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Modification of Dietary Habits for Prevention of Gout in Japanese People: Gout and the Japanese Diet

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Abstract: Gout is the most common form of inflammatory arthritis, and it is characterized by the deposition of monosodium urate crystals that form in the presence of increased uric acid concentrations. A high serum uric acid concentration (hyperuricemia) is frequently associated with gout. The burden of gout has increased between 1990 and 2017 globally. In Japan, most of gout patients are adults, and the number of gout patients are higher in men than in women. The prevalence of gout has increased markedly since the 1960s. The Japanese Society of Gout and Uric & Nucleic Acids has stated that an increase in hyperuricemia and gout patients is attributed to changes in environmental factors (e.g., purine intake, fructose intake, meat and visceral intake, alcohol consumption, strenuous muscle exercise, stress, obesity) rather than genetic factors. The Japanese economy revived to pre-World War II levels around 1955 and the eating habits in 1960s became stable. The menu of Japanese food has been rapidly expanded with a variety of dishes due to the westernization of meals from 1955 to 1965. Compared to the Japanese diet in 1950, in the Japanese diet in 2016, consumption of rice and potatoes decreased, whereas intake of wheat, legumes, seeds and nuts, seaweed, vegetables, fruit, meat, seafood, eggs, milk and dairy products, oils and fats, seasoning and spices increased. This phenomenon is thought to be attributed to the westernization of the Japanese diet since 1955. Recognizing changes in the Japanese diet are important for dietary habits modification to prevent gout in Japanese people. The objective of this article is to propose a preventive method for gout through the evaluation of recent dietary habits in Japanese people. This article suggests that changes in the Japanese diet are possible to be one of the factors contributing to the increase in the number of gout patients in Japan.

Keywords: Comorbidities of Gout, Dietary Habits, Food, Gout, Hyperuricemia, The Japanese Diet, Uric Acid

1. Introduction

Uric acid (UA) is a weak acid with a pKa of 5.75 and, at the physiological pH of 7.40 it exists mainly in the ionized form as urate [1]. Uric acid (UA) can exert, along with its extracellular antioxidant activity, an intracellular prooxidant effect [2]. UA is the end product of purine metabolism, largely derived from endogenous synthesis, but a minor part also arises from exogenous sources such as foods with purine content, alcohol, and fructose drinks [3]. UA is synthesized mainly in the liver and intestines, but it is also synthesized in other tissues, such as muscles, kidneys, and the vascular endothelium [4-6]. The serum uric acid (SUA) concentration is determined by the amount of production of UA and the efficiency of urinary UA excretion [7, 8]. UA is the primary antioxidant in human plasma and accounts for more than 60% of the capacity to scavenge free oxidative radicals in the serum [9]. The antioxidant properties of UA can also protect against free radical damage to vessels, the heart, and neurons [10-12] and prevent bone loss and osteoporosis [2]. However, the association of UA with health risks is biphasic, since low levels of UA are detrimental to neurons, due to impaired antioxidant capacity in the cell [13]. For example, in older individuals, UA may exert neuroprotective actions in Alzheimer's disease and Parkinson's dementia, with hypouricemia representing a risk factor for quicker disease progression and a possible marker of malnutrition; conversely, a high SUA concentrations may negatively affect the disease course in vascular dementia [14]. It is important to maintain SUA concentrations within the normal physiological range in order to exert the beneficial effects of the antioxidant properties of UA. On the other hand, the antioxidant activity

of UA is overcome by the pro-oxidant and proinflammatory effects of reactive oxygen species accumulation under ischemic conditions [15]. 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 [16]. UA can oxidize low-density lipoprotein (LDL) in the presence of copper ions and lipid hydroperoxides, increasing the inflammatory status [17]. The SUA concentrations have been associated with several inflammatory markers [neutrophil count, C-reactive protein, interleukin-1 receptor antagonist (IL-1ra), interleukin-6 (IL-6), interleukin-18 (IL-18), tumor necrosis factor-alpha (TNF-α)] in individuals with or without hyperuricemia [SUA concentration > 7.5 mg/ dL (450 μmol/L) in men and > 6.2 mg/dL (372 μmol/L) in women] [18].

Gout is the most common form of inflammatory arthritis, and it is characterized by the deposition of monosodium urate (MSU) crystals that form in the presence of increased UA concentrations [19, 20]. The global burden of gout is substantial and seems to have been increasing in many parts of the world including Japan over the past 50 years [21-23]. A remarkable increase in gout patients in Japan has been observed since the 1960s [22, 23]. In particular, the increase in gout patients was remarkable after 1965 [23]. In Japan, the 1960s was a time when the post-war chaos calmed down, and eating habits became stable [24, 25]. The menu of Japanese food has shown a rapid increase in the variety of dishes due to the westernization of meals from 1955 to 1965 [24-26]. In the last five or six decades, it is thought that the Japanese diet has become more westernized and dietary habits have changed. Therefore, hypertension, diabetes mellitus, dyslipidemia, and chronic kidney disease (CKD) are major health issues in Japan today. Asymptomatic hyperuricemia is a biomarker of both increased risk for and presence of vascular disease (e.g., hypertension, coronary artery disease, kidney disease), and it may also have certain causal effects on vascular disease, hypertension, and progression of CKD [27]. In the US National Health and Nutrition Examination Survey (NHANES) 2007-2008, the comorbidities of individuals with hyperuricemia, gout, or both hyperuricemia and gout were hypertension, CKD, obesity (body mass index: BMI ≥ 30 kg/m^2), diabetes mellitus, nephrolithiasis, and cardiovascular disease (CVD)(myocardial infarction, heart failure, stroke), though the prevalence of the comorbidities of gout are different from those of hyperuricemia or both hyperuricemia and gout [28]. Prevention of hyperuricemia and/or gout should consider the effects of CKD, urolithiasis, obesity, diabetes mellitus, hypertension, and CVD, which are comorbidities of hyperuricemia and/or gout.

A high SUA concentration (hyperuricemia) is frequently associated with gout [29]. Epidemiological studies have shown that dietary factors affect SUA levels parallel to the direction of the risk of hyperuricemia [30, 31]. A decrease in high SUA concentrations leads to the prevention of hyperuricemia. Therefore, management of SUA concentrations is important for the prevention and suppression of hyperuricemia. The introduction of the Western lifestyle to Japanese people, such as a diet containing greater amounts of meat and saturated fatty acids, has been associated with the increases in SUA levels and the incidence of hyperuricemia [32]. From the results of epidemiological studies and clinical trials, dietary habits and behavior for the prevention and suppression of hyperuricemia have been suggested by Koguchi [31] as follows: higher adherence to the Mediterranean diet (the traditional Mediterranean diet); higher adherence to the dietary approaches to Stop Hypertension (DASH) diet; encourage 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. Since the Japanese Society of Gout and Uric & Nucleic Acids [33] has stated that hyperuricemia is a risk factor for gout (as uratosis), the above dietary habits for the prevention of hyperuricemia seem to lead to the prevention of gout. It is also essential for Japanese people to select and consume foods properly that contain nutrients associated with the prevention of hyperuricemia and/or gout.

From the results of the Comprehensive Survey of Living Conditions in Japan (1986-2016) [34] and the National Health and Nutrition Survey in Japan (1946-2017) [35] conducted by the Ministry of Health, Labour and Welfare in Japan, this article presents the current evidence about the relationship between the number of gout patients and intake of nutrient or food. Furthermore, this article proposes a common preventive method for gout and some of its comorbidities, such as CVD, obesity, and hypertension, that explains the possible role of dietary habits through improvement of Japanese people's nutrient intake. In this article, the author describes the trends in the number of gout patients with changes in the Japanese diet.

2. Gout

2.1. Pathogenesis of Gout

The Japanese Society of Gout and Uric & Nucleic Acids [33] has stated that an increase in hyperuricemia and gout patients is attributed to changes in environmental factors (e.g., purine intake, fructose intake, meat and visceral intake, alcohol consumption, strenuous muscle exercise, stress, obesity) rather than genetic factors.

Pathogenesis of gout is closely related to the increased accumulation and the reduced excretion of uric acid (UA) (the end product of purine metabolism) [36] and begins with excess serum uric acid (SUA) that forms monosodium urate (MSU) crystals in the joints, triggering gouty inflammation via the activation of nucleotide-binding and oligomerization domain-like receptor, leucine-rich repeat and pyrin

domain-containing 3 (NLRP3) inflammasome-mediated IL-1βproduction [37, 38].

Monosodium urate (MSU) has limited solubility under physiological conditions and the saturation level in plasma at a pH of 7.40 is 6.8 mg/dL (408 μmol/L); when the plasma concentration exceeds this, crystals may form in the joints and tissues [39, 40]. The imbalance between UA production and excretion is the hallmark of hyperuricemia and progenitor for MSU crystal formation [41]. It is the consequence of deposition of MSU crystals in joints and other tissues, as a result of persistent hyperuricemia.

Guo et al. [36] reported that the intestinal microbiota distinguishes gout patients from healthy humans in a cross-sectional study in Chinese adults; that is to say, in gout patients, *Bacteroides caccae* and *Bacteroides xylanisolvents* are enriched yet *Faecalibacterium prausnitzii* and *Bifidobacterium pseudocatenulatum* depleted. On the other hand, *Faecalibacterium prausnitzii*, *Clostridium* butyrate-producing bacterium and *Bifidobacterium pseudocatenulatum* were enriched in healthy individuals [36]. Since *Faecalibacterium prausnitzii* has anti-inflammatory properties and contribute to gut health through butyrate production [42], significant depletion of *Faecalibacterium prausnitzii* observed in gout patients explains the decline in butyric acid biosynthesis. A possible link between activity of intestinal microbiota and gout pathogenesis might be that the overly abundant xanthine dehydrogenase and the relative deficiency of allantoinase in the intestinal microbiota have accumulated more UA and consequently aggravated the gout symptoms [36]. Since *Bacteroides caccae* was recognized one biomarker of inflammatory bowel disease (IBD), and the *Omp* W protein produced by *Bacteroides caccae* was a target of the IBD-associated immune response [43], Guo et al. [36] have stated that the enriched intestinal *Bacteroides caccae* in gout patients could potentially induce serious inflammatory response. This result indicates that the reference microbial gene catalogue for gout causes revealed disorders associated with purine metabolism and butyric acid biosynthesis, both of which to be the basis for developing gout.

2.2. Relationship Between Gout and SUA Concentration or Hyperuricemia

Subjects with hyperuricemia have a more than 30 times higher risk of developing gout than persons with normal serum uric acid (SUA) levels [44]. A recent study found that only half of patients with SUA levels above 10 mg/dL will develop gout over 15 years [45]. Hyperuricemia is a strong predictor of incident gout but not all patients with asymptomatic hyperuricemia will develop gout [46]. In a cohort of more than 200 asymptomatic men, the annual incidence rate of gouty arthritis was 4.9% in participants with baseline SUA ≥ 9 mg/dL and the cumulative incidence rate of gouty arthritis was 22% after 5 years, in comparison, the annual incidence rate of gouty arthritis was 0.5% in participants with initial SUA 7-8.9 mg/dL and 0.1% in participants with SUA < 7 mg/dL [47]. A 76.9% of Japanese gout patients were hyperuricemia with SUA levels above 10 mg/dL [48].

There is a strong association between SUA concentration and the risk of developing gout [44, 49]. A population-based study with a 5-year follow-up of 429 patients with incident gout (158 patients in 1989-1992 and 271 patients in 2009-2010) found that the risk of subsequent flares increased by 13% for every 1 mg/dL increase in SUA level, 59% for hyperuricemia [SUA concentration ≥ 7.0 mg/ dL (416.4 μmol/L) among men and ≥ 6.0 mg/dL (356.9 μmol/L) among women], and 34% for kidney disease in 2009-2010 compared to 1989-1992 [50]. Elfishawi et al. [50] stated that hyperuricemia [SUA concentration ≥ 7.0 mg/ dL (416.4 μmol/L) among men and ≥ 6.0 mg/dL (356.9 μmol/L) among women] and kidney disease were predictors of future flares in patients with gout.

2.3. Inflammatory Response in Gout

The serum uric acid (SUA) level is positively associated with several inflammatory markers (e.g., white blood cell count, C-reactive protein, interleukin-6) [18]. Lin et al. [2] reviewed the intracellular pro-oxidant effect of uric acid (UA); that is to say, uric acid (UA) enters the cell via UA transporter 1 (URAT1) on the cell membrane. UA is produced from xanthine via xanthine oxidase (XO) in the cell and also generates superoxide ions (O_2^-), which also promote oxidative stress by superoxide free radicals produced via NADPH oxidase (NOX4). UA intracellularly induces endothelial nitric oxide synthase (eNOs) with a decrease in nitric oxide (NO) generation. It also directly increases inflammation, which leads to cell injury. 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 [51-53]. UA stimulates proliferation of the smooth muscle cells of the vascular system through activating the renin-angiotensin system and inhibiting the synthesis of NO, and finally can impair arterial function and cause arterial stiffening, a risk factor for hypertension and cardiovascular and cerebrovascular events [51]. The SUA concentration has been found to be a risk marker for cardiovascular disease (CVD) and renal disease (especially in patients with hypertension, diabetes mellitus, and heart failure) [54]. Yahfoufi et al. [55] stated that continuous inflammation is known to be a major cause linked to different human disorders involving cancer, diabetes, obesity, arthritis, neurodegenerative diseases, and CVD. Maintaining SUA concentrations within the normal physiological range may prevent gout and its comorbidities caused by inflammation from elevated SUA concentrations.

2.4. Prevalence of Gout in the World

The burden of gout has increased between 1990 and 2017 globally, especially in high sociodemographic index countries [56]. The highest increase in the annual percent change in age-standardized prevalence rate of gout was observed in Canada (1.05%), the USA (0.98%) and Greenland (0.97%) for males and UK (1.01%), Guatemala (0.93%) and the USA (0.91%) for

females between 1990 and 2017 [56]. Whereas the highest decrease in the annual percent change in age-standardized prevalence rate of gout was observed in Northern Mariana Island (-0.11%), Democratic Republic of the Congo (-0.09%) and Qatar (-0.09%) for males and Sweden (-0.93%), Democratic Republic of the Congo (-0.24%) and New Zealand (-0.17%) for females between 1990 and 2017 [56].

The prevalence of gout is < 1% in developing countries in 2010 [57]. The prevalence of gout has increased in the US from 1988 to 2016 [20, 58, 59], the United Kingdom from 1997 to 2012 [60], British Columbia from 2000 to 2012 [61], western Sweden from 2002 to 2012 [62]. Although the prevalence rate of gout among adults in the US has remained substantial from 2007 to 2016 (2.9% in 1988-1994, 3.9% in 2007-08, 3.8% in 2009-10, 3.6% in 2011-12, 4.0% in 2013-14, 3.9% in 2015-16) [20, 58, 59], the estimated total number of persons with self-reported gout in the US was 8.3 million in 2007-2008 and 9.2 million in 2015-2016, respectively [58]. Singh et al. [58] have stated that these results reflect the growth and increased aging of the US population. Castro et al. [63] found that a 30% relative increase in the percentage of patients who had a visit with a diagnosis of gout in the years 2009-2011 compared to 2007-2008 in the US (1.3% vs 1.0%, respectively). They [63] have hypothesized that gout visits are on the rise due to increases in obesity, hypertension, and purine-rich diets. According to the Global Burden of Disease 2017 Study [64], high sociodemographic index regions and countries had a higher intake of red meat, processed meat, seafood omega-3 fatty acids and sugar-sweetened beverages than low-sociodemographic index regions and countries.

In a 5-year follow-up cohort, cumulative incidence of first gout flare in 1989-1992 and 2009-2010 cohorts was similar (62% vs 60% by 5 years in 1989-1992 and 2009-2010, respectively), but overall gout flare rate in 2009-2010 cohort increased by 24% compared to 1989-1992 cohort [50].

2.5. Prevalence of Gout in Japan

There were few gout patients in Japan in the early Meiji era (1868-1889) [33, 65]. In Japan, the first example of gouty arthritis was reported in an academic paper in 1931, and the number of gouty cases in the questionnaire survey and self-study cases was 83 by 1959 [33], 510 in 1963 [22], and 1840 in 1965 [66]. From these reports, the number of gout patients has been increasing each year.

An assessment of residents in particular areas in Japan showed that the prevalence of gout was less than 0.4% between the 1960s and 1980s [23, 48, 67-70] and 0.51% in 2003 [65]. Compared to 2010, the prevalence of gout in 2014 was significantly higher [71].

The number of gout patients going to hospitals estimated based on the Comprehensive Survey of Living Conditions conducted by the Ministry of Health, Labour and Welfare in Japan was 0.255 million in 1986, 0.283 million in 1989, 0.338 million in 1992, 0.423 million in 1995, 0.590 million in 1998, 0.696 million in 2001, 0.874 million in 2004, 0.854 million in 2007, 0.957 million in 2010, 1.063 million in 2013, and 1.105 million in 2016 [34] (Table 1). These values clearly indicate a steady increase in the number of patients with gout in Japan.

Hakoda and Kasagi [72] anticipate that the number of gout patients will peak in 2042. The prevalence of gout in Japanese men in 2013 and 2016 reported by the Comprehensive Survey of Living Conditions was 1.64% and 1.77%, respectively [34], and in 2013 and 2016, it was 1.63% and 1.66%, respectively, as reported by the database of health insurance claims with gout diagnosed by physicians [73].

Table 1. *Trends in estimated number of patients by gout and its comorbidities in Japan in 1998-2016.*

Disease/Year	1998	2001	2004	2007	2010	2013	2016
				million			
Gout	0.59	0.70	0.87	0.85	0.96	1.06	1.11
Kidney disease	0.74	0.80	0.76	0.90	0.97	1.10	1.13
Obesity	0.47	0.44	0.55	0.62	0.67	0.65	0.57
Hypertension	8.03	9.02	10.22	11.11	12.94	14.37	14.55
Diabetes mellitus	2.69	3.10	3.76	4.17	4.86	5.45	5.74
Dyslipidemia	2.72	3.38	3.47	4.20	6.25	5.56	5.80
Stroke	1.13	1.33	1.29	1.37	1.41	1.46	1.31
Myocardial infarction	1.70	1.83	2.00	1.95	2.10	2.24	2.18

Adapted from the Ministry of Health, Labour and Welfare in Japan [34].

2.6. Prevalence of Gout in Men and Women in Japan

The prevalence of gout in Japanese adult males (aged > 30 years) is estimated to be about 1-1.5% [33, 65]. Compared to 2010, the prevalence of gout in males increased significantly in 2014 (2010: 1.54%; 2014: 1.66%) [71]. The annual percent change in age-standardized prevalence rate (males, 0.2-0.4%; females, 0.4-0.6%) and disability-adjusted life-years (males, 0.2-0.4%; females, 0.4-0.6%) of gout increased between 1990 and 2017 in Japan [56].

The number of gout patients was higher in men than in women [23, 33, 34, 48, 57, 63, 65, 67, 71]. For, example, in 2004-2016, the number of male gout patients was 9.5-18.4 times higher than the number of female gout patients [34]. Gout is well known to be more prevalent in males than females [57, 63]. Estrogen is protective in premenopausal women due to its uricosuric effect [74]. However, a higher percent change and annual percent change in gout was observed in females than in males [56]. Since menopause is highly associated with the risk of gout [75], Xia et al. [56] have stated that gout burden in females is likely to increase over the next decades.

2.7. Relationship Between Prevalence of Gout and Age in Japan

In Japan, most gout patients were adults in 1986-2016 [34]. The prevalence of gout in males tended to increase with age [71]. The number of gout patients in the younger generations in 2001 (aged < 35 years) increased more than 6 times in 2016, approximately 20 years later [34].

Hakoda and Kasagi [72] found that the prevalence of gout patients in Japan in 2013 and 2016 were peaking in the 60s and 70s in both the Comprehensive Survey of Living Conditions and the database of health insurance claims with gout diagnosed by physicians. Therefore, they [72] have stated that the increase in the number of gout patients may be due to the increase in the aged population in Japan because the prevalence of gout increased with age.

During the 20 years from 1965 to 1984, the number of gout patients tended to increase and the onset age of gout became younger [33, 65, 76] and the trend has been kept until 2017 [77]. The age of onset of gout was highest in the 40s in the 2020 report [77] and in the 50s in the 1965 [66] and 1974 reports [23]. The number of gout patients from 2004 to 2016 as highest in the 60s [34]. The report by Yamanaka et al. [76] in 1992 showed that the age of onset of gout was highest in the 30s. Compared to the 1965 report [66], the proportion of gout patients who develop at a young age (aged 20-39 years) has increased [10]. As the number of gout patients has been increased, the incidence of gout in the 20s and 30s has been increasing [33, 65]. With respect to the increasing proportion of patients with gout that develops at a young age, some juvenile gout may have congenital factors such as partial deficiency of hypoxanthine guanine phosphoribosyltransferase (HGPRT) and familial renal gout. However, it is unlikely that the proportion of patients with a genetic background will increase above a certain percentage. Yamanaka et al. [76] have speculated that the increase in the number of young gout patients is due to the environmental factors, such as the increase in purine intake and alcohol consumption, and the increase in BMI in young people rather than due to the genetic background.

2.8. Relationship Between Prevalence of Gout and Environmental or Genetic Factors

Gout was highly heritable with estimates of up to 65% [78]. Smoking has been found to be negatively associated with gout [79, 80]. Gout was associated with decreased physical function [81], lower health-related quality of life [82], higher gout-related healthcare costs [83], and increased risk of comorbidities and mortality [84]. A systematic review conducted by Chandratre et al. [82] demonstrated that gout was associated with poorer physical health-related quality of life and poor health-related quality of life in gout was associated with both disease-specific characteristics (attack frequency and intensity, intercritical pain and number of joints involved) and comorbidity (renal and cardiovascular disease, metabolic syndrome).

2.9. Relationship Between Prevalence of Gout and Race

The prevalence of gout varies with race and ethnicity [85]. A higher prevalence of gout is well known in Asians and Pacific Islanders, as well as Africans Americans with genetics playing a role due to hyperuricemia-associated DNA sequence variations [86]. African-Americans and Hmong tend to have a higher prevalence of gout compared to Caucasians and Europeans [85]. This difference in racial prevalence parallels the prevalence of genetic variants, primarily the single nucleotide polymorphisms consistent with those identified by genome-wide association studies (GWAS) [87].

Hispanic/Latino individuals were found to be less likely to have a visit with gout than Non- Hispanic/Latinos [88]. One possible explanation is related to diet. Given that Hispanic/Latino diets are typically more heavily based on grains and beans along with fresh fruit and vegetables, Hispanic/Latinos may produce less UA resulting in a lower incidence of gout [63].

2.10. Subtype of Gout

Defective renal elimination of uric acid (UA), known as UA underexcretion, accounts for 80%-90% of gout cases [41]. Inherited genetic disorders such as Lysch Nyhan Syndrome, Tumor Lysis Syndrome, or high intake of purine sources can result in UA overproduction, which accounts for 10% of gout subtypes [39, 41, 88].

In Japan, Ooyama et al. [77] found that male patients with both hyperuricemia and gout, who first visited their clinic between June 2016 and May 2017, result from UA underexcretion type (70.8%), overproduction type (7.3%) (renal overload type: extra-renal urate underexcretion and genuine urate overproduction), and combination of the two (15.9%).

3. Comorbidities of Gout

In the US National Health and Nutrition Examination Survey (NHANES) 2007-2008, the overall prevalence of gout among US adults, by which reported a physician or health professional diagnosis of gout, is 3.9% (8.3 million total; men, 6.1 million; women, 2.2 million) [20]. The prevalence in the US of comorbidities among individuals with gout are as follows: hypertension, 73.9%, 6.1 million; chronic kidney disease (CKD), stage ≥ 2 (glomerular filtration rate: GFR < 60), 71.1%, 5.5 million and stage ≥ 3 (glomerular filtration rate: GFR < 30), 19.9%, 1.5 million; obesity (body mass index: BMI ≥ 30 kg/m^2), 53.3%, 4.3 million; diabetes mellitus, 25.7%, 2.1 million; nephrolithiasis, 23.8%, 2.0 million; myocardial infarction, 14.4%, 1.2 million; heart failure, 11.2%, 0.9 million; stroke, 10.4%, 0.9 million [28]. These prevalences were 2-3 times higher than among those without gout [28]. The frequencies of CKD, obesity, hypertension, type 2 diabetes mellitus, dyslipidemia, cardiac diseases (including coronary heart disease, heart failure and atrial fibrillation), stroke and peripheral arterial disease have been repeatedly shown to be increased in gout [89]. CKD, obesity,

cardiovascular disease (CVD) and components of the metabolic syndrome, which frequently coexist in patients with gout, but for which causality remains controversial [90]. Overarching principles in the updated the 2016 European League Against Rheumatism (EULAR) recommendations for the management of gout reported by Richette et al. [91] have stated that every person with gout should be systematically screened for associated comorbidities and cardiovascular risk factors, including renal impairment, coronary heart disease, heart failure, stroke, peripheral arterial disease, obesity, hyperlipidemia, hypertension, diabetes mellitus and smoking, which should be addressed as an integral part of the management of gout.

In Japan, Nishioka and Mikanagi [48] reported that body weight, height, age, blood urea nitrogen and serum creatinine concentrations, blood pressure, and alcohol intake were associated with serum uric acid (SUA) concentration, respectively. In Japan, the number of patients with gout, hypertension, diabetes mellitus, dyslipidemia, and kidney disease increased between 1998 and 2016, respectively and the number of patients with myocardial infarction tended to increase between 1998 and 2016 [34] (Table 1). Japanese Society of Gout and Uric & Nucleic Acids Guidelines for Management of Hyperuricemia and Gout established by Hisatome et al. [33] has stated that hyperuricemia and/or gout is associated with CKD, urolithiasis, hypertension, and CVD.

4. Association Between Gout and Mortality

The Ministry of Health, Labour and Welfare in Japan [92] has reported the trends in death rates for heart diseases (excluding hypertensive ones), cerebrovascular diseases, renal failure or pneumonia (per 100,000 population). The trends in death rates for heart diseases (excluding hypertensive ones) of Japanese people have increased over the last six decades (1950: 64.2; 1960: 73.2; 1970: 86.7; 1980: 106.2; 1985: 117.3; 1986: 117.9; 1989: 128.1; 1992: 142.2; 1995: 112.0; 1998: 114.3; 2001: 117.8; 2004: 126.5; 2007: 139.2; 2010: 149.8; 2013: 156.5; 2016: 158.4). The trends in death rates for cerebrovascular diseases of Japanese people have decreased over the last six decades (1950: 127.1; 1960: 160.7; 1970: 175.8; 1980: 139.5; 1985: 112.2; 1986: 106.9; 1989: 98.5; 1992: 95.6; 1995: 117.9; 1998: 110.0; 2001: 104.7; 2004: 102.3; 2007: 100.8; 2010: 97.7; 2013: 94.1; 2016: 87.4). The trends in death rates for renal failure of Japanese people have increased over the last three decades except for the rate in 2013 (1980: 6.1; 1985: 9.6; 1986: 10.0; 1989: 12.1; 1992: 13.7; 1995: 13.0; 1998: 13.3; 2001: 14.0; 2004: 15.2; 2007: 17.2; 2010: 18.8; 2013: 20.7; 2016: 19.7). The trends in death rates for pneumonia of Japanese people have increased over the last six decades except for the rate in 2013 (1950: 65.1; 1960: 40.2; 1970: 27.1; 1980: 28.4; 1985: 37.5; 1986: 39.1; 1989: 48.1; 1992: 60.2; 1995: 64.1; 1998: 63.8; 2001: 67.8; 2004: 75.7; 2007: 87.4; 2010: 94.1; 2013: 97.8; 2016: 95.6).

A large cohort study found a U-shaped association between serum uric acid (SUA) levels and all-cause mortality; SUA levels between 300 and 410 μmol/L were associated with the lowest mortality [13]. The Japanese Society of Gout and Uric & Nucleic Acids Guidelines for Management of Hyperuricemia and Gout established by Hisatome et al. [33] concluded that there is an association between SUA levels and all-cause mortality risk.

In a systematic review of the literature by van Durme et al. [93], compared with the healthy population without gout, the risks of mortality due to stroke and coronary heart disease (CHD) in patients with gout were slightly increased and the risk of mortality due to chronic kidney disease (CKD) in patients with gout was significantly increased.

Gout is an independent risk factor for cardiovascular morbidity and mortality independent of other measured risk factors, with hazard ratios for mortality due to CHD and cardiovascular disease (CVD) of 1.4 (95% CI 1.2-1.6) and 1.3 (95% CI 1.2-1.4), respectively, after adjusting for traditional cardiovascular risk factors [94]. In a large cohort of gout patients, CVD accounted for more than half of the deaths, and increased with gout severity [95]. Clarson, et al. [94, 96] found that peripheral vascular disease and CHD were independently associated with gout and associated with an increased frequency of cardiovascular death. Large epidemiological studies have demonstrated that hyperuricemia and/or gout is an independent risk factor for death due to cardiovascular causes [95, 97].

5. The Japanese Diet

The basic form of Japanese food is a menu consisting of “one soup and three dishes”, that is, rice, soup stock, and three side dishes (one main dish and two side dishes). The form of this menu is changing with the times [25]. There are various cooking methods for side dishes for Japanese-style diet such as stewing, grilling, steaming, boiling, dressing, and deep-frying [25]. By combining these methods with seasonal foods such as vegetables, edible wild plants, seafood, and seaweed, a wide variety of side dishes can be prepared [25]. Foods used in the Japanese-style diet include grains (mainly rice), vegetables, mushrooms, fish, shellfish, seaweed, and wagyu beef [25]. The dishes were prepared mainly using vegetables and seafood [25].

The Japanese economy revived to pre-World War II levels around 1955 [25]. In Japan, the 1960s was a time when the post-war chaos calmed down, and the eating habits became stable [25]. Therefore, it is thought that the menu of Japanese food has been rapidly expanded with a variety of dishes due to the westernization of meals from 1955 to 1965 [25]. For example, as potato dishes, Japanese people ate mainly miso soup and floured potatoes in 1960. The GNP of Japan grew to the second-largest capitalist country in the world in 1968. Along with this economic growth, Japanese people’s dietary habits started to change rapidly, and the protein intake of Japanese people, namely meat, eggs, milk and dairy products, and seafood, increased rapidly, whereas consumption of rice and potatoes has

fallen to less than half of what it was in the 1910s [24]. During the period of high economic growth in Japan from 1955 to 1973, the storage period of foods became longer due to the spread of refrigerators, and it became possible to cook fried foods, stir-fried foods, Chinese dishes, and Western dishes at home with the spread of city gas. The Ministry of Health, Labour and Welfare and Ministry of Agriculture, Forestry and Fisheries in Japan [98] regard eating habits around 1970-1980 as "Japanese eating habits". The Japanese-style diet is a balanced diet that consists of the staple food (e.g., rice), main dish, side dishes, fruit, and a moderate amount of milk and dairy products. Compared to the Japanese diet in 1965, in the Japanese diet in 1980, consumption of rice decreased 20%, intakes of meat, milk, vegetable oils, fruit, and seafood increased 2-fold, 1.5-fold, 2.33-fold, 1.38-fold, and 1.25-fold, respectively, and intake of vegetables was about the same amount [35]. This phenomenon indicates that the Westernization of eating habits has progressed. The basic style of the Japanese-style diet was preserved in each household until about the 1980s. Although the balance of a main dish and side dishes struck an ideal balance by around the 1980s, the consumption of meat, fat, milk and dairy products also increased, and the food self-sufficiency ratio declined [25]. Eating out with family became an everyday affair, and meals at home were also Westernized [25]. The amount of the main dish decreased slightly, and side dishes increased, particularly showing the growth of the ratio of milk and dairy foods and meat [25]. Since 1986, changes in eating habits due to diversified lifestyles have included changes in home cooking, decline in traditional food culture, loneliness of families, advances in food simplification by increased sales of retort pouch foods and increased penetration of microwave ovens (90%), and a decrease in the food self-sufficiency rate. After the 1980s, occasions for eating out with family increased and the Westernization of home cooking progressed [25]. Compared to the Japanese food in 1960, 1990, and 2005, the Japanese food in 1975 used more sugar and sweeteners, legumes, fruit, seaweed, seafood, eggs, seasonings and spices, and there were many kinds of ingredients, whereas consumption of preferred beverages (e.g., soft drinks, coffee, tea, and cocoa) was small [35, 99]. For example, Japanese people ate clam chowder, croquettes, and potato salad in addition to the above dishes in 2005. The Ministry of Agriculture, Forestry and Fisheries [25] has stated that the ideal balance of the caloric ratio of protein, fat and carbohydrate for healthy life is protein: 15%, fat: 25%, and carbohydrate: 60%, and the caloric ratio of the three macronutrients (protein, fat, and carbohydrate) in Japanese people was well balanced in 1980. However, the dietary life of Japanese people thereafter tended to have too much meat and fat, with a decreased amount of rice, and the balance of the caloric ratio of protein, fat, and carbohydrate in Japanese people in 2010 became closer to a Western type of diet (the caloric ratio of protein, fat and carbohydrate in the US and France from 2005 to 2007) [25]. Compared to the Japanese diet in 1980, in the Japanese diet in 2013, consumption of rice, vegetables, fruit, and seafood decreased 25%, 19.4%, 9.1%, and 25%, respectively, intake of meat and vegetable oils increased 1.5-fold and 1.29-fold, respectively, and intake of milk was the same amount [35]. Yamanaka et al. [76] stated that the nutritional intake of Japanese people has changed dramatically due to the westernization of life since around 1965, resulting in primary gout may have increased accordingly by the increase in the number of patients with diabetes mellitus and obesity.

The Dietary guidelines for Japanese (the Japanese food guide spinning top) proposed by the Ministry of Health, Labour and Welfare and Ministry of Agriculture, Forestry and Fisheries in Japan are as follows: (1) daily consumption of staple food must be 4-8 servings (1 serving: the amount of carbohydrates contained in the material is approximately 40 g), depending on an individual's caloric intake; (2) daily consumption of side dish (vegetables, mushrooms, potatoes and seaweed) must be 5-7 servings (approximately 350-490 g), depending on an individual's caloric intake; (3) daily consumption of main dish must be 3-6 servings (1 serving: the amount of proteins contained in the material is approximately 6 g), depending on an individual's caloric intake; (4) 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; (5) daily consumption of fruit must be 2-3 servings (approximately 200-300 g), depending on an individual's caloric intake; and (6) daily total consumption of confectionery (rice crackers: 3-4) and beverages (Japanese rice wine: 180 mL; beer: 500mL; wine: 260mL; distilled spirits: 100mL) must be at approximately 200 kcal [98].

Among Japanese adults, individuals with higher adherence to Japanese dietary guidelines (the Japanese food guide spinning top) was associated with a lower risk of total mortality (cancer, cardiovascular disease, heart disease, cerebrovascular disease) and mortality from cardiovascular disease, particularly from cerebrovascular disease, in Japanese adults [100].

6. Conclusion

In Japan, most of gout patients are adults [34], and the prevalence of gout has increased markedly since the 1960s [22, 34, 65, 66, 71]. The number of gout patients was higher in men than in women [23, 33, 34, 48, 57, 63, 65, 67, 71]. Compared to the Japanese diet in 1950, in the Japanese diet in 2016, consumption of rice and potatoes decreased, whereas intake of wheat, legumes, seeds and nuts, seaweed, vegetables, fruit, meat, seafood, eggs, milk and dairy products, oils and fats, seasoning and spices increased [35]. Since the Japanese economy revived to pre-World War II levels around 1955 and the eating habits in 1960s became stable and the menu of Japanese food has been rapidly expanded with a variety of dishes due to the westernization of meals from 1955 to 1965 [25], this phenomenon is thought to be attributed to the

westernization of the Japanese diet since 1955. In Japan, the number of patients with gout, hypertension, diabetes mellitus, dyslipidemia, and kidney disease increased between 1998 and 2016, respectively and the number of patients with myocardial infarction tended to increase between 1998 and 2016 [34] (Table 1). The Japanese Society of Gout and Uric & Nucleic Acids Guidelines for Management of Hyperuricemia and Gout [33] has stated that hyperuricemia and/or gout is associated with chronic kidney disease (CKD), urolithiasis, hypertension, and cardiovascular disease (CVD). Therefore, it is important to establish dietary habits that have beneficial effects in preventing not only gout but also some chronic diseases and/or comorbidities of gout (e.g., hypertension, diabetes mellitus, dyslipidemia, cardiovascular disease). As future work, the author examines the relationship between the number of gout patients and intake of nutrient or food in Japanese people using updated data and proposes modification of dietary habits for decreasing the number of gout patients.

Conflict of Interest Statement

The author declares that there are no conflicts of interest.

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