 25 kg/m^2), the greater the prevalence of abnormal blood glucose, lipids and blood pressure; hypertension and cardiovascular disease (CVD); diabetes; many cancers; gallstones; sleep apnea; complications of pregnancy; infertility; and premature mortality. Overweight (BMI ≥ 25 kg/m^2) or obesity (BMI >30 kg/m^2) has shown positive association with SUA concentration [13, 50, 503, 504] and hyperuricemia risk [8, 13, 54, 57, 144, 197, 404, 505]. There is a positive correlation between BMI and visceral fat accumulation, SUA concentration, or urinary UA excretion for 24 hours, and there is an inverse correlation between BMI and UA clearance (Cua) [504]. Therefore, it is speculated that obesity *via* both increased production and decreased renal excretion of UA may be responsible for the increase in SUA concentration and hyperuricemia risk.

Increased obesity risk was associated with increased intake of fructose [506-508], sugar [116], and sugar-sweetened beverages [448, 449]. Whereas, decreased obesity risk was associated with increased intake of dietary fiber (DF) [94, 95, 452-454, 509]. Dietary pattern rich in fruit, vegetables, low-fat dairy products and poultry was negatively associated with obesity, whereas dietary pattern high in processed meats, soft drinks, sweets, refined grains, snacks and processed juice was positively associated with obesity [510]. Greater adherence to the Mediterranean dietary pattern was associated with reduced weight gain [304, 305] and overweight or obesity [305]. Individuals with a high adherence to the Mediterranean dietary pattern according to the relative Mediterranean Diet Score showed a 5-year weight change of -0.16 kg [305]. Furthermore, individuals with a high adherence to the Mediterranean dietary pattern were 10% less likely to develop overweight or obesity than individuals with a low adherence to the Mediterranean dietary pattern [305]. The DASH diet reduced weight [316, 318]. Adherence to the DASH dietary pattern was inversely associated with waist circumference [301]. The DASH eating pattern was shown to improve overweight/obesity [316]. These results show that promoting the Mediterranean dietary pattern and the DASH eating pattern as a model of healthy eating may help to prevent the development of overweight and obesity. Bulló *et al*. [511] have expressed the view that considering all the evidence relating to diet and inflammation, the best diet for protecting against the metabolic derangements associated with obesity and metabolic syndrome should be high in fiber-rich cereals, fruit, vegetables, fish, virgin olive oil and nuts; moderate in wine; and low in meat, processed meat foods and trans-fatty acids.

In a cross-sectional study in Japan, moderate-intensity physical activity (3.0-6.0 METs) was associated with lower SUA concentration in obese individuals [512]. The guideline for the management of hyperuricemia and gout in Japan has stated that it is desirable to continue light exercise for about 3 times a week with the aim of achieving proper body weight (BMI <25) in individual with obesity [1]. To reduce body weight in obese individuals, it is important to burn more calories by moderate-intensity physical activity and restrict calorie input, which consequently leads to a reduction in SUA concentration and the prevention and suppression of hyperuricemia.

12.7. Cardiovascular disease (CVD)

Major risk factors for cardiovascular disease (CVD) are hypertension, diabetes, and obesity [454].

In patients with no history of heart disease or stroke, elevated UA levels are associated with higher risk of myocardial infarction or stroke [513]. Increased SUA levels are a risk factor for CVD and other disorders where oxidative stress plays an important pathophysiological role [17, 33, 41-44]. UA may function as a prooxidant in hyperuricemia, despite its antioxidant properties under physiological conditions [514]. Hyperuricemia is an independent risk factor for CVD [29]. A hypothesis has been proposed that hyperuricemia itself can cause arteriosclerosis through injury to the vascular endothelium, which can cause CVD [19]. In the atherosclerotic prooxidative

environmental milieu, the original antioxidant properties of UA paradoxically become prooxidant, thus contributing to the oxidation of lipoproteins within atherosclerotic plaques, regardless of their origins in metabolic syndrome, type 2 diabetes mellitus, accelerated atherosclerosis (atherosclerosis), or non-diabetic vulnerable atherosclerotic plaques [34]. UA can oxidize LDL in the presence of copper ions and lipid hydroperoxides, thereby increasing inflammatory status [45].

Mozaffarian and Wu [515] reviewed available evidence for cardiovascular effects of n-3 polyunsaturated fatty acid (PUFA) consumption. They [515] concluded that not all trials of n-3 polyunsaturated fatty acid (PUFA) demonstrated reductions in CVD, but several adequately powered clinical trials have demonstrated significant benefits. Dietary fiber (DF) intake was inversely associated with CVD risk in adults with chronic kidney disease (CKD) [387]. There was an inverse correlation between intake of green leafy vegetables and death from CVD [516]. Consumption of added sugars, which are fructose-containing sugars, sucrose, and high fructose corn syrup, was associated with the prevalence of CVD [116]. Consumption of legumes 4 times or more per week compared with less than once a week was associated with a 22% lower risk of coronary heart disease (CHD) and an 11% lower risk of CVD [209]. Compared with non coffee consumption, consumption of three to four cups of coffee in a day was associated with a 15% lower risk of CVD [268]. Higher adherence to the DASH-style diet was associated with a lower risk of CHD and stroke among middle-aged women during 24 years of follow-up [319]. Estruch *et al*. [306] examined primary prevention of CVD through a Mediterranean diet in the large, multi-center, randomized control trial among persons at high cardiovascular risk. They [306] found that the incidence of major cardiovascular events (myocardial infarction, stroke, or death from cardiovascular causes) was lower among those assigned to an energy-unrestricted Mediterranean diet supplemented with extra-virgin olive oil or nuts than among those assigned to a reduced-fat (control) diet and the effect of the dietary intervention in reducing stroke risk (extra-virgin olive oil: 35%; nuts: 46%) was greater than the effect on myocardial infarction risk (extra-virgin olive oil: 18%; nuts: 24%). Better adherence to the Mediterranean diet was associated with lower risk of myocardial infarction, heart failure and ischemic stroke [307]. Tektonidis *et al*. [307] have stated that the Mediterranean diet is most likely to be beneficial in primary prevention of all major types of atherosclerosis-related CVD. World Health Organization has stated that eating at least five servings of fruit and vegetables a day, and limiting your salt intake to less than one teaspoon a day, also helps to prevent heart attacks and strokes [517].

12.7.1. Ischemic cardiovascular disease (iCVD)

Decreased ischemic cardiovascular disease (iCVD) risk was associated with increased intake of dietary fiber (DF) [518]. A systematic review demonstrated that consumption of nuts and legumes were inversely associated with the incidence of ischemic heart disease [467].

12.7.2. Coronary artery disease (CAD)-coronary heart disease (CHD)

There is a causal relationship between the onset of coronary artery disease (CAD) and hypertriglyceridemia or low HDL-cholesterol hyperlipidemia which leads to insulin resistance, hypertension, and diabetes [400]. Risk factors for coronary heart disease (CHD) include hypercholesterolemia, hypertension, obesity, and type 2 diabetes [452]. Sattui *et al*. [366] have expressed the view that, although still not conclusive, evidence shows a small but significant increased risk of CHD in individuals with hyperuricemia [519, 520].

Jamshed and Gilani have found that dietary almonds prevented high-fat diet-induced hyperuricemia, followed by reduced nitric oxide (NO) production *via* endothelial NO synthase (eNOS) inhibition, resulting in improved vascular function of isolated aorta in rats [521]. They [39] also found that dietary almond (10 g/day) reduced SUA concentrations in CAD patients in a randomized controlled trial. They infer from these results that the probable mechanism of action of almonds on the prevention of hyperuricemia is mediated through vascular protection in CAD patients.

Increased intake of red meat [446, 522], processed meat [442, 446, 522], and high-fat dairy [522] was associated with increased risk of CHD. In contrast, higher intake of poultry [522], fish [522], legumes [209, 283, 523], nuts [522, 524-527], fruit and vegetables [528-531], low-fat dairy products [532], vitamin C [533], and dietary fiber (DF) [95, 534-538] and moderate alcohol consumption [178, 179] was associated with lower risk of CAD or CHD.

Several studies found an approximate 10% to 30% reduction in CHD risk associated with an increment of 10 g/day of DF intake [539]. A meta-analysis of 13 cohort studies showed that increased consumption of fruit and vegetables from less than three to more than five servings per day was related to a 17% reduction in the risk of CHD [531].

Moderate alcohol intake was associated with a 25-40% decrease in the risk of CHD [178, 179]. Sensible moderate drinking for overall health benefits is 1-2 drinks/day for men and ≤1 drink/day for women; these benefits may be particularly relevant to middle-aged men [178, 179]. Terkeltaub and Edwards [81] have expressed the view that an ideal amount of alcohol intake for patients with hyperuricemia and gout should be one drink per day and ≤ 2 servings in a 24-hour period. Appropriate alcohol consumption that does not raise SUA levels seems to be beneficial to health.

Dietary pattern characterized by higher intake of vegetables, fruit, legumes, whole grains, fish, and poultry was associated with decreased CHD risk, whereas dietary pattern characterized by higher intake of red meat, processed meat, refined grains, sweets and dessert, French fries, and high-fat dairy products was associated with increased CHD risk [283]. A Mediterranean diet, rich in plant food in combination with nonsmoking, moderate alcohol consumption, and daily physical activity was associated with a significantly lower mortality rate of CAD and all-cause mortality [426]. The OmniHeart diet reduced estimated CHD risk [489]. Replacement of saturated with monounsaturated fatty acids was associated with a considerable reduction in CHD risk, through a mechanism involving reduction of LDL-cholesterol, without a reduction of HDL-cholesterol or an increase in triacylglycerols [540]. Reduction of the risk of CHD when replacing one serving meat with one low-fat dairy product, poultry, meat, fish nuts or legumes was 13%, 19%, 24%, 30% and 34%, respectively [527]. Fish products, particularly oily fish that are rich in n-3 polyunsaturated fatty acids (PUFAs), have beneficial effects on CVD [541]. Hu and Willett [542] conclude that three dietary strategies are effective for preventing CHD: substitute nonhydrogenated unsaturated fats for saturated and trans fats; consume n-3 polyunsaturated fatty acids (PUFAs); and consume a diet high in fruit, vegetables, nuts, and whole grains.

In people with low risk of CHD, intake of fruit, vegetables, cereals, pasta/rice, fish, vegetable protein, DF, magnesium, nonheme iron, and potassium was found to be higher [543]. In contrast, in people with low risk of CHD intake of calorie, meats, processed meats, high-fat dairy products, sugar-sweetened beverages, cholesterol, saturated fatty acids, and animal protein was found to be lower [543]. He *et al*. [531] have recommended the consumption of more than 5 servings/day of fruit and vegetables. The American Heart Association Nutrition Committee [544] has come up with the following positive dietary recommendations: “consume a diet rich in vegetables and fruits; choose whole grain, high-fiber foods; consume fish, especially oily fish, at least twice a week”.

12.7.3. Myocardial infarction

Increased myocardial infarction risk was associated with increased intake of red meat and processed meat [527]. In the Health Professionals Follow-up Study with 734 cases of myocardial infarction among 43,757 men followed for six years, a 19% reduction in myocardial infarction risk associated with a 10 g increase in dietary fiber (DF) intake was observed [538].

Compared with the unhealthy dietary pattern (white bread, processed meat, fries, and full-cream milk), the healthy dietary pattern (fruit, vegetables, whole-meal bread, low-fat dairy, and little alcohol) reduced the risk of nonfatal myocardial infarction [545]. Adherence to the 2013 Danish food-based dietary guidelines was inversely associated with the risk of myocardial

infarction [546]. Adherence to the Southern European Atlantic Diet was inversely associated with nonfatal myocardial infarction [547].

12.7.4. Heart failure

Greater whole-grain intake was associated with lower heart failure risk, whereas greater intake of eggs and high-fat dairy was associated with greater heart failure risk [548].

12.7.5. Stroke

A meta-analysis showed that hyperuricemia was associated with stroke risk [549]. However, Sattui *et al*. [366] have expressed the view that epidemiological data causality is still not clear.

Decreased stroke risk was associated with increased intake of white meat [550], fish [551-553], legumes [554], fruit and vegetables [555-557], low-fat dairy products [558], fermented dairy [442, 558], olive oil [559], dietary fiber (DF) [95], and calcium [560]. Consumption of red meat and processed meat [442], and dairy products [561] was not associated with stroke risk. Whereas, red meat and processed meat [562], and alcohol [563] was associated with stroke risk. Higher adherence to the DASH diet was associated with lower risk of stroke [564]. A recent meta-analysis of 12 studies found that better adherence to the Mediterranean diet was associated with reduced risk for stroke (Risk Ratio: 0.71, 95% CI: 0.57, 0.89) [307], which was confirmed in a second systematic re-meta-analysis in 2014 that added an additional three studies (Risk Ratio: 0.68, 95% CI: 0.58, 0.79), which included the PREDIMED trial [308]. Higher adherence to the Mediterranean-style diet was associated with reduced blood pressure variability, which is a novel risk factor for cardiovascular disease (CVD), and subsequent stroke risk in patients with CAD [565]. Results from a systematic review and re-meta-analysis conducted by Kontogianni and Panagiotakos [308] demonstrated that higher adherence to healthy dietary patterns [i.e., Mediterranean or DASH or plant based “prudent (higher intake of fruit, vegetables, legumes, fish, poultry, and whole grains)”] was associated with reduced risk for stroke.

13. Conclusion

It is essential to understand the association between dietary habits and SUA concentrations or hyperuricemia risk and practice dietary habits that do not cause hyperuricemia, gout, and comorbidities of hyperuricemia. This review proposes dietary habits for the prevention and suppression of hyperuricemia and the prevention of gout and some comorbidities of hyperuricemia based on the results obtained from clinical research (clinical trials and epidemiological studies).

Recent large-scale epidemiological studies have shown that dietary factors affect SUA levels parallel to the direction of risk of hyperuricemia [23]. Dietary habits for the prevention and suppression of hyperuricemia are speculated as follows: higher adherence to the Mediterranean diet (The traditional Mediterranean diet); higher adherence to the DASH diet; encouraged intake of legumes, nuts, fruit, vegetables, fiber-rich foods (e.g., cereals, whole grains, high-fiber bread), dairy products (especially, low-fat or nonfat dairy products), and coffee; limiting the intake of meat, seafood, organ meats high in purine content (e.g., liver, kidney), sugar-sweetened beverages, sugary foods including desserts and sweets, and salt; limiting alcohol consumption; maintenance of good hydration; and weight management including proper calorie intake and adequate exercise.

The above dietary habits for the prevention and suppression of hyperuricemia are presumed to contribute to the prevention of some of the comorbidities. For example, in the case of coronary artery disease (CAD) and coronary heart disease (CHD), greater adherence to the Mediterranean diet (The traditional Mediterranean diet) [426], higher intake of poultry [522], fish [522], legumes [209, 283, 523], nuts [522, 524-527], fruit and vegetables [528-531], low-fat dairy products [532], vitamin C [533], and dietary fiber (DF) [95, 534-538] and moderate alcohol consumption [178, 179] have been associated with lower risk of CAD or CHD. Considering both the prevention of CAD-CHD and hyperuricemia, it is necessary to decide on appropriate alcohol consumption. Therefore, taking into consideration the choices and intake of proper foods for the prevention of each comorbidity of hyperuricemia is essential. A large body of evidence supports the utility of

health dietary patterns that encourage whole-grain foods, legumes, vegetables, and fruit, and that limit refined starches, red meat, full-fat dairy products, and foods and beverages high in added sugars [297]. The dietary patterns mentioned above, which have been associated with decreased risk of a variety of chronic disease [566], seem to be common with those for the prevention of hyperuricemia and some of its comorbidities. The dietary habits for the prevention and suppression of hyperuricemia with proper choices of foods may also play a helpful role in the prevention of gout and some of comorbidities of hyperuricemia.

The author wishes to emphasize the importance of recognizing the validity of dietary habits (especially, dietary patterns) as a potential method to prevent hyperuricemia, gout, and comorbidities of hyperuricemia in the general population. The author hopes that the association between dietary factors and SUA levels in hyperuricemia patients with or without comorbidities will be further elucidated in many large-scale prospective cohort studies and randomized controlled trials in the future.

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CONFLICT OF INTEREST STATEMENT

The author declares that there are no conflicts of interest.

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