

# Modification of Dietary Habits for Prevention of Gout in Japanese People: Gout and Macronutrient Intake

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**Abstract:** In Japan, most of gout patients are adults, and the prevalence of gout has increased markedly since the 1960s. This phenomenon is thought to be attributed to the westernization of the Japanese diet since 1955. Monitoring the intake of nutrients and foods in Japanese people is essential in the prevention of gout. The objective of this article is to propose a preventive method for gout through the evaluation of recent dietary habits in Japanese people. In this article, the author suggests what macronutrient intake is important for the prevention of gout in Japanese people referencing the results of clinical research reported. The author used the data of the Comprehensive Survey of Living Conditions in Japan for the number of gout patients (1986-2016) and the data of the National Health and Nutrition Survey in Japan (1946-2017) for the intake of macronutrients. The relationship between the number of gout patients and macronutrient intake in Japanese people was examined. Modification of macronutrient intake for the prevention of gout in Japanese people (especially adults) is suggested as follows: energy-providing nutrient balance (percentages of proteins, fats, and carbohydrates in total energy intake) should be within the range of the tentative dietary goal for preventing lifestyle-related diseases (DG); reduce fat (especially animal fat) intake and maintain the mean ratio of energy intake from saturated fatty acids in total energy intake (Saturated fatty acids/Energy) within the range of the tentative dietary goal for preventing lifestyle-related diseases (DG); limiting or decreasing intake of fat (especially animal fat); replacement of saturated fatty acids (e.g., dairy fats, meat fat) with mono- and polyunsaturated fatty acids (especially n-3 polyunsaturated fatty acids) (e.g., macadamia nuts, almonds, peanuts and peanut butter, olive oil, canola oil, avocados); avoidance of excessive intake of saturated fatty acids and cholesterol; pay attention to sucrose and fructose intake; increase intake of dietary fiber; and maintenance of good hydration.

**Keywords:** Dietary Fiber, Dietary Habits, Food, Gout, Hyperuricemia, Macronutrient, Uric Acid

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## 1. Introduction

In Japan, most of gout patients are adults [1], and the prevalence of gout has increased markedly since the 1960s [1-5]. The number of gout patients was higher in men than in women [1, 3, 5-11]. 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 [12]. 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 [1]. The Japanese Society of Gout and Uric & Nucleic Acids Guidelines for Management of Hyperuricemia and Gout [7] 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).

In the previous report [13], the author described the trends in the number of gout patients with changes in the Japanese diet. This article shows the relationship between the number of gout patients and macronutrient intake in Japanese people and suggests modification of macronutrient intake for the

prevention of gout in Japanese people referencing the results of clinical research.

## 2. Methods

### 2.1. The Number of Gout Patients

The number of gout patients was estimated in the Comprehensive Survey of Living Conditions performed by the Ministry of Health, Labour and Welfare in Japan (1986-2016) [1]. The Comprehensive Survey of Living Conditions was based on self-reporting by residents. This article showed the rate of hospital visits due to gout from 1986 to 2016 based on the Comprehensive Survey of Living Conditions. Hakoda and Kasagi [14] confirmed that the trends in the number of gout patients in Japan in 2013 and 2016 reported by the Comprehensive Survey of Living Conditions were almost equal to those reported by the database of health insurance claims with gout diagnosed by physicians.

### 2.2. The Trends in Nutrient or Food Intake in Japanese People

The intake of nutrients or foods was searched in the National Health and Nutrition Survey, Japan (1946-2017) performed by the Ministry of Health, Labour and Welfare in Japan [12, 15, 16].

Data were extracted from the series of Japanese National Nutrition Surveys that have been carried out every year throughout Japan since 1946 [16]. In these surveys, food consumption by families enrolled in the study was assessed by weighing food items consumed on three consecutive weekdays (until 1994) or one weekday (from 1995).

The daily nutrient or food intakes of Japanese people are shown as the mean values reported by the National Health and Nutrition Survey Japan (1946-2017) [12].

### 2.3. Dietary Reference Intakes for Japanese People

The Ministry of Health, Labour and Welfare in Japan [15] evaluated the intake of nutrients as described below: (1) the estimated average requirement (EAR) indicates the amount that would meet the nutrient requirements of 50% of the population; (2) the recommended dietary allowance (RDA) indicates the amount that would meet the nutrient requirement of most of the population; (3) the adequate intake (AI) indicates the amount adequate to maintain a certain level of nutritional status; (4) the tolerable upper intake level (UL) was determined for the purpose of avoiding adverse health effects due to excessive intake; and (5) the tentative dietary goal for preventing lifestyle-related diseases (DG) was developed for the purpose of prevention of lifestyle-related diseases.

### 2.4. Food Composition

The food composition was extracted from a standard tables of food composition in Japan -2020- (Eighth Revised Edition) of the Council for Science and Technology, Ministry of Education, Culture, Sports, Science and Technology in Japan.

the Ministry of Education, Culture, Sports, Science and Technology [17] and the National Institutes of Health in the U.S. Department of Health & Human Services [18].

### 2.5. Statistical Analysis

The correlation efficient and the significance of the correlation between the number of gout patients and nutrient intake in 1986, 1989, 1992, 1995, 1998, 2001, 2004, 2007, 2010, 2013, and 2016 were analyzed by Pearson Product Moment Correlation. A SigmaPlot 12.0 software program (version 12.0, Systat Software Inc, San Jose, CA) was used for statistical analysis. Differences were considered significant at  $p < 0.05$ .

## 3. Relationship Between the Number of Gout Patients and Macronutrient Intake

The results on the correlation between the number of gout patients and macronutrient intake in Japanese people are shown in Table 1.

### 3.1. Energy

The daily energy intake of Japanese people in 2016 was lower compared to that in 1960, 1965, 1975, 1986, 1989, 1992, 1995, 1998, 2001, 2004, 2007, and 2013 and was higher compared to that in 2010 (1960: 2096 kcal/day; 1965: 2184 kcal/day; 1975: 2188 kcal/day; 1986: 2075 kcal/day; 1989: 2061 kcal/day; 1992: 2058 kcal/day; 1995: 2042 kcal/day; 1998: 1979 kcal/day; 2001: 1954 kcal/day; 2004: 1902 kcal/day; 2007: 1898 kcal/day; 2010: 1849 kcal/day; 2013: 1873 kcal/day; 2016: 1865 kcal/day). In Japanese men and women in 2016, the mean daily intake of energy for men (20-49 years) and women (20-49 years) was 2092-2122 kcal/day and 1631-1694 kcal/day, respectively, and was below the estimation of energy requirement of low physical activity levels [physical activity levels: low: 2300 kcal/day; medium: 2650-2700 kcal/day; high: 3050 kcal/day among men; low: 1700-1750 kcal/day; medium: 2000-2050 kcal/day; high: 2300-2350 kcal/day among women] [15]. In Japanese men and women in 2016, the mean daily intake of energy for men ( $\geq 50$  years) and women ( $\geq 50$  years) was 2092-2122 kcal/day and 1631-1694 kcal/day, respectively, and was within the estimation of energy requirement of low physical activity levels, and below the estimation of energy requirement of medium physical activity levels [physical activity levels: low: 1800-2200 kcal/day; medium: 2100-2600 kcal/day; high: 2750-2950 kcal/day among men; low: 1400-1650 kcal/day; medium: 1650-2190 kcal/day; high: 2100-2250 kcal/day among women] [15].

The daily consumption of energy was negatively correlated with the number of gout patients in 1986-2016 ( $r = -0.984$ ,  $p = 0.0000000514$ ). The daily consumption of energy did not show a significant correlation with the number of gout patients in the adult population (aged  $\geq 20$  years) in 2004-2016 ( $r =$

-0.610,  $p=0.275$ ), with the number of gout patients in adult men (aged  $\geq 20$  years) in 2004-2016 ( $r=-0.610$ ,  $p=0.275$ ), and with the number of gout patients in adult women (aged  $\geq 20$  years) in 2004-2016 ( $r=0.826$ ,  $p=0.0847$ ).

Proper energy intake for gout patients [7] or diabetes mellitus patients [19] is recommended in each guideline. The National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI) [20] has recommended energy intake of 25-35 kcal/kg body weight per day in adults with chronic kidney disease (CKD) (CKD stages 1-5D) or posttransplantation.

### 3.2. Carbohydrates

#### 3.2.1. Carbohydrate

The daily carbohydrate intake of Japanese people in 2016 was lower compared to that in 1959, 1965, 1975, 1986, 1989, 1992, 1995, 1998, 2001, 2004, 2007, 2010, and 2013 (1959: 405 g/day; 1965: 384 g/day; 1975: 337 g/day; 1986: 295 g/day; 1989: 290 g/day; 1992: 289 g/day; 1995: 280 g/day; 1998: 271 g/day; 2001: 274 g/day; 2004: 266 g/day; 2007: 264 g/day; 2010: 258 g/day; 2013: 259 g/day; 2016: 252.8 g/day). The Ministry of Health, Labour and Welfare in Japan [15] has not set the recommended dietary allowance (RDA) for the daily carbohydrate intake in Japanese people.

The daily carbohydrate intake was negatively correlated with the number of gout patients in 1986-2016 ( $r=-0.978$ ,  $p=0.00000215$ ), with the number of gout patients in the adult population (aged  $\geq 20$  years) in 2004-2016 ( $r=-0.909$ ,  $p=0.0327$ ), and with the number of gout patients in adult men (aged  $\geq 20$  years) in 2004-2016 ( $r=-0.909$ ,  $p=0.0323$ ). The daily carbohydrate intake tended to be positively correlated with the number of gout patients in adult women (aged  $\geq 20$  years) in 2004-2016 ( $r=0.864$ ,  $p=0.0590$ ). This result suggests that the correlation of daily carbohydrate intake with the number of gout patients tends to vary with gender and is stronger in adult men than in adult women. The daily carbohydrate intake of adult men and women tended to increase as age increased.

#### 3.2.2. Sugars and Fructose

Effects of sucrose, glucose and fructose on serum uric acid (SUA) levels and hyperuricemia risk are reviewed in detail by Koguchi [21].

##### 1. Fructose

The Ministry of Health, Labour and Welfare in Japan has not investigated the daily fructose intake. In a study incorporating data from the US National Health and Nutrition Examination Survey (NHANES) and the National Food Consumption Survey, the estimated average dietary intake of fructose increased 12 g/day from 1977 to 2005 (1977: 37 g/day; 2005: 49 g/day) [22]. The predominant sources of fructose in the diet are nonalcoholic beverages, which occupy 46% of total fructose intake [22]. In a systematic review and meta-analysis of controlled feeding trials, high fructose intake (213-219 g/day) under hypercaloric feeding conditions (+35% excess energy) raised serum uric acid (SUA) concentrations in people with and without diabetes mellitus [23]. Therefore,

Wang et al. [23] have stated that high fructose intake (213-219 g/day) under hypercaloric feeding conditions (+35% excess energy) leads to increased risk of hyperuricemia and gout.

Acute oral or intravenous administration of fructose rapidly increased SUA levels through accentuated degradation of purine nucleotides in humans [24-28] and increased purine synthesis *de novo* [26, 29]. An intravenous administration of fructose (0.5 g/kg/h) for 2 hours increased blood lactate concentrations, which may be attributable to decrease UA excretion via urate transporter 1 (URAT1/SLC22A12) [30, 31]. Therefore, fructose intake increases SUA level via both decreased UA excretion and increased UA production [31]. Caliceti et al. [32] have stated that it is not yet possible to conclude whether fructose intake alone is the main contributor to increased blood UA concentration.

In epidemiological studies, increased fructose intake was associated with increased SUA concentrations [33, 34], hyperuricemia risk [33-35], and gout risk [35-39]. Higher intake of foods high in fructose was associated with increased SUA concentrations [33, 40-45], hyperuricemia risk [46], and gout risk [40]. These results suggest that decrease in daily intake of fructose-rich foods (e.g., high-fructose corn syrup and sugar-sweetened beverages, soft drinks) in Japanese people is essential for the prevention of gout.

The 2020 American College of Rheumatology (ACR) Guideline [47] has conditionally recommended for limiting high-fructose for patients with gout, regardless of disease activity. Japanese Society of Gout and Uric & Nucleic Acids Guidelines [7] has recommended avoidance of fructose overdose in patients of gout.

##### 2. Sugars

The daily intake of sugar and sweetener of Japanese people in 2016 was lower compared to that in 2001, 2004, 2007, 2010, and 2013 (2001: 7.2 g/day; 2004: 7.1 g/day; 2007: 6.7 g/day; 2010: 6.7 g/day; 2013: 6.6 g/day; 2016: 6.5 g/day). The Ministry of Health, Labour and Welfare in Japan [15] has not set the tentative dietary goal for preventing lifestyle-related diseases (DG) for the daily intake of sugars (monosaccharides, disaccharides, sugar alcohols) in Japanese people.

The daily sugar and sweetener intake was negatively correlated with the number of gout patients in 2001-2016 ( $r=-0.870$ ,  $p=0.0242$ ). The daily sugar and sweetener intake did not show a significant correlation with the number of gout patients in the adult population (aged  $\geq 20$  years) in 2004-2016 ( $r=-0.729$ ,  $p=0.162$ ), and with the number of gout patients in adult women (aged  $\geq 20$  years) in 2004-2016 ( $r=0.782$ ,  $p=0.118$ ). The daily sugar and sweetener intake was negatively correlated with the number of gout patients in adult men (aged  $\geq 20$  years) in 2004-2016 ( $r=-0.915$ ,  $p=0.0295$ ). This result suggests that correlation of daily sugar and sweetener intake with the number of gout patients varies with gender.

Sucrose intake (1.5 g/kg of body weight) increased plasma UA concentrations in healthy subjects through increase in purine degradation [48]. In epidemiological studies, added sugars were related to serum uric acid (SUA) concentration among Whites [49]. Increased intake of sugars [50], added

sugars which are fructose-containing sugars, sucrose and high fructose corn syrup [46] was associated with increased hyperuricemia risk. Therefore, increased the daily sugars intake do not appear to be appropriate for the prevention of gout.

The 2012 American College of Rheumatology (ACR) Guidelines for Management of Gout [51] have recommended limiting intake of table sugar in all gout patients.

Tappy et al. [50] have proposed to set a maximum limit to the intake of total sugars containing fructose (sucrose, glucose fructose syrups, honey or other syrups, and natural concentrates, etc.) of 100 g/day [50].

### 3.2.3. Dietary Fiber

The daily intake of dietary fiber of Japanese people in 2016 was lower compared to that in 1951, 1955, 1960, 1966, 1975, 1986, 1989, 1992, 1998, 2001, and 2007 and was higher compared to that in 2004, and 2010 and was about the same as that in 2013 (1951: 23.3 g/day; 1955: 23.0 g/day; 1960: 19.9 g/day; 1966: 18.1 g/day; 1975: 18.3 g/day; 1986: 16.6 g/day; 1989: 16.4 g/day; 1992: 16.4 g/day; 1998: 15.0 g/day; 2001: 14.6 g/day; 2004: 13.9 g/day; 2007: 14.6 g/day; 2010: 14.0 g/day; 2013: 14.2 g/day; 2016: 14.2 g/day). In Japanese men and women in 2016, the daily dietary fiber intake for men (aged  $\geq 15$  years) and women (aged  $\geq 15$  years) was 12.5-16.9 g/day and 11.3-16.1 g/day, respectively, and was below the tentative dietary goal for preventing lifestyle-related diseases (DG) [men (aged 15-17 years):  $\geq 19$  g/day; men (aged 18-64 years):  $\geq 21$  g/day; men (aged  $\geq 65$  years):  $\geq 20$  g/day; women (aged 15-64 years):  $\geq 18$  g/day; women (aged  $\geq 65$  years):  $\geq 17$  g/day][15]. The daily dietary fiber intake of adult men and women tended to increase as age increased.

The daily intake of dietary fiber was negatively correlated with the number of gout patients in 1986-2016 ( $r = -0.946$ ,  $p = 0.000036$ ). This result suggests that the daily dietary fiber intake below the tentative dietary goal for preventing lifestyle-related diseases (DG) is related to the increase in the number of gout patients. The daily intake of dietary fiber did not show a significant correlation with the number of gout patients in the adult population (aged  $\geq 20$  years) in 2004-2016 ( $r = -0.133$ ,  $p = 0.831$ ), with the number of gout patients in adult men (aged  $\geq 20$  years) in 2004-2016 ( $r = -0.0701$ ,  $p = 0.911$ ), and with the number of gout patients in adult women (aged  $\geq 20$  years) in 2004-2016 ( $r = 0.108$ ,  $p = 0.862$ ). Japanese men and women should increase their daily dietary fiber intake.

In a clinical trial, dietary fiber decreased serum uric acid (SUA) concentrations [52, 53]. In epidemiological studies, increased dietary fiber intake was associated with decreased SUA concentrations [54-57], hyperuricemia risk [55, 56, 58, 59], and gout risk [60]. Dietary fiber intake may prevent gout through reduced SUA concentrations and decreased hyperuricemia risk.

In an experimental model of gout in mice, which are made by injection of monosodium urate crystals into the knee joint, a high-fiber diet (5% cellulose + 10% pectin) controlled the inflammatory response to monosodium urate crystals by favoring the resolution of the inflammatory response [61]. In

the same mouse model of gout, a pectin-rich fiber diet increased serum acetate concentrations and showed reduced joint destruction and decreased joint dysfunction (hypernociception) and interleukin-1 $\beta$  (IL-1 $\beta$ ) production, compared with the cellulose diet [61]. Therefore, high intake of dietary fiber had a positive effect on the resolution of a gout flare in an experimental model of mice with gout [61].

Dietary fiber, such as inulin [62, 63] and konjac glucomannan [64, 65], inhibits xanthine oxidase activity and suppresses uric acid (UA) production. Dietary fiber suppresses digestion and/or absorption of dietary purine [21, 66-73]. Agarose suppresses digestion and/or absorption of dietary purine and increases the renal excretion efficiency of UA [72]. Inulin increased short chain fatty acids (SCFAs) concentrations (acetate, propionate and butyrate concentrations) and SCFAs-producing bacteria (e.g., *Akkermansia*, *Ruminococcus*, *Bifidobacterium*, *Parasutterella*) in the feces and modulated gut microbiota, as well as affecting production of gut microbiota-derived SCFAs [63]. Inulin improved intestinal barrier function, alleviated the inflammatory state, and reduced SUA levels in *Uox*-knockout (urate oxidase) mice [63]. The mechanism may be related to SCFAs, especially propionate and butyrate, providing ATP to the cells of the intestinal wall to show beneficial effects on UA excretion [74, 75], and butyrate improves metabolism of UA through lowering UA concentrations in the colonic mucosa [76]. Future investigations are needed to clarify how dietary fiber suppresses elevation of SUA concentrations, other than the above-mentioned mechanisms.

Increased dietary fiber intake was associated with lower serum C-reactive protein concentrations [77-80], serum high-sensitivity C-reactive protein concentrations [81], plasma interleukin-6 (IL-6) concentrations, and plasma tumor necrosis factor- $\alpha$  receptor 2 (TNF- $\alpha$ -R2) concentrations [82]. Therefore, Ma et al. [79, 82] have stated that a diet high in fiber may play a role in reducing inflammation. Increased dietary fiber intake ( $>16.82$  g [79],  $>18.3$  g [78],  $>20$  g [80]) was significantly associated with lower serum or plasma C-reactive protein (CRP) concentrations. Dietary fiber increases production of SCFAs, which are acetate, propionate, and butyrate, by increasing bacteria that are beneficial to health [83, 84]. The mechanism responsible for the anti-inflammatory effect of dietary fiber has not been fully elucidated but might involve the production of SCFAs by colonic fermentation in rodents [63, 85, 86]. Dietary fiber also acts as a carrier of dietary polyphenols [87-89]; that is to say, most of the polyphenols traverse the small intestine linked to dietary fiber, and they release the fiber matrix in the colon by the action of the bacterial microbiota, producing metabolites and an antioxidant environment [87-89] and exert their anti-inflammatory effects [90-92]. Foods high in both dietary fiber and polyphenols that may have the effect of suppressing elevated SUA concentrations are nuts (almonds, hazelnuts, pistachio nuts), fruit (apples, blackberries, red raspberries, pears), and vegetables (broccoli, globe artichokes) [17, 18]. It is speculated that simultaneous intake of foods high in both dietary fiber and polyphenol compounds, which have the

anti-inflammatory properties, may lead to prevention of chronic diseases related to inflammation including gout.

Epidemiological studies have reported that increased dietary fiber intake was significantly associated with decreased risks of chronic kidney disease (CKD) [93-96], obesity [83, 97-102], diabetes mellitus [83, 97-100, 103, 104], hypertension [93, 97, 99, 105], cardiovascular disease (CVD) [100, 106, 107], coronary artery disease (CAD) and coronary heart disease (CHD) [97, 108-112], stroke [97], CVD in adults with CKD [113], ischemic cardiovascular disease (iCVD) [114], myocardial infarction [115], cancer [100], all-cause mortality [116, 117], CVD-cause mortality [116], respiratory disease-cause mortality [116], and injury-cause mortality [116].

The guidelines have recommended increased intake of fiber for healthy adults for CVD prevention [106, 107], urolithiasis patients [118], and diabetes mellitus patients [19, 119]. The Japanese clinical practice guideline for diabetes 2019 [19] has stated that the daily dietary fiber intake for diabetes patients is more than 20 g. The 2016 European Guidelines on cardiovascular disease prevention in clinical practice [106] has recommended that the daily dietary fiber intake for all individuals is 30-45 g.

Judging from the data of food composition [17, 18], it is important for Japanese people (aged  $\geq 15$  years) to eat seeds and nuts (pumpkin seeds, chia seeds, almonds, pistachio nuts, hazelnuts, peanuts), whole grains (high fiber-bran ready-to-eat cereals, shredded wheat ready-to-eat cereals, whole grain bread, oats, barley, rye), legumes (navy beans, small white beans, yellow beans, cranberry beans, adzuki beans, French beans, split peas, chickpeas, lentils, pinto beans), seaweed, mushrooms (wood ear, shiitake mushrooms, maitake mushrooms), potatoes (konjac, potato with skin), fruit (avocados, apples, raspberries, blackberries, prunes, oranges, bananas, guavas), and vegetables (artichokes, pumpkins, tomatoes, broccoli, carrots, sweet corn, pears) to take in more dietary fiber to reach the tentative dietary goal for preventing lifestyle-related diseases (DG).

### 3.2.4. The Mean Ratio of Energy Intake from Carbohydrate in Total Energy Intake (Carbohydrate/Energy)

The mean ratio of energy intake from carbohydrate in total energy intake (Carbohydrate/Energy) in 1986, 1989, 1992, 1995, 1998, 2001, 2004, 2007, 2010, 2013, and 2016 were 57.8-60.3% of energy. The mean ratio of energy intake from carbohydrate in total energy intake (Carbohydrate/Energy) in 2016 was lower compared to that in 1975, 1980, 1986, 1989, 1992, 2001, 2004, 2007, 2010, and 2013 and was about the same as that in 1995 and 1998 (1975: 63.1%; 1980: 61.5%; 1986: 60.3%; 1989: 58.7%; 1992: 58.9%; 1995: 57.8%; 1998: 57.8%; 2001: 59.7%; 2004: 59.7%; 2007: 59.3%; 2010: 59.4%; 2013: 58.9%; 2016: 57.8%). In Japanese men and women in 2016, the mean ratio of energy intake from carbohydrate in total energy intake (Carbohydrate/Energy) of Japanese men (aged  $\geq 1$  year) and women (aged  $\geq 1$  year) was 56.8-60.7% of energy and 54.4-58.9% of energy, respectively, and was within the tentative dietary goal for preventing life-style related diseases (DG) [men (aged  $\geq 1$  year): 50-65%

of energy; women (aged  $\geq 1$  year): 50-65% of energy] [15].

The mean ratio of energy intake from carbohydrate in total energy intake (Carbohydrate/Energy) did not show a significant correlation with the number of gout patients in 1986-2016 ( $r = -0.058$ ,  $p = 0.865$ ), and with the number of gout patients in adult women (aged  $\geq 20$  years) in 2004-2016 ( $r = 0.591$ ,  $p = 0.294$ ). Whereas the mean ratio of energy intake from carbohydrate in total energy intake (Carbohydrate/Energy) tended to be negatively correlated with the number of gout patients in the adult population (aged  $\geq 20$  years) in 2004-2016 ( $r = -0.875$ ,  $p = 0.0518$ ). The mean ratio of energy intake from carbohydrate in total energy intake (Carbohydrate/Energy) was negatively correlated with the number of gout patients in adult men (aged  $\geq 20$  years) in 2004-2016 ( $r = -0.899$ ,  $p = 0.0377$ ). This result suggests that the correlation of the mean ratio of energy intake from carbohydrate in total energy intake (Carbohydrate/Energy) with the number of gout patients varies with gender.

The ideal balance of the caloric ratio of protein, fat, and carbohydrate for healthy life is protein: 15%, fat: 25%, and carbohydrates: 60% [120]. It seems better to increase the mean ratio of energy intake from carbohydrate in total energy intake (Carbohydrate/Energy) until 60%. In particular, intake of fiber-rich foods (e.g., whole grains, legumes, seeds and nuts, fruit, vegetables) seems to be important for the prevention of gout.

## 3.3. Proteins

### 3.3.1. Total Protein

The daily total protein intake of Japanese people in 2016 was lower compared to that in 1960, 1965, 1975, 1986, 1989, 1992, 1995, 1998, 2001, 2004, 2007, and 2013 and was higher compared to that in 2010 (1960: 69.7 g/day; 1965: 71.3 g/day; 1975: 80.0 g/day; 1986: 78.9 g/day; 1989: 80.2 g/day; 1992: 80.1 g/day; 1995: 81.5 g/day; 1998: 79.2 g/day; 2001: 73.4 g/day; 2004: 70.8 g/day; 2007: 69.8 g/day; 2010: 67.3 g/day; 2013: 68.9 g/day; 2016: 68.5 g/day). In Japanese men and women in 2016, the mean daily total protein intake for Japanese men (aged  $\geq 1$  year) and women (aged  $\geq 1$  year) was 45.1-79.1 g/day and 43.1-67.8 g/day, respectively, and exceeded the recommended dietary allowance (RDA) [men (aged  $\geq 1$  year): 20-65 g/day; women (aged  $\geq 1$  year): 20-55 g/day] [15].

The daily total protein intake was negatively correlated with the number of gout patients in 1986-2016 ( $r = -0.937$ ,  $p = 0.0000215$ ). The daily intake of total protein did not show a significant correlation with the number of gout patients in the adult population (aged  $\geq 20$  years) in 2004-2016 ( $r = -0.559$ ,  $p = 0.327$ ), and with the number of gout patients in adult men (aged  $\geq 20$  years) in 2004-2016 ( $r = -0.577$ ,  $p = 0.308$ ). Whereas the daily total protein intake was positively correlated with the number of gout patients in adult women (aged  $\geq 20$  years) in 2004-2016 ( $r = 0.896$ ,  $p = 0.0399$ ). This result suggests that the correlation of daily total protein intake with the number of gout patients varies with gender.

In a prospective cohort study in a Chinese population, higher intake of total protein was associated with increased gout risk,

whereas higher intake of soy protein was associated with decreased gout risk [121]. This population-based cohort study in a Chinese adult population (aged 45-74 years) revealed that daily total protein intake of subjects with gout was significantly higher than that of subjects without gout (subjects with gout:  $15.4 \pm 2.5\%$  energy; subjects without gout:  $15.2 \pm 2.4\%$  energy) and daily soy protein intake of subjects with gout tended to decrease compared to that of subjects without gout (subjects with gout:  $1.47 \pm 0.99\%$  energy; subjects without gout:  $1.50 \pm 1.01\%$  energy). The daily total protein intake (the mean ratio of energy intake from protein in total energy intake) of Japanese adult population (aged  $\geq 40$  years) in 2016 was 14.4-15.2% energy. The daily total protein intake of Japanese adult population (aged  $\geq 40$  years) was as same as that of Chinese adult population without gout (aged 45-74 years).

The Ministry of Health, Labour and Welfare in Japan [15] has not set a tolerable upper intake level (UL) for healthy individuals because there are insufficient reports of clear scientific evidence for health problems due to excessive daily intake of protein. However, excessive intake of protein can reduce renal function. A meta-analysis concluded that higher protein intake ( $\geq 20\%$  but  $< 35\%$  of energy or  $\geq 10\%$  higher than a comparison intake) within the range of recommended intakes for protein was consistent with normal renal function in healthy individuals in the short term (and did not reduce renal function) [122]. In healthy adults, consuming a higher-protein diet did not cause changes in kidney function compared with lower- or normal-protein diets [123]. In healthy adult men and women, protein intake should not exceed the World Health Organization (WHO) recommendation ( $0.83 \text{ g/kg body weight/day}$  for adults [124]).

Clinical practice guideline for nutrition in chronic kidney disease (CKD) have recommended for protein intake as follows: (1) protein restriction in CKD patients [125]; (2) protein restriction in adults with CKD (CKD stages 3-5) not on dialysis with or without diabetes [20]; and (3) protein intake of  $1.0\text{-}1.2 \text{ g/kg body weight/day}$  in adults with CKD (CKD stages 5D) on maintenance hemodialysis or peritoneal dialysis [20]. European Association of Urology 2018 has recommended for limited daily animal protein intake ( $0.8\text{-}1.0 \text{ g/kg/day}$ ) for patients with urolithiasis [118].

### 3.3.2. Animal Protein

The daily animal protein intake of Japanese people in 2016 was higher compared to that in 1960, 1965, 2010, and 2013 and was lower compared to that in 1975, 1986, 1989, 1992, 1995, 1998, 2001, 2004, and 2007 (1960:  $24.7 \text{ g/day}$ ; 1965:  $28.5 \text{ g/day}$ ; 1975:  $38.9 \text{ g/day}$ ; 1986:  $40.1 \text{ g/day}$ ; 1989:  $42.4 \text{ g/day}$ ; 1992:  $42.5 \text{ g/day}$ ; 1995:  $44.4 \text{ g/day}$ ; 1998:  $42.8 \text{ g/day}$ ; 2001:  $39.9 \text{ g/day}$ ; 2004:  $38.0 \text{ g/day}$ ; 2007:  $38.0 \text{ g/day}$ ; 2010:  $36.0 \text{ g/day}$ ; 2013:  $37.2 \text{ g/day}$ ; 2016:  $37.4 \text{ g/day}$ ).

The daily intake of animal protein was negatively correlated with the number of gout patients in 1986-2016 ( $r = -0.823$ ,  $p = 0.00185$ ). The daily intake of animal protein did not show a significant correlation with the number of gout patients in the adult population (aged  $\geq 20$  years) in 2004-2016 ( $r = -0.241$ ,  $p = 0.696$ ), with the number of gout patients in adult men (aged

$\geq 20$  years) in 2004-2016 ( $r = -0.376$ ,  $p = 0.532$ ), and with the number of gout patients in adult women (aged  $\geq 20$  years) in 2004-2016 ( $r = 0.717$ ,  $p = 0.173$ ).

In a clinical trial, animal sources of protein (e.g., casein, lactalbumin [126, 127]) decreased serum uric acid (SUA) concentrations. An increase in intake of milk and cheese seems to be important for the prevention of gout through a decrease in SUA concentrations.

### 3.3.3. Vegetable Protein

The vegetable protein is from grains, potatoes, legumes, seeds, nuts, fruit, vegetables, mushrooms, and seaweed. The daily vegetable protein intake of Japanese people in 2016 was lower compared to that in 1960, 1965, 1975, 1986, 1989, 1992, 1995, 1998, 2001, 2004, 2007, 2010, and 2013 (1960:  $45.0 \text{ g/day}$ ; 1965:  $42.8 \text{ g/day}$ ; 1975:  $41.1 \text{ g/day}$ ; 1986:  $38.8 \text{ g/day}$ ; 1989:  $37.8 \text{ g/day}$ ; 1992:  $37.6 \text{ g/day}$ ; 1995:  $37.1 \text{ g/day}$ ; 1998:  $36.4 \text{ g/day}$ ; 2001:  $33.5 \text{ g/day}$ ; 2004:  $32.8 \text{ g/day}$ ; 2007:  $31.8 \text{ g/day}$ ; 2010:  $31.3 \text{ g/day}$ ; 2013:  $31.7 \text{ g/day}$ ; 2016:  $31.1 \text{ g/day}$ ).

The daily vegetable protein intake was negatively correlated with the number of gout patients in 1986-2016 ( $r = -0.974$ ,  $p = 0.000000417$ ). The daily intake of vegetable protein did not show a significant correlation with the number of gout patients in the adult population (aged  $\geq 20$  years) in 2004-2016 ( $r = -0.674$ ,  $p = 0.312$ ), and with the number of gout patients in adult men (aged  $\geq 20$  years) in 2004-2016 ( $r = -0.740$ ,  $p = 0.153$ ). The daily intake of vegetable protein tended to be positively correlated with the number of gout patients in adult women (aged  $\geq 20$  years) in 2004-2016 ( $r = 0.854$ ,  $p = 0.0656$ ). This result suggests that the correlation of daily vegetable protein intake with the number of gout patients tends to vary with gender.

Vegetable sources of protein (e.g., wheat gluten [128], rice endosperm protein [129]) decreased SUA concentrations. An increase in intake of wheat gluten and rice endosperm protein seems to be important for the prevention of gout through a decrease in SUA concentrations.

### 3.3.4. The Mean Ratio of Energy Intake from Protein in Total Energy Intake (Protein/Energy)

The mean ratio of energy intake from protein in total energy intake (Protein/Energy) in 1986, 1989, 1992, 1995, 1998, 2002, 2005, 2007, 2010, 2013, and 2016 were 14.7-16.1% of energy. The mean ratio of energy intake from protein in total energy intake (Protein/Energy) in 2016 was higher compared to that in 1975 and 2010 and was lower compared to that in 1980, 1986, 1989, 1992, 1995, 1998, 2002, and 2005 and was about the same as that in 2007 and 2013 (1975: 14.6%; 1980: 14.9%; 1986: 15.2%; 1989: 15.6%; 1992: 15.6%; 1995: 16.1%; 1998: 16.1%; 2002: 15.1%; 2005: 15.1%; 2007: 14.8%; 2010: 14.7%; 2013: 14.8%; 2016: 14.8%). In Japanese men and women in 2016, the mean ratio of energy intake from protein in total energy intake (Protein/Energy) of Japanese men (aged  $\geq 1$  year) and women (aged  $\geq 1$  year) was 14.1-15.0% of energy and 13.9-15.6% of energy, respectively, and was within the tentative dietary goal for preventing lifestyle-related diseases (DG) [men ( $\geq 1$  year): 13-20% of energy; women (aged  $\geq 1$  year): 13-20% of energy] [15].

The mean ratio of energy intake from protein in total energy intake (Protein/Energy) was negatively correlated with the number of gout patients in 1986-2016 ( $r = -0.697$ ,  $p = 0.0172$ ). The mean ratio of energy intake from protein in total energy intake (Protein/Energy) did not show a significant correlation with the number of gout patients in the adult population (aged  $\geq 20$  years) in 2004-2016 ( $r = -0.405$ ,  $p = 0.499$ ), with the number of gout patients in adult men (aged  $\geq 20$  years) in 2004-2016 ( $r = -0.147$ ,  $p = 0.813$ ), and with the number of gout patients in adult women (aged  $\geq 20$  years) in 2004-2016 ( $r = 0.855$ ,  $p = 0.0648$ ).

The ideal balance of the caloric ratio of protein, fat, and carbohydrate for healthy life is protein: 15%, fat: 25%, and carbohydrates: 60% [120]. It seems better to increase the mean ratio of energy intake from protein in total energy intake (Protein/Energy) until 15%.

### 3.4. Fats

#### 3.4.1. Total Fat

The daily total fat intake of Japanese people in 2016 was higher compared to that in 1960, 1965, 1975, 1986, 2001, 2004, 2007, 2010, and 2013 and was lower compared to that in 1989, 1992, 1995, 1998 (1960: 24.7 g/day; 1965: 36.0 g/day; 1975: 52.0 g/day; 1986: 56.6 g/day; 1989: 58.9 g/day; 1992: 58.4 g/day; 1995: 59.9 g/day; 1998: 57.9 g/day; 2001: 55.3 g/day; 2004: 54.1 g/day; 2007: 55.1 g/day; 2010: 53.7 g/day; 2013: 55.0 g/day; 2016: 57.2 g/day). The Ministry of Health, Labour and Welfare in Japan [15] has not set the recommended dietary allowance (RDA) for the daily total fat intake in Japanese people.

The daily intake of total fat was negatively correlated with the number of gout patients in 1986-2016 ( $r = -0.677$ ,  $p = 0.0221$ ). The daily intake of total fat did not show a significant correlation with the number of gout patients in the adult population (aged  $\geq 20$  years) in 2004-2016 ( $r = 0.771$ ,  $p = 0.127$ ), with the number of gout patients in adult men (aged  $\geq 20$  years) in 2004-2016 ( $r = 0.805$ ,  $p = 0.100$ ), and with the number of gout patients in adult women (aged  $\geq 20$  years) in 2004-2016 ( $r = -0.387$ ,  $p = 0.519$ ).

#### 3.4.2. Animal Fat

The daily animal fat intake of Japanese people in 2016 was higher compared to that in 1972, 1975, 1980, 1986, 1989, 1992, 2001, 2004, 2007, 2010, and 2013 and was lower compared to that in 1995 and 1998 (1972: 27.0 g/day; 1975: 27.4 g/day; 1980: 26.9 g/day; 1986: 27.9 g/day; 1989: 28.3 g/day; 1992: 28.5 g/day; 1995: 29.8 g/day; 1998: 29.2 g/day; 2001: 27.2 g/day; 2004: 26.8 g/day; 2007: 27.7 g/day; 2010: 27.1 g/day; 2013: 28.1 g/day; 2016: 29.1 g/day).

The daily animal fat intake did not show a significant correlation with the number of gout patients in 1986-2016 ( $r = -0.285$ ,  $p = 0.396$ ), with the number of gout patients in the adult population (aged  $\geq 20$  years) in 2004-2016 ( $r = 0.848$ ,  $p = 0.0692$ ), and with the number of gout patients in adult men (aged  $\geq 20$  years) in 2004-2016 ( $r = 0.860$ ,  $p = 0.0617$ ), and with the number of gout patients in adult women (aged  $\geq 20$  years) in 2004-2016 ( $r = -0.426$ ,  $p = 0.474$ ). This result suggests that

the correlation of daily animal fat intake with the number of gout patients tends to vary with gender and is stronger in adult men than in adult women.

#### 3.4.3. Vegetable Fat

The vegetable fat is from grains, potatoes, legumes, seeds, nuts, fruit, vegetables, mushrooms, and seaweed. The daily vegetable fat intake of Japanese people in 2016 was lower compared to that in 1986, 1989, 1992, 1995, and 1998 and was higher compared to that in 2007, 2010, and 2013 (1986: 28.7 g/day; 1989: 30.6 g/day; 1992: 29.9 g/day; 1995: 30.2 g/day; 1998: 28.7 g/day; 2007: 27.3 g/day; 2010: 26.7 g/day; 2013: 26.9 g/day; 2016: 28.1 g/day).

The daily intake of vegetable fat was negatively correlated with the number of gout patients in 1986-2016 ( $r = -0.840$ ,  $p = 0.00121$ ). The daily intake of vegetable fat did not show a significant correlation with the number of gout patients in the adult population (aged  $\geq 20$  years) in 2004-2016 ( $r = 0.580$ ,  $p = 0.306$ ), with the number of gout patients in adult men (aged  $\geq 20$  years) in 2004-2016 ( $r = 0.691$ ,  $p = 0.197$ ), and with the number of gout patients in adult women (aged  $\geq 20$  years) in 2004-2016 ( $r = -0.240$ ,  $p = 0.698$ ).

#### 3.4.4. Saturated Fatty Acids

The daily saturated fatty acids intake of Japanese in 2016 was lower compared to that in 1995, and 1998 and was higher compared to that in 2002, 2005, 2007, 2010, and 2013 (1995: 18.4 g/day; 1998: 17.7 g/day; 2002: 14.3 g/day; 2005: 14.8 g/day; 2007: 15.0 g/day; 2010: 14.7 g/day; 2013: 15.1 g/day; 2016: 15.7 g/day).

Though the daily saturated fatty acids intake was negatively correlated with the number of gout patients in 1995-2016 ( $r = -0.873$ ,  $p = 0.0233$ ), Japanese adult men (aged 20-49 years) and women (aged  $\geq 20$  years) should reduce the daily saturated fatty acids intake for the prevention of lifestyle-related diseases including gout.

The Japanese Society of Hypertension Guidelines for the Management of Hypertension [130] have recommended refraining from consuming saturated fatty acids and cholesterol for patients with hypertension. Some guidelines for the prevention of cardiovascular disease (CVD) have stated that reducing intakes of total fat (to less than 30% of total energy intake) and saturated fatty acids (to less than 10% of total energy intake) and replacement of saturated fatty acids with polyunsaturated fatty acids are likely to be beneficial for the prevention of CVD in healthy adults [106, 107]. The 2016 European Guidelines on cardiovascular disease prevention in clinical practice [106] has stated that trans unsaturated fatty acids intake should be as little as possible, with preferably no intake from processed food, and  $< 1\%$  of total energy intake from natural origins for CVD prevention.

#### 3.4.5. The Mean Ratio of Energy Intake from Saturated Fatty Acids in Total Energy Intake (Saturated Fatty Acids/Energy)

In Japanese men and women in 2016, the mean ratio of energy intake from saturated fatty acids in total energy intake (Saturated fatty acids/Energy) for men (aged 20-49 years) and



women (aged  $\geq 20$  years) was 7.21-7.83% of energy and 7.01-8.44% of energy, respectively, and exceeded the tentative dietary goal for preventing lifestyle-related diseases (DG) ( $\leq 7\%$  of energy) [15]. In Japanese men and women in 2016, the mean ratio of energy intake from saturated fatty acids in total energy intake (Saturated fatty acids/Energy) for men (aged  $\geq 50$  years) was 6.50-6.97% of energy and was within the tentative dietary goal for preventing lifestyle-related diseases (DG) ( $\leq 7\%$  of energy) [15].

The mean ratio of energy intake from saturated fatty acids in total energy intake (Saturated fatty acids/Energy) did not show a significant correlation with the number of gout patients in 1995-2016 ( $r = -0.757$ ,  $p = 0.0817$ ), with the number of gout patients in the adult population (aged  $\geq 20$  years) in 2007-2016 ( $r = 0.889$ ,  $p = 0.111$ ), with the number of gout patients in adult men (aged  $\geq 20$  years) in 2007-2016 ( $r = 0.922$ ,  $p = 0.0775$ ), and with the number of gout patients in adult women (aged  $\geq 20$  years) in 2007-2016 ( $r = 0.452$ ,  $p = 0.548$ ). This result suggests that the correlation of the mean ratio of energy intake from saturated fatty acids in total energy intake (Saturated fatty acids/Energy) with the number of gout patients tends to be stronger in adult men than in adult women.

#### 3.4.6. Polyunsaturated Fatty Acids

The Ministry of Health, Labour and Welfare of Japan [15] has not set the tentative dietary goal for preventing lifestyle-related diseases (DG) for the daily intake of n-3 polyunsaturated fatty acids and n-6 polyunsaturated fatty acids in Japanese men and women.

##### 1. n-3 polyunsaturated fatty acids

The daily n-3 polyunsaturated fatty acids intake of Japanese people in 2016 was less than that in 2007, 2010, and 2013 (2007: 2.37 g/day; 2010: 2.24 g/day; 2013: 2.17 g/day; 2016: 2.16 g/day). In Japanese men and women in 2016, the daily n-3 polyunsaturated fatty acids intake for men (aged 20-49 years and aged  $\geq 60$  years) and women (aged  $\geq 15$  years) was 2.27-2.35 g/day, 2.53-2.67 g/day, and 1.84-2.33 g/day, respectively, and exceeded the adequate intake (AI) [men (aged 20-49 years): 2.0 g/day; men (aged  $\geq 60$  years): 2.1-2.2 g/day; women (aged  $\geq 15$  years): 1.6-2.0 g/day] [15]. This result suggests that the daily n-3 polyunsaturated fatty acids intake in Japanese men (aged 20-49 years and aged  $\geq 60$  years) and women (aged  $\geq 15$  years) appears to be very unlikely to cause a deficiency.

The daily n-3 polyunsaturated fatty acids intake was negatively correlated with the number of gout patients in 2007-2016 ( $r = -0.975$ ,  $p = 0.0246$ ). Diets enriched in both linolenic acid and eicosapentaenoic acid (EPA) significantly suppressed urate crystal-induced inflammation in a rat model [131]. These fatty acids show a potential protective role against gout flares.

Eating foods rich in n-3 polyunsaturated fatty acids is recommended to prevent or treat cardiovascular disease (CVD) [119]. Fatty fish contains rich in n-3 polyunsaturated fatty acids [eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)]. Fish 1-2 times per week, one of which should be oily fish, is recommended for the prevention of CVD [106]. One

should consume at least 250 mg/day of long-chain n-3 polyunsaturated fatty acids or at least 2 servings/week of oily fish [132]. Nuts and seeds contain rich in n-3 polyunsaturated fatty acids [alpha linolenic acid (ALA)]. It seems important for Japanese people to eat fatty fish, nuts, and seeds to take in more n-3 polyunsaturated fatty acids for the prevention of gout and CVD.

##### 2. n-6 polyunsaturated fatty acids

The daily n-6 polyunsaturated fatty acids intake of Japanese people in 2016 was higher compared to that in 2007, 2010, and 2013 (2007: 9.45 g/day; 2010: 9.27 g/day; 2013: 9.28 g/day; 2016: 9.61 g/day). In Japanese men and women in 2016, the daily n-6 polyunsaturated fatty acids intake for men (aged  $\geq 20$  years) and women (aged  $\geq 20$  years) was 9.30-11.47 g/day and 8.15-9.45 g/day, respectively, and exceeded the adequate intake (AI) [men (aged  $\geq 20$  years): 8.0-11.0 g/day; women (aged  $\geq 20$  years): 7.0-8.0 g/day] [15]. This result suggests that the daily n-6 polyunsaturated fatty acids intake in Japanese men (aged  $\geq 20$  years) and women (aged  $\geq 20$  years) appears to be very unlikely to cause a deficiency.

The daily n-6 polyunsaturated fatty acids intake did not show a significant correlation with the number of gout patients in 2007-2016 ( $r = 0.221$ ,  $p = 0.779$ ).

#### 3.4.7. Cholesterol

The Ministry of Health, Labour and Welfare of Japan [15] has not set an index for the daily intake of cholesterol in Japanese adults.

The daily cholesterol intake of Japanese people in 2016 was lower compared to that in 1995, 1998, 2001, 2004, and 2007 and was higher compared to that in 2010 and 2013 (1995: 383 mg/day; 1998: 370 mg/day; 2001: 346 mg/day; 2004: 320 mg/day; 2007: 323 mg/day; 2010: 307 mg/day; 2013: 307 mg/day; 2016: 311 mg/day). In Japanese men and women in 2016, the daily cholesterol intake for men (aged  $\geq 1$  year) and women (aged  $\geq 1$  year) was 206-431 mg/day and 200-351 mg/day, respectively. The Ministry of Health, Labour and Welfare in Japan [15] has stated that, for the daily cholesterol intake, it is desirable to take less than 200 mg from the viewpoint of preventing aggravation of dyslipidemia. Thus, it is important for Japanese people to reduce daily cholesterol intake to prevent the aggravation of dyslipidemia.

The daily cholesterol intake did not show a significant correlation with the number of gout patients in the adult population (aged  $\geq 20$  years) in 2004-2016 ( $r = -0.609$ ,  $p = 0.216$ ), with the number of gout patients in adult men (aged  $\geq 20$  years) in 2004-2016 ( $r = -0.610$ ,  $p = 0.275$ ), and with the number of gout patients in adult women (aged  $\geq 20$  years) in 2004-2016 ( $r = 0.544$ ,  $p = 0.343$ ).

#### 3.4.8. The Mean Ratio of Energy Intake from Fat in Total Energy Intake (Fat/Energy)

The mean ratio of energy intake from fat in total energy intake (Fat/Energy) in 1986, 1989, 1992, 1995, 1998, 2001, 2004, 2007, 2010, 2013, and 2016 were 24.5-27.4% of energy. The mean ratio of energy intake from fat in total energy intake (Fat/Energy) in 2016 was higher compared to that in 1975, 1980, 1986, 1989, 1992, 1995, 1998, 2001, 2004, 2007, 2010,



and 2013 (1975: 22.3%; 1980: 23.6%; 1986: 24.5%; 1989: 25.7%; 1992: 25.5%; 1995: 26.2%; 1998: 26.1%; 2001: 25.2%; 2004: 25.3%; 2007: 25.8%; 2010: 25.9%; 2013: 26.2%; 2016: 27.4%). In Japanese men and women in 2016, the mean ratio of energy intake from fat in total energy intake (Fat/Energy) of Japanese men (aged  $\geq 1$  year) and women (aged 1-14 years and  $\geq 30$  years) in 2016 was 24.3-28.8% of energy, 27.6-29.4% of energy, and 25.6-29.4% of energy, respectively, and was within the tentative dietary goal for preventing lifestyle-related diseases (DG) [men (aged  $\geq 1$  year): 20-30% of energy; women (aged  $\geq 1$  year): 20-30% of energy] [15]. In Japanese men and women in 2016, the mean ratio of energy intake from fat in total energy intake (Fat/Energy) for women (15-29 years) exceeded the tentative dietary goal for preventing lifestyle-related diseases (DG)(30.1-30.8% of energy) [15].

The mean ratio of energy intake from fat in total energy intake (Fat/Energy) did not show a significant correlation with the number of gout patients in 1986-2016 ( $r=0.514$ ,  $p=0.106$ ). The mean ratio of energy intake from fat in total energy intake (Fat/Energy) was positively correlated with the number of gout patients in the adult population (aged  $\geq 20$  years) in 2004-2016 ( $r=0.856$ ,  $p=0.0453$ ), and with the number of gout patients in adult men (aged  $\geq 20$  years) in 2004-2016 ( $r=0.924$ ,  $p=0.0247$ ). The mean ratio of energy intake from fat in total energy intake (Fat/Energy) did not show a significant correlation with the number of gout patients in adult women (aged  $\geq 20$  years) in 2004-2016 ( $r=-0.677$ ,  $p=0.209$ ). This result suggests that the correlation of the mean ratio of energy intake from fat in total energy intake (Fat/Energy) with the number of gout patients varies with gender and is stronger in adult men than in adult women.

In epidemiological studies, increased intake of fat was associated with increased SUA concentrations [54]. The ideal balance of the caloric ratio of protein, fat, and carbohydrate for healthy life is protein: 15%, fat: 25%, and carbohydrates: 60% [120]. It seems better to decrease the mean ratio of energy intake from fat in total energy intake (Fat/Energy) until 25%. Especially decrease in the daily saturated fatty acids intake for Japanese adult men (aged 20-49 years) and women (aged  $\geq 20$  years) is important.

### 3.5. Caloric Ratio of Protein, Fat, and Carbohydrate

The balance of the caloric ratio of protein, fat, and carbohydrate in Japanese people in 1965 was protein: 13.1%, fat: 14.8%, and carbohydrates: 70.3% [120]. The balance of the caloric ratio of protein, fat, and carbohydrate in Japanese people in 1975 was near the ideal balance for healthy life (protein: 14.6%, fat: 21.4%, and carbohydrates: 61.6%)[120]. Compared to the Japanese diet in 1965, in the Japanese diet in 1975-2016, the mean ratio of energy intake from protein in total energy intake (Protein/Energy) and the mean ratio of energy intake from fat in total energy intake (Fat/Energy) increased and the mean ratio of energy intake from carbohydrate in total energy intake (Carbohydrate /Energy) decreased.

Compared to the Japanese diet in 2010, in the Japanese diet in 2016, the mean ratio of energy intake from protein in total

energy intake (Protein/Energy) and the mean ratio of energy intake from fat in total energy intake (Fat/Energy) increased by 0.7% and 5.8%, respectively and the mean ratio of energy intake from carbohydrate in total energy intake (Carbohydrate /Energy) decreased by 2.7%. The balance of the caloric ratio of protein, fat, and carbohydrate in Japanese people in 2016 was weighted toward fat (protein: 14.8%, fat: 27.4%, and carbohydrates: 57.8%). Japanese people need to decrease fat (especially saturated fatty acids) intake.

**Table 1.** Correlation between number of gout patients and macronutrient intake in Japanese people in 1986-2016.

Macronutrient	coefficient	p-value
Energy	- 0.984	0.0000000514
Carbohydrate	- 0.978	0.00000215
Dietary Fiber*	- 0.946	0.000036
Carbohydrate/Energy	- 0.058	0.865
Total Protein**	- 0.937	0.0000215
Animal Protein	- 0.823	0.00185
Vegetable Protein	- 0.974	0.000000417
Protein/Energy	- 0.697	0.0172
Total Fat	- 0.677	0.0221
Animal Fat	- 0.285	0.396
Vegetable Fat	- 0.840	0.00121
Fat/Energy	0.514	0.106

\*The daily dietary fiber intake of Japanese people (aged  $\geq 15$  years) in 2016 was below the tentative dietary goal for preventing lifestyle-related diseases (DG).

\*\*The daily total protein intake for Japanese people (aged  $\geq 1$  year) exceeded the recommended dietary allowance (RDA). Abbreviation: Carbohydrate/Energy, The mean ratio of energy intake from carbohydrate in total energy intake; Protein/Energy, The mean ratio of energy intake from protein in total energy intake; Fat/Energy, The mean ratio of energy intake from fat in total energy intake.

### 3.6. Water Intake

The mean total water intake of Japanese adults (aged 30-76 years), Japanese men (aged 30-76 years), Japanese women (aged 30-69 years) was 2230 g/day, 2423 g/day, and 2037 g/day, respectively [133]. Since there is only this report on water intake of Japanese people, the Ministry of Health, Labour and Welfare in Japan [15] has not established the adequate intake (AI) for water intake of Japanese people.

Consumption of water to maintain hydration was associated with decreased risk of gout flares in an internet-based case-crossover study [134]. Specifically, consumption of five to eight glasses (250 mL each) of water in a 24-hour period or drinking more than eight glasses of water in a 24-hour period was associated with decreased risk of gout flares [134]. Therefore, Terkeltaub and Edwards [135] have stated that the gout patient can help lessen gout flares by moderating food portion sizes and content, by not drinking alcohol in excess in short time periods, and by staying well hydrated (five or eight 250-mL servings of water daily unless medically contraindicated).

The guidelines have stated importance of fluid intake for management in patients with gout [7, 51], urolithiasis [118], diabetes mellitus [119]. Japanese Urological Association., Japanese Society of Endourology., Japanese Society on Urolithiasis Research [136] has recommended that fluid amount is more than 2.0 L/day for patients with urolithiasis.

## 4. Limitation

Jakše et al. [137] have stated that a patient's individual risk likely represents a complex interplay between nonmodifiable factors (e.g., age, gender, race, and genetics) and modifiable factors (e.g., diet, body weight, and lifestyle). Lifestyle-related diseases including gout are not caused or prevented by a single nutrient, but they involve environmental and genetic factors. The number of patients with gout estimated from the Comprehensive Survey of Living Conditions was based on self-reporting by residents. In the National Health and Nutrition Survey performed by the Ministry of Health, Labour and Welfare in Japan, the daily intake of nutrients, etc. was calculated using the Standard Tables of Food Composition in Japan prepared by the Ministry of Education, Culture, Sports, Science and Technology in Japan. Regarding the method of quantifying nutrients contained in food, it is unavoidable that there will be discrepancies in the calculated values depending on which ingredient table is used. The Standard Tables of Food Composition in Japan are revised every five years. It is necessary to consider that the content of nutrients in foods reported in the Standard Tables of Food Composition in Japan fluctuates because the analysis method is different or is improved due to technological progress. It must be also taken into account that the content of nutrients in foods differ from the cooked meals that the person actually consumes.

## 5. Conclusion

The phenomenon that the number of gout patients has increased with the westernization of the Japanese diet since 1955 was described in the previous report [13]. This article showed the relationship between the number of gout patients and macronutrient intake in Japanese people and suggested modification of macronutrient intake for the prevention of gout in Japanese people referencing the results of clinical research. Modification of macronutrient intake for the prevention of gout in Japanese people (especially adults) is suggested as follows: energy-providing nutrient balance (percentages of proteins, fats, and carbohydrates in total energy intake) should be within the range of the tentative dietary goal for preventing lifestyle-related diseases (DG); reduce fat (especially animal fat) intake and maintain the mean ratio of energy intake from saturated fatty acids in total energy intake (Saturated fatty acids/Energy) within the range of the tentative dietary goal for preventing lifestyle-related diseases (DG); limiting or decreasing intake of fat (especially animal fat); replacement of saturated fatty acids (e.g., dairy fats, meat fat) with mono- and polyunsaturated fatty acids (especially n-3 polyunsaturated fatty acids) (e.g., macadamia nuts, almonds, peanuts and peanut butter, olive oil, canola oil, avocados); avoidance of excessive intake of saturated fatty acids and cholesterol; pay attention to sucrose and fructose intake; increase intake of dietary fiber; and maintenance of good hydration. It is necessary to recognize how much micronutrient (vitamin and mineral) intake and alcohol consumption is important as potential dietary habits to

prevent gout in Japanese people.

## Conflict of Interest Statement

The author declares that there are no conflicts of interest.

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