USDA and ODS-NIH Database for the Purine Content of Foods

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USDA Database for Purine Content of Foods (2022)

A. Introduction and need for purine data

What are Purines: chemical definitions; sources (broad categories)

Purines are molecules of great interest in relationship to disease risk. In the body, these groups of chemicals form nucleotides (such as ATP and GTP) as components of nucleic acids (such as DNA and RNA) (Kaneko et al., 2020; Nelson & Voruganti, 2021). Purines are also found in the body's nucleosides such as adenosine and inosine (Kaneko et al, 2020). They function as metabolic signals within and between cells, provide energy, and regulate enzymatic activity (Nelson & Voruganti, 2021).

Purines are produced endogenously from the degradation of nucleic acids in live and dying cells in the body; they are also obtained by consuming specific foods, beverages, and dietary supplements (DS) (Nelson & Voruganti, 2021; Ridi & Tallima, 2017).

B. Purines in health and disease: differences in metabolism among purines

Mechanistically, various purines are metabolized differently, although related chemically (Clifford et al., 1976; Brulé et al., 1992). Some purines are used to make DNA & RNA, others are hydrolyzed into adenine & guanine (purine bases), and still others are degraded to produce xanthine & hypoxanthine (Maiuolo et al., 2016). Metabolic end products, especially urate, are excreted through the kidneys & intestines (Chittoor & Voruganti, 2020). Paradoxically, purine metabolites, especially urate, have both beneficial & detrimental roles. For example, they serve as antioxidants for tissue repair, mediators of immune responses, and defense against neurological & autoimmune diseases, while also showing pathogenic effects such as the potential for gout, a painful form of arthritis (Nelson & Voruganti, 2021; Ridi & Tallima, 2017).

C. Public health picture

Hyperuricemia

Elevated urate levels (serum urate >7 mg/dL in men and >6 mg/dL in women) define the condition known as hyperuricemia. This condition is caused by lowered urate excretion and/or increased urate production through endogenous and/or dietary factors (Chittoor & Voruganti, 2020). Hyperuricemia is associated with a higher risk of hypertension, cardiovascular disease, kidney diseases, metabolic syndrome, and gout (Chittoor & Voruganti, 2020). Hyperuricemia prevalence rates in the United States are 20.2% in adult men and 20.0% in adult women, according to the National Health and Nutrition Examination Survey (NHANES) 2015-2016 (Chen-Xu et al., 2019).

Gout

Gout, an acute inflammatory form of arthritis, is caused by deposits of urate in the joints. Gout, along with hyperuricemia, is a worldwide health issue (Juraschek et al., 2021; Luk & Simkin, 2005). The burden of gout grew globally from 1990 to 2017 and is generally highest in developed regions and countries, especially in New Zealand, Australia, and the United States (Safiri et al., 2020; Xia et al., 2020). Japan has experienced an annual increase in hyperuricemia in recent years, afflicting 20-25% of adult males in 2010. Gout incidence is rising as well in Japan, affecting over 1% of males aged 30 years and older (Hisatome et al., 2020)).

According to NHANES 2015-2016, nearly 4% of U.S. adults (9.2 million people) have gout, including 5.2% of men and 2.7% of women (Chen-Xu et al., 2019). The lower

incidence in women is related to endocrine differences, where estrogen may inhibit the onset of arthritis and promote urate excretion (Hak et al., 2010; Luk & Simkin, 2005). Gout occurs in about 25% of individuals with hyperuricemia. Thus, although hyperuricemic individuals are often asymptomatic and untreated until concerns arise, their elevated urate levels increase disease risk (Chittoor & Voruganti, 2020). While gout incidence is closely related to diet (Chittoor & Voruganti, 2020; Nuki & Simkin 2006; Zhang et al., 2012), additional causes often attributed to gout include affluent or "western" lifestyle, obesity, ethnicity, biologic sex, and genetics (Kuo et al., 2015; MacFarlane & Kim, 2014; Todd & Wright, 2020). Furthermore, gout and cardiovascular issues are closely related. For example, individuals with gout who also experienced a cardiovascular event were more likely to have had a recent gout flare than gout patients who did not have a cardiovascular event, suggesting that episodes of gout are linked to increased risk for cardiovascular events (Cipolletta et al., 2022).

Treatment – drugs, diet, lifestyle changes

Conventional treatment options for hyperuricemia include exercise, weight loss if warranted, restriction of alcoholic and sugary beverages, anti-inflammatory agents, or urate-lowering medications, as well as avoiding excessive meat and seafood intake (Mallen et al., 2017; Richette & Bardin, 2017). Dietary modification is considered a primary preventive strategy to avoid gout flares (Nuki & Simkin, 2006; Chittoor & Voruganti, 2020; Todd & Wright, 2020). Weight loss is often recommended to gout patients since a lower body mass index has been associated with lower risk of gout (Choi et al., 2005). However, reducing subjects' body mass indices resulted in either higher urate or no effect in a recent randomized clinical trial, so additional studies are needed (Hu et al., 2021).

Nonetheless, although various lifestyle factors are hypothesized to affect urate levels, diet seems very influential. For example, a higher risk of hyperuricemia was observed with higher intake of red meat, poultry, seafood, and legumes in a large cross-sectional study of Chinese adults, independent of sex, age, geographic region, body mass index, hypertension, consumption of refined grains, and alcohol intake (Aihemaitijiang et al., 2020). However, the relationship between diet and hyperuricemia is complex. There have been few if any published well-controlled trials documenting the relationship between different known levels of dietary purines intake and serum urate (SU) in healthy individuals and persons with hyperuricemia or diagnosed gout.

Purine content is generally considered to be highest in meats, seafood, and some vegetables (MacFarlane & Kim, 2014). The traditional dietary approach to lowering urate levels has been reducing the intake of high-purine foods (Rai et al., 2017) or foods common in an affluent diet (Nuki & Simkin, 2006). In fact, serum urate (SU) levels increase with frequent and high quantities of high purine foods and beverages (Kaneko et al., 2014; Zgaga et al., 2012). More specifically, diets high in meat and seafood are associated with elevated urate levels (Kaneko et al., 2014; Li et al., 2018; Villegas et al., 2012). However, different cuts of meat and different types of seafood vary substantially in their total purine content, highlighting the importance of having purine data for specific foods to inform appropriate dietary choices instead of avoiding all meats and all seafood. Also, data for various types of vegetables, such as different Brassicas, are inconsistent and may lead to undue dietary restrictions. The data discussion section of this document, below, presents examples of this principle.

D. What dietary factors have an influence on urate other than total purine intake?

Effects of specific purine bases on urate levels

Other dietary factors besides total purine intake can impact urate levels, such as levels of specific purine bases in foods. The key purine bases found in foods are adenine, guanine, hypoxanthine, and xanthine. Uricogenic bases are purine bases that increase serum and urinary urate concentrations (Sarwar & Brulé, 1991). Hypoxanthine, a uricogenic purine base, has shown the greatest dietary impact on increasing the risk for gout due to its effect on urate levels in the body (Clifford et al., 1976). The purine base adenine also seems to increase urate levels (Clifford et al., 1976; Sarwar & Brulé, 1991; Brulé et al., 1992). More generally, the ratio of the four purine bases (adenine, guanine, hypoxanthine, and xanthine) relative to total purine in a food seems influential in affecting SU, especially the impact of hypoxanthine (Kaneko et al., 2014).

Foods and beverages associated with mechanisms affecting urate levels

Consuming dairy foods can decrease the risk of gout and hyperuricemia due to inverse associations with SU (Choi et al., 2004; Li et al., 2018; Zgaga et al., 2012). In one large observational study, low-fat dairy products were inversely associated with incidence of gout (Choi et al., 2004). Dairy's effect has been attributed to the milk proteins casein and lactalbumin (Choi et al., 2005) and to the dairy fractions glycomacropeptide and G600 milk fat extract (Dalbeth et al., 2012). Soy food intake is also negatively associated with the risk of hyperuricemia and gout (Villegas et al., 2012; Li et al., 2018). In contrast, high-purine vegetables are not associated with the risk of hyperuricemia or gout (Choi et al., 2004; Li et al., 2018; Villegas et al., 2012; Zgaga et al., 2012, Jakse et al., 2019). These studies highlight the need for accurate understanding of which food products, including DS with high purine content, increase the risk for gout. Since various mechanisms affect hyperuricemia, restricting all purine-rich foods would unnecessarily eliminate certain foods that confer other health benefits.

Sugar-sweetened beverages are not sources of purines but should be avoided by those wishing to control urate levels because added sugar, especially fructose, elevates SU (Luk & Simkin, 2005; Nelson & Voruganti, 2021) and appears to compete with urate excretion (Maiuolo et al., 2016; Chittoor & Voruganti, 2020).

Alcohol consumption has multiple mechanisms which raise SU (Pillinger & Keenan, 2008). These include increased urate production and increased reabsorption of urate by the kidneys (Todd & Wright, 2020). The purine content of alcoholic beverages is apparently only one of several factors involved. Gout patients are typically advised to limit alcohol to one drink per day for women or two drinks per day for men (Khanna et al., 2012).

Caffeine decreases the concentration of urate by inhibiting xanthine oxidase activity (Chittoor & Voruganti, 2020). Similarly, coffee consumption has shown an inverse association with gout incidence (Choi et al., 2007). Coffee consumption also has an inverse association with hyperuricemia in men but is associated with increased hyperuricemia in women (Li et al., 2018). On the other hand, tea consumption does not appear to be associated with hyperuricemia, urate levels, or gout (Zhang et al., 2017).

High doses of vitamin C (i.e., 400-500 mg/day) have beneficial effects such as increased urinary urate excretion (Azzeh et al., 2017; Berger et al., 1977; Stein et al., 1976) and reduced SU concentration (Huang et al., 2005; Juraschek et al., 2011). In addition, vitamin C is highly associated with reduced risk of gout (Choi et al., 2009).

Vitamin C supplementation at 500 mg/day reduced serum urate and modestly reduced the incidence of new or recurrent gout diagnoses in middle-aged male physicians (Juraschek et al., 2022).

Eating patterns

Individual nutrients and certain foods have been associated with hyperuricemia and gout risk. Since they are consumed as part of a total diet, research on the effect of various eating patterns has presented an opportunity to examine the combination of a number of the micronutrient effects above (Rai et al., 2017). For example, the Dietary Approaches to Stop Hypertension (DASH) diet, which focuses on fruit, vegetables, and low-fat dairy products, is being studied as a dietary intervention pattern for gout. The DASH diet is associated with lower gout risk among men (Rai et al., 2017) and lowered SU (Juraschek et al., 2016; Rai et al., 2017; Belanger et al., 2021). In a recent study, gout patients were instructed to follow the DASH diet along with other guidelines such as avoiding red meat, organ meat, shellfish, and excess alcohol consumption (Juraschek et al., 2021), presumably because those foods and beverages are traditionally considered high dietary sources of purine. In these and other scenarios, data for the purine content of specific foods can be beneficial for making food choices and optimizing established healthy dietary patterns for adults at risk for gout.

Relationship between other factors and SU

Effects on SU can differ according to race and sex. For example, legume intake increased SU among African Americans (AA) compared to White adults while alcohol intake increased SU to the same extent among AA and White adults in the United States (Beydoun et al., 2018). Dairy intake had an inverse effect on SUfor AA women but not White women (Beydoun et al., 2018).

E. Challenges for dietary guidance and research

Estimating total intake of various purines

Exact amounts of individual purines in most foods, especially cooked foods, are not well-established (Gibson et al., 1983; Choi et al., 2004). In addition, the bioavailability of different purines varies considerably in specific foods. For example, studies which supplemented subjects' diets with RNA or DNA showed that RNA influenced urate concentration more than an equivalent amount of DNA (Zollner & Griebsch, 1974). Other dietary studies found that oral doses of adenine and hypoxanthine increased subjects' SU levels while guanine and xanthine had no effect (Clifford et al., 1976).

Predicting the effect of a commonly consumed food or food group on SU levels, although challenging, has been investigated. Researchers determined that higher levels of meat and seafood consumption, but not total protein intake, were linked to higher serum urate levels, while dairy intake was inversely associated with serum urate levels (Choi et al., 2005).

Very few intervention trials have been conducted in recent years to examine how people with hyperuricemia respond to dietary changes; some observational studies are available with self-selected diets. We are not aware of research conducted to establish guidance on intakes of various purines. The American College of Rheumatology rated the certainty of evidence as "low" between limiting purine intake and gout management (FitzGerald et al., 2020) while noting the dose-response relationship between higher

consumption of purines and risk for gout flares (acute episodes of joint pain and swelling) (Zhang et al., 2012). This gap suggests the need for more research.

As a result, current U.S. dietary guidance does not provide recommended intake levels of various or total purines for healthy adults or hyperuricemia patients. In contrast, Japan has set recommendations limiting purine intake to 400 mg/day to prevent hyperuricemia and gout (Kaneko et al., 2020).

Existing resources for patients

In our multiple searches for sources of purine food composition data for dietary guidance to assist patients or clinicians, data are rarely or poorly documented or are very outdated. Websites focusing on gout treatment typically provide only limited total purine values and do not give data on purine bases, nor do they cite their data sources. A table of purine values is provided in a classic food composition reference (Pennington & Spungen, 2012), although there is a fee for accessing these data.

Some guidance sources group foods into nominal scale categories (low, medium, high, very high) or numbered, such as 1-4, as a way of suggesting which foods should be restricted. For best patient guidance, these categories should be based on consistent sampling and assay methodology and should be relevant to the food supply of the country where the patient is residing.

Many patient-facing materials on health websites (e.g., Cleveland Clinic or WebMD) or patient advocacy groups (e.g., the Arthritis Foundation) provide similar recommendations for restricting purines, often focused on less commonly consumed food items (e.g., game meats and organ meats). Many of these blanket recommendations to reduce purine intake leave patients with little recourse, as the purine content of commonly consumed U.S. foods is not well-documented. The absence of a centralized and consistently structured database has also contributed to the proliferation of home-based approaches based on personal anecdotes that have long challenged gout patients seeking evidence-based dietary solutions to prevent flares.

Data for DS guidance

Purines are found in DS as well as foods (Kaneko et al, 2014). Numerous DS on the market claim to contain purine nucleotides. These include yeast and meat extracts, products promoted for increasing energy or losing weight and products containing adenosine, ATP, and GTP. However, some DS that might have purines as a significant component do not specifically list purines in the Supplements Facts panels. These products could pose a health risk to people who must limit their purine intake and are unaware that the product provides purines. An analytical study of purine-containing DS sold in the U.S. is planned. The goals of the study are to quantify purine levels in DS and to identify discrepancies between the actual and labeled purine content. For complete characterization of DS quality, disintegration performance tests of dosage forms will also be conducted.

F. Creation of USDA purine database

Purpose

As previously stated, data for purine content of foods and DS are very limited. Purine data are needed to help address gaps in knowledge (Choi et al., 2004). Therefore, collecting available data as a foundation for developing an expanded publicly available database could be an invaluable resource for scientists and clinicians interested in purines, urate metabolism, and related conditions. The database can function as an

essential source of current data for researchers, health professionals, and other persons striving to monitor purine consumption (USDA & NIH ODS, 2021).

Nutrient data on purine amounts in foods from reliable sources, especially data for potentially high purine contributors, can be useful in managing gout and hyperuricemia incidence. Data can also provide useful insights and inform dietary guidance based on associations between dietary intake and SU levels and can support future research. Thus, an initial database was developed by USDA scientists in collaboration with scientists from NIH and Beth Israel Deaconess Medical Center to: (a) provide existing data for purine bases in foods within a usable format; and (b) identify data gaps using the existing data to develop targeted plans for obtaining analytical values for key sources of purines in selected U.S. foods and DS.

Procedures

1. Data sources

We compiled published data for four purine bases (adenine, guanine, hypoxanthine, and xanthine) in foods and alcoholic beverages reported in fourteen studies conducted in various countries. Data came primarily from Japan; less than 20% of the food items in the database were from North American sources (United States and Canada). The database includes 370 different foods. Table 1 displays 75 foods from North American sources to facilitate inspection of data for foods analyzed domestically, while Table 2 reports 321 foods from other countries to provide a broadened perspective of available published data, thus a total of 396 food listings. Table 3 includes 13 alcoholic beverages from Japan, Austria, Hungary, Romania, and Poland. Food data from countries beyond North America can be applicable in the U.S. due to availability in Asian or other specialty markets. However, differences among species, growing conditions, storage, laboratory methods, and other factors can impact reported purine values and should be considered when referencing data from various sources.

The studies were published between 1976 and 2020 with nearly half of them occurring prior to 1989. Other studies were found but were not included because they reported total purine values but not values for individual bases or disseminated their data only in the German or Japanese languages.

2. Analytical laboratory methodology

Analytical laboratory methods for measuring purine content in the foods and beverages in the database are listed with respective data sources in Table 4. High performance liquid chromatography (HPLC), which has been effective for many years in measuring purine content of foods, was used in all studies except for one, which used capillary zone electrophoresis for analysis of beers.

3. Data evaluation methods

The purine data were evaluated for quality using procedures developed by scientists at USDA's Methods of Analysis and Food Composition Laboratory (MAFCL, formerly the Nutrient Data Laboratory) (Bhagwat et al., 2009). The scientists used a modified version of the USDA Data Quality Evaluation System (DQES) to assign a numeric score to each data source (Holden et al., 2002, 2005). Five categories of documentation were initially evaluated: sampling plan, sample handling, number of samples, analytical method, and analytical quality control. However, scoring of the analytical method could not be accomplished due to lack of standardized evaluation

criteria. Notable characteristics of the studies reporting data used in this purine database (except for additional data published in 2020) are reported in Wu et al., 2019.

4. Reporting protocols

For the final database, values listed as "ND" (not detected) were shown as zero. Units for purine content were converted where necessary for consistency in observing data across studies. Means, standard error of the mean (SEM), and minimum (Min) and maximum (Max) values were reported as milligrams per 100 grams. Data were grouped into typical U.S. food categories for presentation in the database (e.g., beef organ meats, legumes, vegetables) to enable interpretation and for planning future work.

5. Data discussion

As observed in Tables 1 and 2, purine content varied among foods and varied for the same food in different studies. For example, total purine in raw beef cuts in the database ranged from 77 to 123 mg/100g (chuck ribs and round, respectively), while liver had up to 220 mg/100g. Among canned seafood items in the database, clams had 62 mg/100g while anchovies had 321 mg/100g. Furthermore, the overall category of finfish and shellfish ranged from 7.7 to 1,400 mg/100g total purine content.

Variation in purine content may be due to natural differences in foods (such as vegetable cultivars or animal breeds), different sampling plans, sample handling, cooking, laboratory methods, and other factors. Overall, purine values in the database were generally highest in animal-based products (especially some organ meats) and lowest in dairy, eggs, grains, fruits, and most vegetables. Moreover, in most cases products from animal sources (other than dairy and eggs) contained higher amounts of the uricogenic bases hypoxanthine and adenine than other food groups. More specifically, the food category with highest mean hypoxanthine values was the 'soups and sauces' group which was mostly influenced by the dehydration process, and certain fish and poultry species. Mean hypoxanthine was lowest in plant-based foods, dairy, eggs, and sweets. Mean values for adenine were highest in organ meat products, dried yeast, and milt (e.g., chicken and beef liver, pork kidney, cod milt) and lowest in dairy and eggs, fruits, and sweets.

Dark and traditional-type beers had higher adenine and hypoxanthine values than other types of beers and other alcoholic beverages reported, although the highest total purine value among alcoholic beverages was only 13.5 mg/100g (or about 46 mg/12 ounce serving) (Table 3).

The database has several strengths. It provides a basic overview of the content of purine bases in foods covering many different food categories, obtained from an expansive literature search. The data are based on research findings from studies whose published reports met the minimal criteria for inclusion using established data evaluation protocols. Values for 13 alcoholic beverage listings are also included. Limitations include the scarcity of data for U.S. and Canadian foods, and nearly half of all data in the database originated from studies performed 3 decades ago.

G. Planned approach for foods and DS for future data releases

Foods from the U.S. food supply relevant for estimating purine intake will be sampled, with the greatest emphasis on foods with anticipated substantial purine content and for which gaps or conflicting approaches in dietary guidance have been identified. For example, MAFCL plans to expand the purine database to include more meat items, in

parallel with efforts to analyze meats for inclusion in FoodData Central's Foundation Foods.

Information on the food and dietary supplement contents of various methylxanthines may prove a useful adjunct to this purine dataset, as well. Plant origin and processed sources of caffeine, theobromine, and theophylline from their original plant sources (coffee, tea, cocoa, cola nuts, guarana, and yerba mate) as well as foods and supplements derived therefrom could be assayed and included as data fields to allow better estimates of total intake and as effect modifiers in studies of purine metabolism.

Several approaches have been utilized for identifying commonly used DS in the U.S. market that might be high in purine:

1. Literature review
2. Search of the ODS Dietary Supplement Label Database (DSLD) for previously tested DS categories using the DS names and terms related to high purine content that could be found anywhere on labels
3. NHANES search using terms related to high purine content in supplements
4. NHANES search of the terms related to high purine content in the ingredient list variable as well as the blend information list

A recent audit of the DSLD (USDHHS & NIH ODS, 2021) using an advanced search indicated there are 149 products which contain adenosine in the Supplement Facts panel when multiple package sizes are combined; when multiple flavors within brand are combined, there are 71 products.

The DSLD was also searched using the terms describing names or categories of DS with high purine content (Kaneko et al., 2014). A search for these terms found anywhere on DS label returned the following results (of "simple" DSLD search conducted in July 2022):

DNA, RNA -1,548 labels
DNA - 1,532 labels
RNA - 668 labels
Beer yeast- 57,365 labels
Chlorella - 11,432 labels
Royal jelly -972 labels
Spirulina- 3,737 labels.

Appropriate reference materials for foods and DS will be developed in collaboration with a research laboratory. Food and DS samples will be analyzed along with the reference materials at a qualified laboratory using established methods for reversed-phase HPLC and cation exchange HPLC. After rigorously evaluating laboratory results using established criteria, acceptable data will be added to the database and made publicly accessible.

H. Conclusions

The first data release includes purine values for 396 food listings from 20 food groups and 15 alcoholic beverages. These data were derived from fourteen published international studies. Although limited in scope, food descriptions, and quality, these data provide a scientific base for identifying additional U.S. foods for purine analysis and in determining foods of substantial purine content for which expanded sample sizes would be advantageous. This database is dynamic and will be expanded as soon as data from

analyses of U.S. foods become available. Thus, subsequent releases with additional food and DS data are anticipated.

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