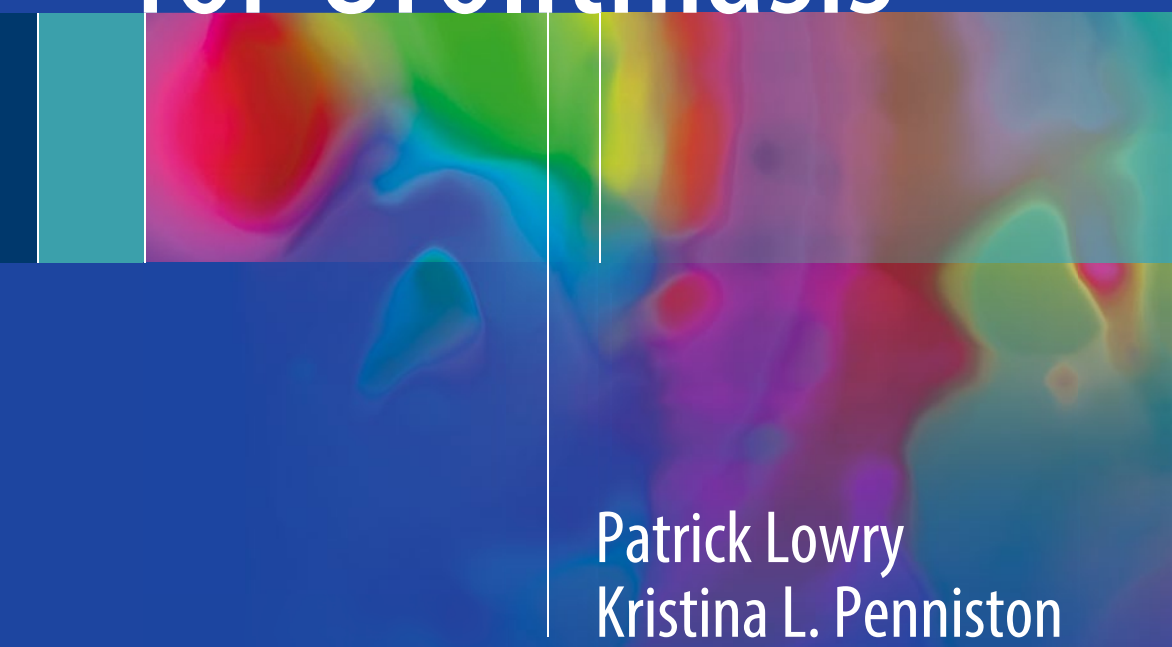
# Nutrition Therapy for Urolithiasis



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1

Cassandra Vanderwall

## Introduction

Hippocrates said, "Let food be thy medicine and medicine be thy food." This statement is the essence of medical nutrition therapy (MNT). MNT is nutritional diagnostic, therapeutic, and counseling services for the purpose of disease management, which are provided by a nutrition professional [1]. While dietary recommendations or clinical practice guidelines offer general healthy dietary strategies, MNT is a recognized and individualized therapeutic approach to treat disease, medical conditions, and associated symptoms with diet. MNT is similar to other therapeutic domains, e.g., physical, occupational, psychological, and speech therapies, which are medically recognized and deployed by trained experts. Food and nutrition professionals, including registered dietitian nutritionists (RDN, also known as registered dietitians), are the purveyors of MNT. For some patients, depending on the patient and his/her medical condition(s), broad recommendations such as the Dietary Guidelines for Americans (developed by the US Departments of Health and Human Services and Agriculture) [2] or those of the American Heart Association [3] may suffice. But when patients need or inquire about diet related to special concerns or risk factors, consultation with a RDN is appropriate. This consult is especially appropriate for patients with multifactorial conditions with variable expression and symptomology between patients.

The educational background of RDNs includes a minimum of (a) a bachelor's degree incorporating approved didactic programming, (b) a dietetic internship consisting of at least 1,200 h of supervised practice with a variety of patient populations, and (c) passage of a national registration exam. Most dietitians go on to receive advanced academic degrees and/or specialized training and certifications in their area

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of expertise, such as board certification as a specialist in renal nutrition or nutrition support. The Academy of Nutrition and Dietetics (AND or the "Academy"), the professional organization for RDNs, and its credentialing agency require that all RDNs be Master's prepared at a minimum; this will take effect in within several years. The Centers for Medicare and Medicaid Services acknowledge that physicians, nurse practitioners, and non-RDN nutrition professionals who meet certain professional requirements can provide MNT services.

The Institute of Medicine (IOM) issued a report in 1999 supporting the utilization of MNT to improve clinical outcomes and healthcare costs associated with older adults with diabetes. The IOM issued recommendations that individualized MNT, provided by a RDN, become a covered Medicare benefit for diabetes and other select conditions [3, 4]. Medicare will thus cover a limited number of hours of MNT for patients with diabetes, kidney disease, and/or those who have had a kidney transplant in the last 3 years [5]. Recently, the U.S. Preventive Services Task Force recommended that physicians refer patients to dietitians for "intensive behavioral counseling" for diet-related chronic disease [6]. The Patient Protection and Affordable Care Act, signed in 2010, requires health plans to cover certain preventive services (including counseling for obesity or to promote a healthy diet) without patient cost [7]. However, there is variable compliance among insurers with this requirement.

## What Is Medical Nutrition Therapy (MNT)?

MNT is a cost-effective treatment for the prevention and management of disease [8–10]. Dietitians thus strongly advocate for the expansion of insurance coverage for MNT for all health conditions that are influenced by diet. Research demonstrates that MNT provided by a dietitian to manage disease yields improvements in clinical outcomes and reductions in costs related to physician time, medication use, and hospital admission for individuals with chronic disease [10]. Multidisciplinary care that includes a dietitian is a cost-effective treatment for chronic kidney disease, for example, resulting in fewer hospitalizations and decreased need for renal replacement therapies, including hemodialysis, peritoneal dialysis, and transplant [11].

While patients may ask their primary care or other physicians for advice about diet, studies have shown that doctors are not always comfortable or confident in advising patients about making dietary changes [12, 13], specifically when it requires the need to individualize recommendations with respect to a patient's comorbid conditions, lifestyle, and other factors. Research confirms that patients perceive RDNs as most knowledgeable about nutrition and its relationship to disease [14]. MNT is a prescriptive treatment that requires an individualized assessment, diagnosis, intervention, and monitoring plan. When this process is performed by a RDN, it is referred to as the "nutrition care process" (NCP). Current evidence supports that MNT provided by a RDN is more cost-effective [3, 4, 8, 9, 11, 15] and elicits more positive outcomes than generic recommendations and general

guidelines [16–18] for patient populations and disease states [19]. MNT is different from nutrition education. Nutrition education is the provision or reinforcement of basic nutrition-related knowledge. MNT is also different from general dietary recommendations, which may be developed for public policy/health purposes or as disease-specific guidelines and provided to anyone. While there is no governance over who can provide nutrition education or general dietary recommendations, legislation does exist to protect the delivery of MNT. For this reason, and because a RDN may not be available in all clinical areas, it is helpful to distinguish patients for whom dietary recommendations or nutrition education may be sufficient from those who need MNT.

## What Is the Nutrition Care Process (NCP)?

Because of the strong correlation between diet and health as well as gene expression and function, MNT provided by a RDN is a key component of medical management for many chronic and other conditions. Whether aimed at primary, secondary, or tertiary prevention, there is a role for MNT in many medical conditions and disease processes. NCP is the framework that guides the provision of MNT [1, 20]. The NCP has four steps, each of which will be described in detail: (1) nutrition assessment, (2) nutrition diagnosis, (3) nutrition intervention, and (4) nutrition monitoring and evaluation (Fig. 1.1). The NCP was originally developed by a workgroup of the Academy to standardize the care process related to MNT in order to provide a framework for outcomes research and also to standardize clinical care and management. Dietitians are encouraged to follow the NCP and its parallel standardized language, the International Dietetic and Nutrition Terminology (IDNT) [1]. The standardized language allows nutrition practitioners to document the impact of MNT in a clear and consistent manner across medical conditions and institutions. IDNT articulates all four steps of the NCP – from assessment to monitoring and evaluation – with codes similar to international classification of disease codes.

## Nutrition Assessment

Nutrition assessment is the collection, integration, and analysis of nutrition-related data in order to craft a nutrition diagnosis that calls for an individualized intervention. It is the first step of the NCP and involves collecting, verifying, interpreting, and documenting key data necessary to identify nutrition-related problems [20]. The NCP has five assessment domains: (1) food- and nutrition-related history; (2) anthropometric measurements; (3) biochemical data, medical tests, and procedures; (4) nutrition-focused physical findings; and (5) client history. These data are usually available in any healthcare setting, and sources include the patient and family interview; food, beverage, medication, and activity logs; medical record; referring provider(s); and nutrition-related physical assessment.

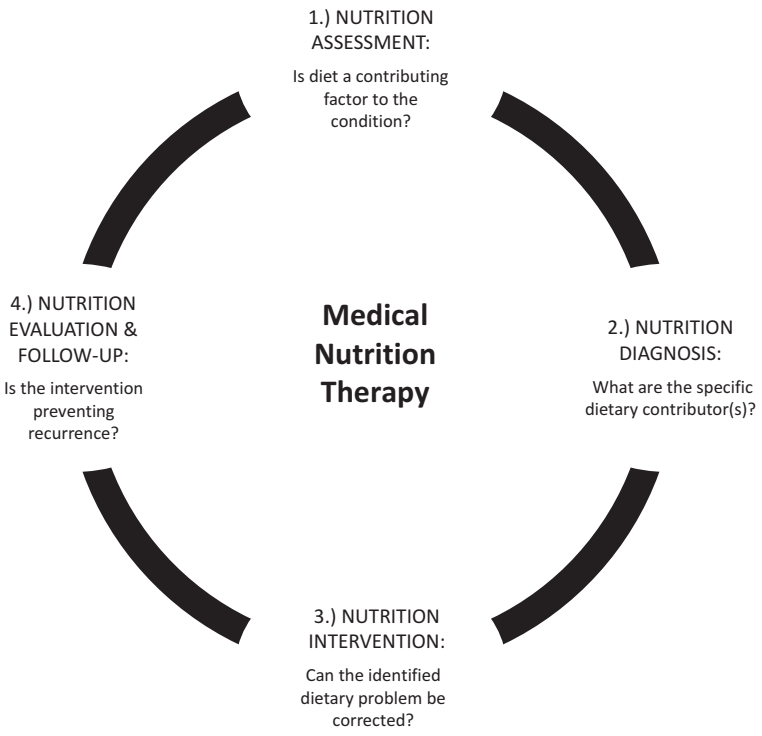


**Fig. 1.1** The nutrition care process involved in the practice of medical nutrition therapy by a registered dietitian nutritionist. The central question to be answered within each stage of the process is shown

The patient interview may be the best source of information related to the patient's food and nutrition history. The RDN assesses the patient's past and present food intake, factors that influence food intake (such as food security, access to cooking and food storage facilities, transportation, dentition, and cultural and religious observances), and food and nutrition knowledge. The RDN may collect dietary data from the patient via detailed, multiple-day diet records, a 24-h dietary recall (asking the patient to recall everything he/she ate or drank in the last 24 h), a brief diet history (querying about usual dietary patterns, food frequency, and food propensity), or a food screener or food frequency questionnaire (FFQ). While there are an abundance of validated FFQs available for use, their accuracy in assessing the intake of specific nutrients and dietary habits has been questioned [21]. FFQs and food screeners may be appropriate in identifying patients whose medical and nutritional needs are more complex and who would benefit from the involvement of a RDN to obtain and interpret their dietary intake and nutritional risk factors.

In addition to dietary assessment, the patient's past medical history, surgical history, social history, and readiness to change are assessed.

> Dietary assessment in patients with kidney stones, depending on the type of stone(s) he/she forms and on 24-h and other biological risk factors, might focus particularly on nutrients and other food-derived components that contribute to high urinary excretion of calcium and oxalate or on low urinary excretion of citrate, magnesium, and volume.

In addition to the patient's report, other critical data can be acquired from the patient's medical record and from the referring provider. Pertinent information from these sources may include the following: anthropometric data, past and present medications, biochemical data, medical test results, relevant procedures, and documentation from past providers related to the present medical diagnosis. With patient permission, a nutrition-related physical assessment can reveal signs and symptoms of deficiency or malnutrition [22]. By reviewing all of these sources, the patient's dietary intake and nutritional status can be adequately assessed.

## Nutrition Diagnosis

The second step of the NCP is the nutrition diagnosis: the identification and labeling of a nutrition-related problem that can be treated independently. The purpose of the nutrition diagnosis is to link the findings from diet assessment with the manifestations or exacerbation of a disease or medical condition. A nutrition diagnosis is not a medical diagnosis. A medical diagnosis, usually made by a MD or other advanced practice medical provider, identifies a diseased organ or body system or an aberrant metabolic process that can be treated and/or prevented. A medical diagnosis does not change until the disease has resolved. A nutrition diagnosis identifies an aberrant dietary practice or habit that is contributory to a patient's medical diagnosis. A nutrition diagnosis can change over time as the patient and/or his/her risk factors for disease progression or recurrence changes. Confirming the appropriate nutrition diagnosis is critical because it is the pathway to appropriate nutrition intervention and evaluation.

As earlier noted, the IDNT has terms for stating nutrition diagnoses related to food and/or nutrient intake, clinical diagnoses, and behavioral/environmental issues. The approved terminology supports identification of the three components of the nutrition diagnosis: problem, etiology, and signs and symptoms (PES) [20, 23, 24]. The "problem" is the diagnostic label that describes the patient's response to a nutrition-related practice or habit. The "etiology" is the cause or related factors contributing to the problem. An example of the wedding of the problem to a nutrition-related etiology is "overweight/obesity related to excessive energy intake." The "signs and symptoms" are the results or defining characteristics of the problem.

These are objective data that are observed by the clinician. Examples may include a patient's altered laboratory values, patient-reported information, and medical diagnosis. Upon diagnosing the problem, etiology, and signs and symptoms, the RDN can craft the PES statement. The final PES statement from the example above would be "Overweight/obesity related to excessive energy intake as evidenced by patient's 24-hour dietary recall and BMI of 42.0." The nutrition diagnosis is a pivotal step in the nutrition care process and guides the clinician to the appropriate intervention.

An example of a PES statement (nutrition diagnosis) related to the risk for kidney stone recurrence might be "High oxalate absorption related to low calcium intake as evidenced by findings from dietary assessment of the patient's diet and high urinary oxalate excretion."

## Nutrition Intervention

An intervention is a purposeful series of events aimed at addressing a problem. Nutrition interventions are designed with the primary intent of improving or correcting the problem declared in the diagnostic PES statement. This third step of the NCP includes the selection, planning, and implementation of specific actions to address the problem or nutrition diagnosis. The nutrition intervention typically includes strategies by which patients may achieve the goals of the intervention and, in that sense, provides the foundation for measuring and evaluating nutrition-related outcomes over time. The patient and his/her family are always at the center of successful nutrition interventions. In designing and implementing the nutrition intervention, the RDN collaborates with the patient, the patient's family, and/or other members of the healthcare team as needed to ameliorate the nutrition-related problem or signs and symptoms that result from the problem.

A common nutrition intervention in patients with stones is to increase fruit and vegetable intake. This might especially be relevant for patients with suboptimal urinary citrate excretion as fruits and vegetables provide bicarbonate precursors that can promote higher urinary citrate excretion. It could also be part of the intervention to reduce oxalate absorption and urinary excretion as fruits and vegetables provide substrate (prebiotics) for the growth and colonization of gastrointestinal tract bacteria favoring oxalate degradation.

The nutrition intervention includes the identification and implementation of the appropriate therapeutic approach. The MNT appropriate for the primary problem, or diagnosis, is determined by using evidence-based nutrition guidelines, relevant research, and current clinical guidelines. The Academy created and manages an Evidence Analysis Library (EAL) [10] and three nutrition care manuals, each

containing the most up-to-date information regarding nutrition-related diseases and conditions. The Academy's EAL is available for use at www.andeal.org. The nutrition care manuals are updated regularly and contain content for normal nutrition as well as for acute and chronic diseases states for adult and pediatric populations. The third nutrition care manual is specific to sports nutrition.

The implementation of the intervention may include patient education materials (nutrition education), strategies and ideas for how to make the recommended changes, and tools for implementing and complying with the intervention. The development of the intervention is grounded in behavior change theory (nutrition counseling) as deemed appropriate for each patient [25–30]. It is thus highly individualized per patient factors, such as motivation and enthusiasm to change, educational needs, and learning style. Productive nutrition education delivery is patient and family centered as the success of the intervention hinges on the involvement of the patient in his/her own care [25–28]. In an effort to enhance the patient's involvement or compliance with the intervention, two counseling approaches used by RDNs are cognitive behavioral therapy and motivational interviewing. Cognitive behavioral therapy is counseling that is focused on identifying the mental and emotional relationships between thoughts, feelings, and behaviors that are related to a specific dietary practice or habit [29, 30]. Motivational interviewing is a nonjudgmental and non-confrontational counseling approach that is aimed at increasing patients' awareness of the necessity for specific changes while guiding them through the stages of change [30].

For the intervention described earlier – increasing fruit and vegetable intake – patient education materials might include information about how to prepare and store fresh fruits and vegetables. Tools to aid in the implementation might include schedules or plans for including more fruits and vegetables within the day.

Documentation of the nutrition intervention – its effects on the patient as well as on his/her disease process – is an ongoing process, especially if the patient is seen in follow-up on a regular or serial basis and if modifications to the initial MNT are needed. Documentation of MNT includes date and time of intervention; treatment goals, patient-stated goals, and expected outcomes; patient receptivity and readiness to change; resources utilized; and recommended interventions and/or topics of education for further follow-up.

## Nutrition Monitoring and Evaluation

The results of the nutrition intervention on the targeted problem(s) must be evaluated for its effectiveness. If the intervention was ineffective in managing the problem intended, the reasons for its failure should be evaluated and corrected. Thus, the

fourth and final step of the nutrition care process is monitoring and evaluation. Monitoring is the review and measurement of the patient's nutritional status and response to MNT over time, whereas evaluation is the comparison of present findings to previous. This step has three interrelated processes: (1) monitor progress (monitoring), (2) measure outcomes (reassessment), and (3) evaluate outcomes (evaluation) [23, 24].

Key sources of data for monitoring and evaluation are similar to that of nutrition assessment and include patient and family interview; food, beverage, medication, and activity logs (or diet assessment by other means); medical record and notes about disease process; documentation from follow-up visits; and nutrition-related physical assessment. Measureable outcomes should be directly related to the patient's diagnosis and goals for MNT. Examples may be changes in the patient's nutrition or health status, increases in food-related knowledge, or cost-related outcomes such as medication changes, decreased length of stay in a hospital, or fewer hospitalizations or procedures.

Based on the findings of this final step in the nutrition care process, the RDN will determine the patient's need for continuing care. Depending on the patient and his/her progress, MNT and nutritional counseling may continue to be provided. Alternatively, the patient may be transitioned to another setting or healthcare provider or discharged from MNT altogether.

Documentation of the monitoring and evaluation step is critical not only to communicate the effect of MNT but also to a clinical nutrition program's quality control and quality improvement initiatives (also known as outcomes management system). As the provision of healthcare is increasingly driven by the need to demonstrate "best practices" and comparative effectiveness, the outcomes management system of a clinical nutrition program provides a means to evaluate the effectiveness of the entire nutritional care process within an institution, with specific attention paid to measurable outcomes and the processes by which they were achieved [20].

Evaluation of the nutrition intervention for patients with stones may reveal the need for modification. For example, a patient whose high urinary oxalate excretion is not corrected by reducing intake of high-oxalate foods may require additional – or a completely alternative – approach. This could include intake of calcium-containing foods or beverages with meals to reduce oxalate absorption and/or higher intake of fermented foods (probiotics) to enhance oxalate degradation by gastrointestinal tract bacteria.

## How Can I Collaborate with a Dietitian?

Collaboration involves the cooperation of parties to produce an outcome. Healthcare collaboration includes the exchange of ideas, strategies, and goals while also distributing responsibilities within the provider team to advance the health and well-being of a patient. In conditions with dietary modulators, RDNs can provide expertise

about physiology and nutritional biochemistry related to the disease process and about dietary changes that could address it. The National Kidney Disease Education Program (NKDEP) supports physician collaboration with a RDN and the utilization of MNT to improve the prevention and management of kidney disease. While physicians initiate the discussion of the need for therapeutic dietary changes, a RDN provides the MNT, which results in cost-savings, enhanced physician efficiency, and positive outcomes. Medicare and most health insurance companies with a physician referral cover MNT services for diabetes and kidney disease. Eligible patients can receive up to 3 h of MNT in the first year and 2 h in the following years. NKDEP referral forms can be found at http://nkdep.nih.gov/resources/kidney-diet-referral-form-mnt-508.pdf. An example of a referral form that could be used to refer patients with stones to a RDN is provided (Fig. 1.2).

In many cases, insurers will allow for MNT for other services, including kidney stones, and this may be especially true when RDNs are integrated into a multidisciplinary care team or are otherwise made available to patients at the time of their clinic appointment with the physician. Currently, many RDNs are joining multidisciplinary teams in patient-centered medical homes and primary care offices [31–33]. If a RDN is not available on a team, one can usually be accessed within the physician's hospital or healthcare system. All hospitals and long-term care facilities, for example, have RDNs; their availability to specific physicians, clinics, or patient populations can usually be requested of the facility's clinical nutrition manager. Most health maintenance organizations and outpatient clinics now make RDNs available for patient appointments that may be scheduled either by patients themselves or by the referring providers. Additionally, the Academy provides a national directory of RDNs, and this may be a resource for some.

Urologists wanting to refer patients to a RDN for dietary intervention to reduce stone recurrence risk might first look for one available within the hospital or clinic in which they see patients. If one is not available, then a referral to an outside RDN, perhaps in a private practice setting or within the patient's healthcare maintenance organization, might be in order. The referral might (a) provide a brief history of the patient's stone-related history and relevant risk parameters, (b) request a dietary assessment to identify any factors that contribute to the observed risk factors, (c) request the design of an intervention to address the contributing dietary factor(s), and (d) provide a way for the RDN to communicate his/her findings to the referring physician.

## Conclusion

The MNT provided by RDNs can identify nutrition-related problems that may be prevented or treated independently via nutrition intervention. MNT involves a four-step process that includes assessment, diagnosis, intervention, and monitoring and

**SAVE THIS FORM TO YOUR COMPUTER BEFORE ENTERING DATA. Complete as much of the form as you are able.** Also, to comply with the Health Insurance Portability and Accountability Act of 2002, please protect the personal health information contained in the completed form.

## KIDNEY STONE COUNSELING REFERRAL FORM – FOR MEDICAL NUTRITION THERAPY

**NAME OF PATIENT** _____ **DATE OF BIRTH** _____ **MEDICAL RECORD NUMBER** *(IF APPLICABLE)* _____

**LAST APPOINTMENT DATE** _____ **WEIGHT** _____ **HEIGHT** _____ **DOES THE PATIENT CURRENTLY HAVE STONES?** _____

**DID YOU PRESCRIBE ANY MEDICATIONS TO PREVENT STONES? - LIST**

**DID YOU RECOMMEND ANY DIETARY CHANGES TO PREVENT STONES? - LIST**

**REASON FOR YOUR REFERRAL:** ***Medical nutrition therapy for prevention of kidney stone recurrence***. Please detail any specific concerns or questions:

**NUMBER OF PRIOR STONE EVENTS** _____ **YEAR OF (OR AGE AT) FIRST STONE EVENT** _____ **FAMILY HISTORY FOR STONES** *(LIST RELATIONS)* _____

**PRIOR SURGERIES FOR STONES, IF ANY, AND YEAR(S)** _____ **PRIOR PASSAGES OF STONES, IF ANY, AND YEAR(S)** _____

**PRIOR STONE COMPOSITION RESULTS** *(LIST PERCENTAGE(S) OF EACH COMPONENT & YEAR OF ANALYSIS, IF AVAILABLE)*

CaOx monohydrate (whewellite):_____
CaOx dihydrate (weddellite):_____
CaPhos carbonate (carbonate apatite):_____
Calcium hydroxyl phosphate (hydroxyapatite):_____
CaPhos dihydrate (brushite): _____
Cystine: _____
Tricalcium phosphate (whitlockite):_____
Uric acid (urate):_____
Sodium urate monohydrate):_____
Ammonium urate:_____
Silica:_____
Xanthine:_____

**24-H URINE RESULTS** *(FOR MOST RECENT ANALYSES; GIVE DATES AND AMOUNTS OF EACH COMPONENT)*

**Date 1:** _____ Ca (mg) _____ Ox (mg) _____ Cit (mg) _____ Uric acid (mg) _____ Phos (mg) _____ Vol (L) _____ pH _____
Mg (mg) _____ $Na^+$ (mEq) _____ $K^+$ (mEq) _____ $SO_4$ (mmol) _____ $NH_4$ (mmol) _____ UUN (g) _____ Creatinine (mg) _____

**Date 2:** _____ Ca (mg) _____ Ox (mg) _____ Cit (mg) _____ Uric acid (mg) _____ Phos (mg) _____ Vol (L) _____ pH _____
Mg (mg) _____ $Na^+$ (mEq) _____ $K^+$ (mEq) _____ $SO_4$ (mmol) _____ $NH_4$ (mmol) _____ UUN (g) _____ Creatinine (mg) _____

**Date 3:** _____ Ca (mg) _____ Ox (mg) _____ Cit (mg) _____ Uric acid (mg) _____ Phos (mg) _____ Vol (L) _____ pH _____
Mg (mg) _____ $Na^+$ (mEq) _____ $K^+$ (mEq) _____ $SO_4$ (mmol) _____ $NH_4$ (mmol) _____ UUN (g) _____ Creatinine (mg) _____

**LIST PATIENT'S CURRENT MEDICATIONS**: _____

**LIST COMORBIDITIES, MEDICAL CONCERNS**: _____

**REFERRING PROVIDER** _____ **NPI #** _____

**SIGNATURE** _____ **DATE** _____

**PHONE** _____ **FAX** _____ **EMAIL** _____

**Fig. 1.2** NIDDK's referral form for dietary counseling or medical nutrition therapy

evaluation of a patient's nutrition-related disease or condition. By utilizing the IDNT, the standardized language created by the Academy, the professional organization for dietitians, and tools within a clinical nutrition program's outcomes management system, RDNs can provide, measure, and evaluate evidence-based nutrition care and thus significantly contribute to patients' health and well-being.

**SAVE THIS FORM TO YOUR COMPUTER BEFORE ENTERING DATA. Complete as much of the form as you are able.** Also, to comply with the Health Insurance Portability and Accountability Act of 2002, please protect the personal health information contained in the completed form.

## RATIONALE FOR DATA INCLUSION

The following information explains why it is important to include data for the referral to a Registered Dietitian Nutritionist for medical nutrition therapy. While you may not be able to provide all the information requested, any data you are able to provide will be useful.

| | |
|---|---|
| REASON FOR REFERRAL TO DIETITIAN FOR MEDICAL NUTRITION THERAPY | Can list specific concerns, underlying diseases or conditions that are thought to contribute to stone formation, information about length and/or aggressiveness of patient's stone history, etc. |
| NEW Rx PRESCRIPTIONS | Important for interpreting results of 24-h urine collections and other parameters from before any new medications were being used by the patient |
| NEW DIETARY CHANGES | Important for distinguishing between prior dietary habits (and over-the-counter supplement use) and those only recently implemented. Also important when evaluating patients' knowledge and understanding of impact of diet on stones. |
| STONE EVENTS & FAMILY HISTORY | The number of prior stone events, surgeries, and existence of family medical history related to stones can help to assess severity and aggressiveness of stone disease and may inform nutritional prioritization. |
| STONE COMPOSITION | If available, stone composition is important in guiding the prioritization of medical nutrition therapy for stone prevention. |
| 24-HOUR URINE RESULTS | Provides important data to assess risk and points the way for specific lines of investigation during diet assessment. The date of the collection reveals its proximity to prior stone event(s) and to initiation of any new therapies. The 24-h urine creatinine measure is important in assessing accurateness of the time period during which the urine was collected. |
| CURRENT MEDICATIONS | Certain medications - such as antibiotics and carbonic anhydrase inhibitors - can promote stone formation. Dietary strategies to compensate for these effects and for others can be implemented. Other medications have interactions with dietary components and are thus crucial in assessing nutritional status as well as effects on stone promoters and inhibitors. |
| COMORBIDITIES | Important to assess contributing or co-mingling factors that affect stone formation and growth. Also important for integrating dietary recommendations with those received and in place for other conditions. |
| ADDITIONAL INFORMATION & COMPLICATING FACTORS | Certain laboratory measures may be useful, such as vitamin D status, parathyroid hormone, and serum calcium, potassium, and phosphorus. Other complicating factors, such as prior bowel or bariatric surgery, short bowel, or neurogenic bladder, are also important to note as they may have implications for the nutrition therapy regimen. |

For more information about DIET AND STONES, visit the AMERICAN UROLOGICAL ASSOCIATION (AUA) website at: **https://www.auanet.org/education/guidelines/management-kidney-stones.cfm**. There you may read an abstract of the guidelines, view the individual guideline statements, and download the unabridged version of the guideline.

Also refer to the AUA PATIENT GUIDE TO KIDNEY STONES. This may be downloaded and provided to patients. Visit **http://www.urologyhealth.org/educational-materials/kidney-stones-a-patient-guide**. Additional stone materials are available for download at **http://www.urologyhealth.org/educational-materials?filters=769**. These additional materials include the following factsheets: "Diagnosing and Treating Kidney Stones," "Kidney Stones-What You Should Know," and "Preventing Kidney Stones."

Registered dietitian nutritionists may also wish to review the chapter on diet and kidney stones in the Nutrition Care Manual of the ACADEMY OF NUTRITION AND DIETETICS. Patient educational materials are also available there.

**Fig. 1.2** (continued)

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# Health-Related Quality of Life and Urolithiasis

2

Cynthia Sharadin and Patrick Lowry

Symptomatic urinary stone disease mandates treatment to help patients. Stone-free status has been the principle measure of success to determine how well stone formers have been treated. Although stone elimination remains paramount, success outcomes, as in other disease processes, will begin to include the patient's perception of treatment and hopeful prevention of further disease. Health-related quality of life (HRQoL) addresses more than simple assessments of desired endpoints, such as stone-free status, or physical symptoms, such as pain. Measuring HRQOL includes assessing domains related to physical, mental, emotional, and social functioning in order to evaluate the impact health status has on patient perception of quality of life.

## Overview

### History

Urinary calculi have plagued humans since early civilization. Uncovered mummies have been found with retained bladder stones from over 4,500 years ago. Written accounts from between 3000 and 1500 BC describe symptoms and give treatment recommendations for stones. While surgery, via perineal lithotomy, was the final alternative for eradication, even then, dietary recommendations were made to preclude these bothersome stones [1].

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## Epidemiology

Urinary stone disease is a chronic condition which results in extremely painful episodes that are responsible for a multibillion-dollar financial burden in the United States alone [2, 3]. Most recent calculations of NHANES data in 2012 estimates an 8.8% prevalence of stones in the United States, with males being more affected than females (10.6% and 7.1%, respectively) [4]. Incidence rates have been reported between 10% and 15% which is comparable with other developed countries [5, 6]. The prevalence of urolithiasis has increased in the last several decades and is projected to continue its uphill climb as the risk factors for stones also increase in prevalence [7, 8].

Those at increased risk for urinary calculi include the male gender, those living in warmer climates, the obese, those with a family history, and the working, social age groups (20–60 years of age) [7]. Without preventative treatment, the recurrence rate is 50% at 5 years, 50–60% at 10, and up to 75% at 20 years [2, 6, 8]. With the help of pharmacotherapy, dietary changes, or both, the risk of stone recurrence rates can be decreased [9, 10].

## General

The formation of urinary calculi is a condition that depends on the tipping of a delicate balance of biologic ions in saturation, leading to a crystallization and ultimately stone formation at the filtration level. Stone formation has been associated with obesity, GI pathology, dietary patterns, and certain pharmacotherapies [7, 11, 12]. There are many solute concentrations which influence stone development, including calcium, phosphate, oxalate, uric acid, citrate, magnesium, sulfate, and other proteins and macromolecules [13]. While calcium is the most common stone component, many different stone types exist that affect the urinary tract [2, 14]. Various etiologies of stone formation require different approaches for treatment and prevention.

## Management

As our knowledge of these stones has progressed, management has evolved to become two-part; treatment of acute stones and prevention of the secondary stone event.

Acute management consists of surgical intervention and medical expulsive therapy (MET), the two current methods which strive to resolve the episode of renal colic and bring HRQoL back to baseline.

Surgical management has been evolving since the first documented renal extraction in 1550, when 18 stones were drained through the opening of a lumbar abscess [14]. Modern techniques are well known and include shockwave lithotripsy (SWL), ureteroscopy (URS), or percutaneous nephrolithotomy (PNL)

[15]. Rarely, unique or extreme circumstances may require open or laparoscopic procedures for stone removal. Surgery brings stone-free rates that range from 68% to 100%, with PNL (the more invasive of modern techniques) having the highest rate of success.

Although surgical intervention resolves the patient symptoms, complications may occur. Infectious complications include UTI, sepsis, peritonitis, and perinephric abscess [16]. Other complications of surgery, in addition to the anesthesia risk, include major hemorrhage, steinstrasse, ureteral perforation and injury, stricture, and the need for further procedures [15–17]. Additionally, postoperative ureteral stents may be poorly tolerated, preventing patients from returning to usual activities, including their jobs.

In appropriate patients, MET has the potential to spare patients from the morbidity associated with a surgical procedure. MET started making strides in the early 1990s with calcium channel blockers and alpha-adrenergic blockers taking the spotlight, with supplemental NSAIDs and steroids providing marginal benefit [10, 17, 18]. MET stone passage rates see an absolute increase between 9% and 29% with alpha-adrenergic blockers as the only statistically significant therapy. Side effects that are commonly seen with MET are generally mild, including orthostatic reactions, nasal congestion, and ejaculatory disturbances [10]. Unsuccessful MET, however, subjects patients to both the trial of passage and the surgery and the HRQoL impact from both approaches.

While a stone-free state is the goal of therapy in acute stone events, surgery and expulsion do not address the underlying cause of the stone formation. Therefore, identification of risk factors and preventative management are the next steps in therapy. Prevention by pharmacotherapy has been studied since the early 1980s and was neglected for a time when advances in SWL and URS lasers were burgeoning [9].

The variety of stones and variability of their etiologies necessitate a variety of therapies to be utilized in prevention. The most commonly utilized drug classes include thiazide diuretics, alkali citrates, xanthine oxidase inhibitors, and chelating agents [10]. Though not all have proven statistically significant, they have all been shown to provide some sort of reduction in stone recurrence. The side effects of these drugs range from minor rashes or GI upset to more major effects, such as thrombophlebitis or leukopenia [10, 19].

Dietary and nutritional changes also play a key role to reduce stone recurrence. While other chapters in this book go into further detail on nutritional approaches, basic principles include increased intake of fluid, reasonable intake of ion-containing products, and, if necessary, restriction of purine-rich foods [10]. Adhering to a healthy diet and maintaining an appropriate weight are also beneficial since obesity is a risk factor for stone formation [20]. These recommendations have shown to have an overall benefit of stone prevention, especially in the population with mild-moderate metabolic abnormalities [21]. While there have been less than a handful of adverse events reported in trials, dietary intervention comes without any well-documented or observed side effects [22].

## Health-Related Quality of Life

Am I able to carry on with my essential responsibilities? Am I being hindered from doing the things I love due to pain? Do I have a normal amount of energy? Am I happy with my life?

Quality of life (QoL) is a very personal and individual interpretation of, what most can appreciate to be known as, "effective" life. While calculating and exacting something so subjective seems, at times, inconceivable, QoL has taken a front seat and effective role in our healthcare system [23, 24]. It promotes patient-centered care through consideration of medical outcomes along with the psychosocial implications from disease and its therapies. When evaluating successful outcomes, these patient-reported subjective perceptions provide a different point of view than the physician's traditional objective endpoints for success.

## History

The concept to formally measure "life satisfaction" began in the mid-twentieth century [25]. Most of the initial tools/surveys were single dimension scales, which were disputably only applicable to certain population groups. They addressed general themes such as zest and apathy. In the 1980s, Deiner et al. developed a five-question scale that exhibited potential for both favorable psychometric properties and the ability to be applied to the clinical setting.

As sophistication of disease study and healthcare advanced, health status amended to also include the measure of QoL in patients. The term *health-related quality of life* (HRQoL) emerged to help identify the impact of disease, or its treatment, on patients [26]. The HRQoL concept encompasses life duration, impairments, individual perceptions, and social circumstances. The early 1990s brought SF-36, a relatively brief survey that would prove valid, reliable, and a springboard for many modern HRQoL surveys [24, 27]. The SF-36 survey displayed utility for all different populations, spanning all disease types. This survey like many others correlates a lower score with a lower HRQoL.

The desire for disease-specific surveys was encouraged when unique QoL profiles were noted among different chronic diseases [23, 26]. The subtle nuances of disease-specific tools could provide a better understanding of treatment responses. And it was postulated that if they were properly formed and used, predictions of populations and their prognoses might be possible [5, 26].

## Urology in HRQoL

HRQoL has been incorporated into the urologic community; however much of its earlier attention was focused on prostatic disease and malignancies [28, 29]. While those topics expanded concurrently with the blossom of all HRQoL topics, nephrolithiasis remained mostly unexplored [5, 23, 30]. At the turn of the millennia, there

were still only a handful of studies addressing the HRQoL in nephrolithiasis patients, and they only focused on HRQoL comparisons between different surgical preferences [31–33].

Only in the last decade have there been strides to understand HRQoL in recurrent urolithiasis patients. Most of those studies have utilized SF-36 survey. In 2010, in a study designed to assess the reading level of questionnaires in urology, Bergman concluded that, while stones remained one of the most financially burdensome urologic diseases, there were no disease-specific instruments in existence [34].

Donnally et al. conducted a longitudinal study in 2011 to assess the HRQoL over time in stone formers [35]. All patients completed two separate SF-36 surveys with an average 18-month interval. Comparing the scores of the first and second forms, they found no difference in HRQoL over time, even in those patients who had a new stone event within the interval period. This study, and the lack of its ability to find a difference between the groups compared, highlighted how important the creation of a stone-specific instrument would be. So, while SF-36 had utility in assessing HRQoL in a variety of patients, there remained a need for a stone-specific instrument.

In 2013, Penniston and Nakada revealed the development of the Wisconsin Stone-QoL instrument [36, 37]. This 28-question survey, the WiSQoL, demonstrated the ability to distinguish survey responses between stone formers, both with and without active stones, as well as distinguish stone formers from healthy non-stone-forming individuals.

## HRQoL in Stone Formers

It is well known that active stone patients commonly present with nausea, vomiting, cramping, hematuria, and/or dysuria in addition to the renal colic pain [11]. This pain can be very debilitating and commonly results in emergency room visits. Heavier prescription analgesics are frequently prescribed for these patients with refractory pain.

In addition to the physical symptoms that these patients endure, they also report sleep disturbances, feelings of isolation, low mood, and problems with intimacy [36, 37]. They bear the obligatory accommodations that come with having kidney stones that includes missing work and social/family time. Most unfortunate is that in between events, stone formers will commonly be, in some part, consumed by anxiety and worry about when their next stone event will be.

The HRQoL in stone formers has been consistently poor when compared to the general public [5, 36, 39, 40]. Because of the novelty of WiSQoL, most formal investigations have measured HRQoL with SF-36 survey.

Penniston et al. conducted a cross-sectional study in 2007 to characterize the HRQoL of stone formers at their institution [5]. They employed the use of SF-36 survey for these patients and compared them to US norms. They found that the overall HRQoL of stone formers was less than US norms, with statistically significant differences in the domains of general health and bodily pain. They also observed

that females reported greater HRQoL detriment when compared to their male counterparts, specifically in physical functioning, general health, and vitality.

Bensalah et al. conducted a similar study with the SF-36 survey comparing stone patients to the general American population [41]. They determined that stone formers had significantly lower physical composite scores along with general health, emotional role, and social functioning. In assessing predictors of QoL, they found that BMI was a strong predictor of lower QoL. Additionally, while the number of stone events did not predict lower QoL, they did observe that the number of surgical procedures negatively impacted both mental and physical components of HRQoL.

Bryant et al. produced a study very similar to the two mentioned above, where they found stone formers had significantly lower scores in six out of eight domains when compared to the average American population [42].

The same year that Penniston et al. defined HRQoL differences between male and female stone formers, Diniz conducted a case-control study investigating the HRQoL of stone formers with recurrent renal colic pain to control patients from an outside outpatient center without associated disease [39]. With the use of the SF-36 form, they determined the HRQoL of stone patients to be worse than the control group and that the number of renal colic pain episodes correlated with worse impact on both functional capacity and vitality [39].

Several studies found the HRQoL in stone formers to be even lower in stone-forming patients with comorbidities that increase stone risk (diabetes type 2, obesity) as well as other comorbidities (hypertension, depression, musculoskeletal complaints) [5, 41].

While there are some variances between studies, it can be safely said that HRQoL is overall worse in stone formers (without active stones) when compared to non-stone-forming patients. While there are a few studies outside the United States that show comparable HRQoL between the two groups [33, 38], a majority of studies found HRQoL of stone formers to be worse in all or most of the eight domains of the SF-36 survey [5, 39, 41, 43]. Table 2.1 lists those domains.

HRQoL has been shown to be decreased even in asymptomatic stone-forming patients. Penniston et al. evaluated a cohort of patients who completed the WiSQoL at a time they were symptom-free [48]. Patients with stones, even when

**Table 2.1** The MOS 36-item short-form health survey (Ware, et al. [24])

| SF-36 QoL domains |
|---|
| Physical functioning |
| Role limitations |
| Bodily pain |
| Social functioning |
| General mental health |
| Role limitations (due to emotional problems) |
| Vitality |
| General health perceptions |

symptom-free, had a lower WiSQoL score compared to a stone-free cohort. Interestingly, even stone patients who were unaware that they had current stones displayed a decreased WiSQoL score compared to those without stones.

## QoL Between Different Treatment Options

We have discussed the different treatment options for urinary calculi. While there are a few number of studies addressing the HRQoL in different surgical options or in MET, there are even less investigations that address the HRQoL comparing surgical vs. pharmacotherapy vs. dietary intervention of urinary calculi.

Studies comparing HRQoL in surgical options have found conflicting conclusions. While some studies show favorable outcomes for SWL [33, 44], others have found the HRQoL between SWL and PNL to be comparable [31, 32]. Additionally, while there has been SWL popularity in some studies [33, 45], it has been concluded that HRQoL is negatively affected by those patient with residual fragments [43]. And though the HRQoL is largely influenced by the size of those fragments, it is still important to bear in mind their undesirable impact.

Staios et al. prospectively evaluated 22 patients undergoing PNL [46]. They were administered SF-36 before the procedure and again 6 weeks after PNL. While there was an overall improvement of HRQoL, only two of the domains saw statistically significant difference. They concluded that, despite a high stone-free rate (87%), less than half of the patients were found to have benefited subjectively from PNL [46].

Kuo et al. surveyed a group of stone formers to compare surgical vs pharmacotherapy. They were able to observe a preference for a quick and painless solution, which equated to SWL intervention for mild pain [44]. However, patients who had undergone more stone retrievals, or who were further out from their last stone event, were more apt to avoid surgical intervention and choose long-term medical therapy. These findings were similar to the additional results from Bensalah et al. study in 2008 [41] where they found the number of URS procedures as well as stent placement to negatively impact mental well-being. They also found a favorable association with HRQoL with medical therapy, particularly with potassium citrate [41].

A recent Internet-based survey, with a non-validated questionnaire, assessed general satisfaction in 443 patients who had undergone all intervention strategies for an acute stone [47]. Those strategies included surgery, pharmacotherapy, home remedy (dietary intervention), as well as observation for spontaneous passage. While a majority of patients (51%) reported "success of treating stones" for being the reason they liked their treatment method, there were 37% of patients who were favorable to their treatments due to QoL factors such as avoiding surgeries or hospitalizations as well as appreciation for quick recovery times.

While there are no studies that formally investigate HRQoL in medically or nutritionally treated stone formers, much less ones that compare them to non-stone-forming individuals, there are certain aspects that can be taken from complications and withdrawal rates from their trials. Two pharmacotherapy trials not only had a

majority of their studies with higher relative risk (RR) of withdrawal rates when compared to the control group, but they had higher RR of withdrawal due to adverse events [19].

In the investigations of dietary intervention trials, only one of eight studies reported any adverse events. And while one study had a higher RR of withdrawal when compared to the control group, there were none that found higher RR of withdrawal due to adverse events [19].

## Future

There are still many HRQoL aspects of nephrolithiasis management that need to be further investigated so that we might be able to improve patient outcomes, and newer evaluation tools, such as the Wisconsin Stone-QoL instrument, will allow even better insight into methods to improve the QoL in our patients. However, what may be gleaned from the currently available information is that:

1. HRQoL in stone-forming patients is negatively impacted by the chronicity of this disease.
2. Surgical options for stone removal can be highly successful, but they come with their own QoL detriments and do not address the primary preventative aspect.
3. Pharmacotherapy provides good evidence in its reduction of stone recurrence but has its assortment of side effects that may negatively affect HRQoL.
4. While the impact of dietary intervention on HRQoL has not been well studied, medical nutrition therapy can certainly decrease the risks of stone formation, with anticipated subsequent positive effects on HRQoL.

With the increasing awareness of patient-reported outcomes, more attention is being given to HRQoL. Perhaps, in order to improve HRQoL, endpoints for acute stone management should not only address physical domains such as stone-free status and pain scores but should also strive to positively impact the mental health, emotional well-being, and social functioning of the patient.

Additionally, maybe the long-term management of this chronic disease could include more than simply screening for recurrence and counseling for future prevention; perhaps a team outside urology could be collaborating in order to monitor and manage the domains of mental health, emotional well-being, and social functioning.

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# Myths Regarding Nutrition and Stone Management

3

Chad Huckabay, Michael Wood, and Clayton Newell

## Introduction

Kidney stone formation is related to both genetic and environmental factors. Diet is the major environmental factor, and as such, there is much data in the literature regarding dietary modifications to reduce the risk of stone formation. Most urologists, and even some patients, are familiar with the benefits of increased fluid intake and reduced consumption of nondairy animal foods and sodium to help prevent stone formation. However, there are myriad myths and half-truths that are often perpetuated, not only by patients but by clinicians as well. The internet probably plays a significant role in this. The Pew Internet Project survey showed that 113 million American adults use the internet to search for information on health-related topics [1]. Traver et al. evaluated the accuracy of internet information in regards to the dietary modifications of increased fluid intake, normal calcium consumption, reduced sodium intake, and reduced animal protein consumption. Even among urology and nephrology web sites, correct information is only provided in 41% and 51% of sites, respectively, and other sites are much lower overall at 16% [2]. This implies that although as many as 88% of practicing urologists provide dietary recommendations to their patients, overall knowledge and/or confidence in dietary modifications may be lacking, and in fact, self-reported confidence in providing appropriate nutrition strategies is variable [3].

The purpose of this chapter is to discuss and dispel the commonly recognized myths associated with nutritional management of recurrent urolithiasis.

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## Calcium

Many patients believe, and are often counseled, that they should avoid dairy products and/or calcium supplements if they are stone formers, but the literature does not support this. This section will address and review the pertinent literature regarding this common myth.

The most prevalent kidney stone constituent is calcium oxalate, comprising 75–85% of stones in the western hemisphere [4]. A common myth is that a high-calcium diet causes kidney stones. Historically, patients with calcium-containing stones were advised to restrict calcium intake. The reason for this is that 20–40% of patients with recurrent stones have hypercalciuria, most commonly idiopathic hypercalciuria. With similar levels of calcium ingestion, patients with idiopathic hypercalciuria excrete more calcium than normal subjects [5]. However, calcium restriction increases the absorption of oxalate in the GI tract leading to an increase of 16–56% in urinary oxalate excretion, and calcium oxalate saturation of urine increases rapidly with small increases in oxalate concentration [6]. Therefore, calcium restriction can lead to increased urinary oxalate excretion and increased incidence of oxalate stone formation [7]. Furthermore, severe calcium restriction is also associated with secondary hyperparathyroidism and bone demineralization [8]. Interestingly, although increasing calcium intake may increase the risk of hypercalciuria [8], clinical data do not support the notion that normal or even high levels of dietary calcium intake lead to increased stone formation.

However, one caveat to this that should be mentioned is the milk-alkali (calcium-alkali) syndrome. This was first described in 1915 after the introduction of a cocktail of large amounts of dietary calcium with multiple alkali-containing compounds. Known as the Sippy method, named after its inventor Bertram Welton Sippy, this cocktail was introduced to treat gastric and duodenal ulcers, and although it did improve ulcer symptomatology, some patients were noted to develop toxicity, including hypercalcemia, a strong distaste for milk, headache, nausea, vomiting, mental status changes, renal failure, and renal calcinosis. As many as one third of cases resulted in permanent renal impairment. The incidence declined after the advent of modern pharmacotherapy for peptic ulcer disease such as H2 receptor blockers, proton pump inhibitors, and antibiotics when associated with *H. pylori* infections. However, cases of milk-alkali syndrome have increased over the last two decades, mostly in postmenopausal women taking large amounts of calcium and vitamin D supplements for osteoporosis. Typically, the amount of calcium intake thought to cause milk-alkali syndrome is greater than 4 g per day, although cases have been reported at lower amounts of supplementation in the 1–1.5 g per day range. Other issues to consider are that thiazide diuretics can predispose to milk-alkali syndrome by enhancing renal calcium absorption by causing volume depletion and promoting alkalosis and ACE inhibitors and NSAIDs can contribute by reducing GFR thereby reducing calcium excretion [9].

The first major investigation into dietary calcium and risk of symptomatic stone disease was by Curhan et al. in 1993. This was a prospective study with a cohort of 45,619 men, ages 40–75 years, using data from the Health Professionals Follow-up

Study. Patients were followed for 4 years. The highest quintile of daily calcium intake was 1218 g/day. In this cohort, higher intake of dietary calcium and calcium supplements was strongly associated with a reduced risk of symptomatic urolithiasis. The relative risk of kidney stones in the highest versus the lowest quintile was 0.56 (95 % confidence interval 0.43–0.73, $P < 0.001$) [10]. These findings are supported in a twin study on genetic and dietary influence on stone formation, based on reports from the Vietnam Era Twin Registry. This group was comprised of 7,500 male-male twin pairs born between 1939 and 1955 with both twins having served in the military from 1965 to 1975. In 1990, a mail and telephone health survey was sent to these men that included questions regarding history of kidney stones and detailed dietary habits. Goldfarb et al. analyzed these data and found decreased risk of urolithiasis with increased milk consumption, and importantly, no association between increased consumption of other sources of dietary calcium/calcium supplements and stone formation [11]. Similar results were also seen in the Nurses' Health Study II that evaluated 96,245 women ages 2–44 years. Curhan et al. analyzed these data after 8 years of follow-up. Relative risk among women in the highest quintile (1,300 mg/day) of intake of dietary calcium compared with women in the lowest quintile (540 mg/day) was 0.73 (95% confidence interval, 0.59–0.90). Supplemental calcium intake was not associated with risk of stone formation [12].

Based on the above, current recommendations are to avoid very high (>2,500 mg/day) or very low <500 mg/day) calcium intake. The goal for most patients is for intake to be around the dietary reference intake of 1,000 mg/day [4].

## Vitamin D

Vitamin D is integral in calcium homeostasis as well as neuromuscular and immune function. One of the most important roles is to maintain skeletal calcium balance by promoting calcium absorption in the intestines, promoting bone resorption by increasing osteoclast number, maintaining calcium and phosphate levels for bone formation, and allowing proper functioning of parathyroid hormone to maintain serum calcium levels. Vitamin D deficiency can result in lower bone mineral density and an increased risk of osteoporosis or bone fracture [13].

Adequate daily intake (AI) of vitamin D is 5–15 μg or 200–600 IU/day for adults age 19 and older. The Recommended Dietary Allowance (RDA) for vitamin D is 600 and 800 IU/day, depending on age. Most Americans, however, fail to achieve even the AI for vitamin D and are at risk of osteomalacia and osteoporosis [14].

Clinicians typically recommend against vitamin D supplementation in recurrent stone formers. Vitamin D increases intestinal calcium absorption and therefore subsequent urinary calcium excretion, and the concern is that this can contribute to calcium stone formation. However, the true risk of stone formation related to vitamin D supplementation is not known, and there is conflicting data in the literature [15–17]. Hypercalciuric stone formers in particular are most often counseled to avoid vitamin D supplements, although it is also known that this population is at increased risk of osteoporosis and, therefore, would likely benefit significantly from vitamin D supplementation from a bone health standpoint.

There have been several recent studies aimed at evaluating the effects that vitamin D supplementation might have on recurrent stone formers. Penniston et al. evaluated vitamin D repletion and urinary calcium excretion in a group of postmenopausal women. This study included 18 women at greater than or equal to 5 years after menopause who had vitamin D insufficiency (16–24 mg/dL) but no history of urolithiasis. Twenty-four-hour urine tests were performed before and after vitamin D supplementation. They found that urinary calcium excretion did not change after vitamin D supplementation (212 mg/day before vs. 195 mg/day after, $P = 0.60$) [18].

Leaf et al. later conducted a similar study, this time in a population of recurrent stone formers. They enrolled 29 patients with history of nephrolithiasis, urinary calcium excretion between 150 and 400 mg/day, and serum vitamin D levels <30 ng/mL. Baseline serum and 24-h urine tests were performed. Patients were given 50,000 international units oral ergocalciferol per week for a total of 8 weeks, at which time serum and 24-h urine tests were repeated. Results revealed that serum levels of vitamin D did increase significantly after repletion but average 24-h urinary calcium excretion did not change (257 ± 54 and 255 ± 88 mg/day at baseline and follow-up, respectively, $P = 0.91$). They concluded that vitamin D therapy should not be withheld on the basis of stone disease [19].

Overall, current data seem to support vitamin D repletion in stone formers with vitamin D insufficiency as there is no proven risk of increased stone formation, and importantly, adequate vitamin D intake can decrease the risk of bone mineral density loss and osteoporosis.

## Beverages and Fluids

Patients are routinely counseled to increase water intake to help prevent recurrent stone formation. This is well founded as a higher intake results in higher urine output, thus reducing urinary calcium oxalate, calcium phosphate, and uric acid saturation and preventing stone formation [20]. Because of this, many believe that water is the only beverage that can help prevent kidney stones. However, the reality is that many different beverages are associated with reduced stone risk/recurrence. The most important factor is total fluid intake [10].

Curhan et al. in 1996 prospectively studied 21 different beverages and their effect on risk of symptomatic stone recurrence in 45,289 men. Interestingly, their data was significant for decreased risk of stone formation with coffee, both caffeinated and decaffeinated (10% reduction), tea (14%), beer (21%), and wine (39%) [21]. Tea, specifically, is often associated with increased stone risk. Tea does contain oxalate, and consumption of tea has been shown to increase urinary oxalate concentrations thereby theoretically increasing risk of calcium oxalate stone formation [22]. However, as previously stated, studies indicate a protective effect by tea on stone formation [21]. More recent date by Ferraro et al. as a continuation of Curhan's previous study analyzed date from three cohorts, the Health Professionals Follow-up Study (51,590 men), the Nurses' Health Study I (121,700 women), and the Nurses' Health Study II

(116,430 women), and again found tea consumption to be associated with an 11% risk reduction in renal stone formation [23]. Furthermore, if the tea is consumed with milk or dairy products, the amount of oxalate absorbed is negligible, as the calcium in dairy products will bind oxalate in the gut, thereby preventing absorption [22]. Ferraro's investigation also confirmed Curhan's previous results in that both increased coffee and alcohol consumption were associated with decreased risk of stone formation [23].

The common factor seems to be increasing total volume of fluid intake and, therefore, urinary volume, regardless of the type of beverage consumed. Current recommendations are that stone formers should drink 2,800–3,800 mL of fluids to produce at least 2,500 mL of urine per day [4].

An important caveat is that there are a few beverages of which stone formers should be cautious. Those include sugar-sweetened beverages and some sodas [21]. Shuster et al. found that stone patients randomized to abstain from soft drinks had a 7% reduced incidence of stone recurrence compared to those who continued their usual soda consumption [24]. Ferraro et al. also found that study participants consuming one or more sugar-sweetened soda per day had a 23% higher risk of developing kidney stones compared with those consuming less than one serving per day and those consuming one or more sugar-sweetened non-soda servings per day had a 33% higher risk [23].

Increased urinary citrate is known to be protective of stone formation, but dark sodas are high in phosphoric acid, which, according to some reports, may reduce urinary citrate and possibly also increase oxalate excretion [4]. Moreover, there is data to suggest that hypercalciuria may be related to renal phosphate leak, and that renal phosphate reabsorption capacity is decreased in stone formers. This low reabsorption is associated with hypercalciuria and hyperuricosuria, and in fact, renal phosphate handling has been shown to be an independent independent predictor for recurrence in stone formers [25]. Also, calcium phosphate crystal formation and attachment to the renal epithelium are associated with both the formation of calcium phosphate stones and calcium oxalate stones [26, 27].

In contrast to dark sodas, however, beverages that contain citrate are protective. These include light diet sodas/citrus beverages, specifically Diet Sunkist Orange, Diet Mountain Dew, Diet 7Up, Diet Canada Dry Ginger Ale, and Sprite Zero, as well as lemonade, all of which contain enough citrate to be protective of renal stones [28]. It is important to note as well that all of these are nonsugar-containing soda beverages.

| Beverages that may be beneficial to stone formers | Beverages that should be avoided by some stone formers |
|---|---|
| Water, flavored noncaloric waters | Sugar-/fructose-sweetened beverages and sodas |
| Light diet sodas | Dark sodas (high in phosphate) |
| Citrus beverages (i.e., lemonade); fruit and low-sodium vegetable juices | |
| Coffee (caffeinated and decaf) | |
| Tea | |
| Beer/wine | |

The most important factor is total volume of fluid intake. The goal is to drink enough fluids to produce at least 2,500 mL of urine per day

In order to better understand the mechanism behind sodas and increased risk of renal stones, one must consider the role that fructose may play in stone production. Most Americans report drinking sugar-sweetened beverages daily, almost all of which contain fructose [29], which has been shown to increase urinary excretion of calcium, oxalate, and uric acid [30, 31], although the exact mechanisms by which these alterations in urinary excretion occur have not been elucidated. Taylor and Curhan, again, examined the cohorts of the Health Professionals Follow-up Study and Nurses' Health Study I and II. They found that the relative risk of kidney stones was significantly increased for participants in the highest compared to the lowest quintile of total fructose intake for all three study groups. Non-fructose carbohydrates were not associated with increased risk in any cohort [32].

A discussion of sugar/fructose would not be complete without going a step further to discuss the role metabolic syndrome and diabetes mellitus play in stone formation. Metabolic syndrome is a set of cardiovascular disease risk factors that are commonly found together, including abdominal obesity, impaired carbohydrate metabolism (hyperglycemia and/or insulin resistance), dyslipidemia, and hypertension. Previous analyses have demonstrated an association among obesity, type 2 diabetes mellitus, and renal stone disease, and a recent systematic review and meta-analysis by Rendina et al. revealed metabolic syndrome to be associated with nephrolithiasis [33]. Furthermore, Weinberg et al. investigated the severity of type 2 diabetes mellitus and stone disease by performing a cross-sectional analysis of all adult participants in the 2007–2010 National Health and Nutrition Examination Survey (NHANES). They concluded that among persons with type 2 diabetes mellitus, more severe disease is associated with increased risk of kidney stones [34]. Unfortunately, the exact pathophysiological mechanisms behind this have not been established, but hyperglycemia and resulting glucosuria have been associated with altered renal handling of calcium, phosphorus, and uric acid, and studies have demonstrated increased urinary calcium, phosphorus, and oxalate excretion in type 2 diabetics [35–39].

## Vitamin C

Intake of vitamin C has long been associated with an increased risk of kidney stone formation. The most common component of kidney stones is primarily calcium oxalate crystals. Vitamin C is metabolized to oxalate, which, with increased intake, could lead to higher rates of oxalate excretion and increased risk of stone formation. However, studies have yielded contradictory results. Curhan et al. reviewed subjects consuming 1,000 mg or more of vitamin C (normal for men is 90 mg/day and women 75 mg/day) and found no increased risk for stone formation. In fact, those consuming a normal daily amount showed a 10% reduction in stone formation [40].

A recent well-designed prospective randomized trial was conducted by Traxer et al. to further evaluate possible risk of vitamin C supplementation. In this study, 12 normal subjects and 12 stone formers were randomized to either 1,000 mg of vitamin C twice daily or placebo. Diets were strictly controlled. They found a

statistically significant increase in urinary oxalate in the vitamin C group versus placebo for both normal subjects (34.7 vs. 28.5 mg, $P = 0.008$) and stone formers (41 vs 30.5 mg, $P = <0.001$). Overall, urinary oxalate increased by 20% in normal subjects and by 33% in stone formers. Calcium oxalate relative saturation ratio was also significantly higher in the vitamin C versus placebo group. Based on these findings, they recommend limiting vitamin C use to less than 2 g per day in calcium oxalate stone formers [41].

It would appear that there could be an increased risk of stone formation in the setting of vitamin C supplementation as extremely high levels of vitamin C intake (>1,000 mg/day) may increase urinary oxalate excretion, but reports on actual stone formation are conflicting. It has been concluded that an intake of 90–100 mg per day is required for optimal chronic disease prevention [42]. Therefore, it is currently recommended that intake not exceed the daily reference intake for vitamin C, 75 mg/day for women and 90 mg/day for men [4].

## Cranberry Juice

Cranberry juice has long been recommended for its potential beneficial effects in preventing urinary tract infections. Cranberries contain two compounds with anti-adherence properties that prevent fimbriated *E. coli* from adhering to uroepithelial cells. There have been several trials to test this effect, and although data is conflicting, there is at least some good evidence to recommend cranberry juice for prevention of UTIs [43]. However, many in the lay public also perceive cranberry juice to be beneficial in preventing kidney stone formation. Cranberry juice does contain citric acid, and, therefore, it has been assumed that cranberry juice's ability to increase urinary citrate may potentially prevent stone formation. However, there is little data to support the use of cranberry juice for the prevention of renal stones. Most studies have produced mixed results. Indeed, the most recent data seem to suggest the same. Cranberry juice may increase the propensity for crystallization of calcium oxalate from enhanced urinary saturation of calcium oxalate. It reduces urinary pH, thereby increasing the propensity for uric acid crystallization, although it does partly offset this by decreasing urinary uric acid levels. Overall, it is unlikely that cranberry juice does anything to substantially affect the risk of renal stone formation [44]. As such, it should not be recommended as a preventive strategy for recurrent stone formers.

## Sodium (Salt)

The major source of sodium in the American diet is sodium chloride (salt). Thus, the terms "sodium" and "salt" are largely interchangeable in the common vernacular. The relationship between salt intake and stone risk has been well established. Studies have examined the effect of a low-sodium diet on the crystallization of stone-forming salts in urine. When comparing a low- to a high-sodium diet, it was

observed that high sodium intake increased urinary sodium, calcium, and pH while decreasing urinary citrate, thus causing an increased tendency for the crystallization of calcium salts in urine. For this reason, stone-forming patients, particularly those with hypercalciuria and/or who are prone to forming calcium stones, should reduce their dietary sodium intake to 1,500 mg, 35% below the daily recommended value (2,400 mg) [45]. The problem, however, is that most patients far underestimate their intake, in large part because they fail to consider the sodium content in many foods. Patients tend to believe simply not adding salt to food is enough. In fact, however, many foods contain large amounts of sodium. These can include, but are not limited to, canned foods, fast food, frozen foods, bread, and especially cheese. Penniston et al. evaluated dietary sodium intake among 83 stone formers, and the results were striking. Mean sodium intake was high (3,300 mg/day), exceeding the recommended intake of 1,500 mg/day for recurrent stone formers, despite the fact that most patients had previously been instructed to reduce sodium intake. This study also found that greater than 85% of total sodium intake was from foods, most commonly processed meats (15%), bread and baked goods (14.1%), canned and pickled goods (8.5%), various condiments (8.4%), cheese (7.2%), and snacks (6.8%) [46]. This demonstrates the importance of counseling patients such that they fully understand the many potential sources of excess sodium in their diet.

## Animal Protein

Foods of animal origin, particularly their protein component, are known to lower urinary pH and increase urinary uric acid [47, 48], both of which are risk factors for uric acid and calcium stone formation, and multiple studies have shown a correlation between increased animal protein intake and stone formation [10, 49]. Most physicians and patients are aware that diets which are more carnivorous are associated with increased risk of stone formation but may not be clear on specifically which types are most contributory. A common myth, for example, is that the protein from all animal foods, including dairy, is the same. This has been shown to be not true with respect to both acid load of diet [50] and to uric acid production [51]. Another myth is that "red meats" are somehow more lithogenic than fish or poultry. In truth, all meats appear to be equally lithogenic. Tracy et al. compared the effects of three different animal protein sources (beef, chicken, and fish) on renal stone risk. They performed a 3-phase randomized cross-over metabolic study with a total 15 subjects. Each phase was 1 week, during which patients consumed a standard diet containing either beef, chicken, or fish. Serum chemistry and 24-h urine samples were obtained after each phase. They found that beef was associated with lower serum uric acid than chicken or fish and that fish was associated with higher urinary uric acid levels than either beef or chicken. There were no differences in other urinary parameters such as pH, calcium, citrate, oxalate, or sodium [52]. Based on this, patients with relatively high intakes of meats should limit the intake of all animal tissue, including fish. Conversely, dairy sources of protein, such as yogurt and milk,

do not increase renal acid load or uric acid production, and patients should have no need to limit dairy intake.

To expound further on how animal tissue contributes to stone formation, one must consider urinary acid load. Uric acid becomes less soluble as urine becomes more acidic which leads to precipitation and formation of uric acid stones as well as nucleation of calcium oxalate crystals, hence promoting formation of calcium oxalate stones [53]. High-protein, low-carbohydrate diets are associated with a significant increase in net acid excretion by approximately 50 mEq/day [54]. There are two possible mechanisms by which this occurs. First, the protein component of animal-derived foods tends to be rich in sulfur-containing amino acids, and oxidation of sulfur to sulfate generates protons [55]. Second, severe carbohydrate restriction results in production of keto acids [56]. Reddy et al. evaluated this by enrolling ten subjects in a prospective metabolic study. Patients initially consumed their usual diet, followed by induction regimen of high protein, severely carbohydrate-restricted diet for 2 weeks, and then maintenance regimen of a moderately carbohydrate-restricted diet for 4 weeks. Twenty-four-hour urine and serum studies were performed for each phase. They found a significant increase in net acid excretion and urinary calcium levels, and urinary saturation of uric acid increased twofold. Urine pH decreased to an average in the 5.6 range, and urinary citrate levels decreased significantly as well [54].

**Key Points**

- Calcium intake should not routinely be restricted in stone formers. The goal is for the intake of most patients to be around the dietary reference intake of 1,000 mg/day.
- Vitamin D should not routinely be restricted in stone formers. Moreover, vitamin D repletion in stone formers with vitamin D insufficiency is safe. There is currently no proven risk of increased stone formation, and importantly, vitamin D intake can decrease the risk of bone mineral density loss and osteoporosis.
- Some beverages are associated with decreased risk of stone formation, such as water, coffee, tea, light diet sodas, citrus-containing beverages, and even alcohol. Beverages that should be avoided if their consumption is excessive include sugar/fructose-containing drinks and dark sodas. Most importantly, total volume of fluid intake seems to be the main protective factor against stone formation. Patients should be counseled to drink enough fluid to produce at least 2,500 mL of urine daily.
- There could be an increased risk of stone formation in the setting of vitamin C supplementation as extremely high levels of vitamin C intake (>1,000 mg/day) may increase urinary oxalate excretion. However, reports on actual stone formation are conflicting. Current recommendations are to achieve the daily reference intake value for vitamin C, 75 mg/day for women and 90 mg/day for men.
- Cranberry juice should not be recommended as a preventive strategy for recurrent stone formers as there are no data to suggest any protective benefit against stone formation.

- The association between increased salt intake and stone formation is well established. Stone formers should reduce their sodium intake to 1,500 mg, 35% below the daily recommended value (2,400 mg). Many patients underestimate their sodium intake and should be counseled on the many sources of sodium in the typical western diet. Even small reductions in salt intake, though they may not reach the goal of 1,500 mg/day, may be of benefit.
- The tissue or flesh portion of animal-derived foods, including fish, is associated with increased risk of calcium oxalate and uric acid stones if consumed in excess. This is true of all such foods, not just red meat. If their intake is high, stone formers should lower their intake of nondairy animal-derived foods.

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# Part II

# Role of Diet in Urolithiasis

# Digestion and Absorption

4

Desiree de Waal

The gastrointestinal tract (gut) is an organized, specialized, and segmented filter designed to absorb nutrients and other beneficial food-derived compounds and allow the rest to pass unabsorbed in stool. Prior to elimination, however, a rich milieu of microorganisms is nourished and sustained by this unabsorbed dietary material. The processes of digestion and absorption, as well as bacterial processes in the intestinal tract, influence kidney stones and other aspects of health. This chapter provides a brief review of normal gastrointestinal digestion and absorption and also includes a focus on specific mechanisms contributing to kidney stones, including common gut disorders.

## Digestion

Digestion is a complex process that actually begins with food preparation. The process of cooking causes proteins in foods to vibrate, resulting in the breakage of the weak hydrogen bonds that hold individual amino acids together. This contributes to protein denaturation. In vegetables, the cooking process induces the degradation of polysaccharides such as cellulose and pectin to their monosaccharide components, which are more easily digested [1]. After consumption, digestion continues with actions on foods in the oral cavity.

*Mouth and Pharynx* The aromas of food, as well as other sensory factors, stimulate saliva in the mouth [2] and the secretion of acids in the stomach via chemosensory pathways [3, 4]. Salivary glands in the mouth produce enzymes that degrade carbohydrates. Foods are masticated by the teeth, which not only aids swallowing but also increases the surface area of foods so that oral enzymes and those further down the

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gut can have maximum effect. The tongue assists in moving around and mixing the food material within the oral cavity and assists the swallowing process.

The combined actions of the teeth, tongue, and saliva produce a soft, moist, rounded food mass (bolus) that is propelled through the pharynx. The function of the pharynx is to transfer the food material from the mouth to the esophagus and also to filter, warm, and moisten air before it moves into the trachea. The swallowing (pharyngeal) reflex prevents food from entering the trachea when the epiglottis, a flap-like structure that covers the larynx, closes in order to prevent aspiration.

*Esophagus* Muscles in the esophagus contract and relax to guide the food material to the stomach. No digestion occurs in the esophagus. The pressure of food at the lower end of the esophagus signals a muscular valve, the lower esophageal sphincter, to relax and let food enter the stomach.

*Stomach* In the stomach, mechanical forces and acidic secretions continue the process of the breakdown of nutrients and other food-derived particles. Emulsification of lipids begins with mechanical shearing in the acidic gastric environment. Proteins are denatured, making them more susceptible to hydrolysis and proteolysis. The low pH of the stomach allows for activation of the enzyme pepsin which contributes to further digestion. Intrinsic factor, a glycoprotein produced by gastric parietal cells, binds with food-derived vitamin B12 in the stomach. Carbohydrate digestion, which began in the mouth, does not resume until the food bolus, which is eventually broken down to a more liquefied state known as chyme, is released into the small intestine. Under normal physiologic conditions, the pyloric sphincter connecting the stomach to the proximal small intestine (duodenum) regulates the movement of chyme so that only a small amount enters at one time. Liquids generally exit the stomach before solids; denatured proteins and carbohydrates exit before lipids. Gastrointestinal hormones such as cholecystokinin contribute to the slowing of gastric emptying [3, 5] and to the stimulation of enzyme and bicarbonate secretions from the pancreas. The gastric vagal nerve, which responds to stretch and tension (volume), signals the brain to reduce food intake [3] which further slows the rate of gastric emptying [5].

*Small Intestine* Contractions of the duodenum help to regulate the rate of stomach emptying. The acidic chyme leaving the stomach enters the duodenum where it mixes with a variety of digestive juices from the pancreas, liver, and gallbladder. Humoral and neural mediators (secretin, glucose-dependent insulinotropic polypeptide, and vasoactive intestinal peptide) released into the duodenum also help to regulate the motility of material from the stomach to the small intestine [5], the secretion of digestive juices, and the insulin release from the pancreas [6]. Pancreatic bicarbonate neutralizes the emptied gastric contents; pancreatic enzymes (e.g., trypsin, chymotrypsin) help to digest proteins, carbohydrates, and fats. Bile, produced in the liver and stored in the gallbladder, is released into the duodenum to aid overall fat emulsification and digestion. Triglycerides are digested by pancreatic lipase into fatty acids and monoglycerides [6].

The final step in digestion occurs in the brush border (the "gateway" to absorption) that lines the small intestine. Starches that were partially degraded earlier are now degraded to their simplest forms (oligosaccharides and disaccharides) by enzymes in the brush border, near the active sites of absorption. Enzymes released from the brush border complete the final phase of protein and carbohydrate digestion [6].

## Absorption

Throughout the small intestine, the end products of food digestion pass into the blood through the intestinal wall via either diffusion or active transport. The wall (mucosa) of the small intestine contains villi, specialized absorptive cells, which increase the surface area available for absorption. Most macronutrient absorption occurs in the upper small intestine because of the presence of bile and pancreatic secretions. Smaller compounds, such as dipeptides and tripeptides, are absorbed by specific transporters as are individual amino acids. Cholesterol combines with bile salts to create micelles, which are circulated in the lymphatic system. Most water-soluble vitamins (e.g., folate and most of the other B vitamins) enter the bloodstream by passive diffusion. Minerals (e.g., iron, calcium) require the presence of specific carriers and use energy for active transport. The jejunum, the second segment of the small intestine, is the site of most nutrient absorption. In fact, most nutrients are absorbed by the time they reach even the mid-jejunum [6]. The ileum, which extends into the large intestine, is the final section of the small intestine. The digestion of previously undigested food particles (e.g., tiny carbohydrate molecules, small proteins, and fats) continues here. Primarily, however, the ileum is the site of bile salt absorption and that of fat-soluble vitamins as well as some fluids and electrolytes. The ileum is also where the vitamin B12-intrinsic factor complex finally dissolves, allowing for the binding of the vitamin to transcobalamin and its eventual absorption and distribution through the body [6]. The ileocecal valve links the ileum and the colon (large intestine) and plays a role in decreasing intestinal motility and preventing the reflux of colonic flora into the small intestine [6, 7].

*Large Intestine and Colon* After nutrients are absorbed, undigested material and water move through the large intestine where most of the water gets absorbed. Muscles in the colon separate this undigested material into small segments. Some carbohydrate forms, notably fiber, reach the colon intact where they are fermented by intestinal microbes into several products, including short chain fatty acids, which aid in nutrient absorption and help to maintain colonic health and function [8]. The material that remains after these processes is fecal matter (stool). As this material moves further down the tract via peristalsis, the rectal wall is stretched, signaling the need for a bowel movement. A combination of both involuntary and voluntary sphincter muscles in the anus works to relax and contract the rectal walls to increase the pressure required to expel the stool. Figure 4.1 illustrates the transit and fate of foods from the mouth to anus.

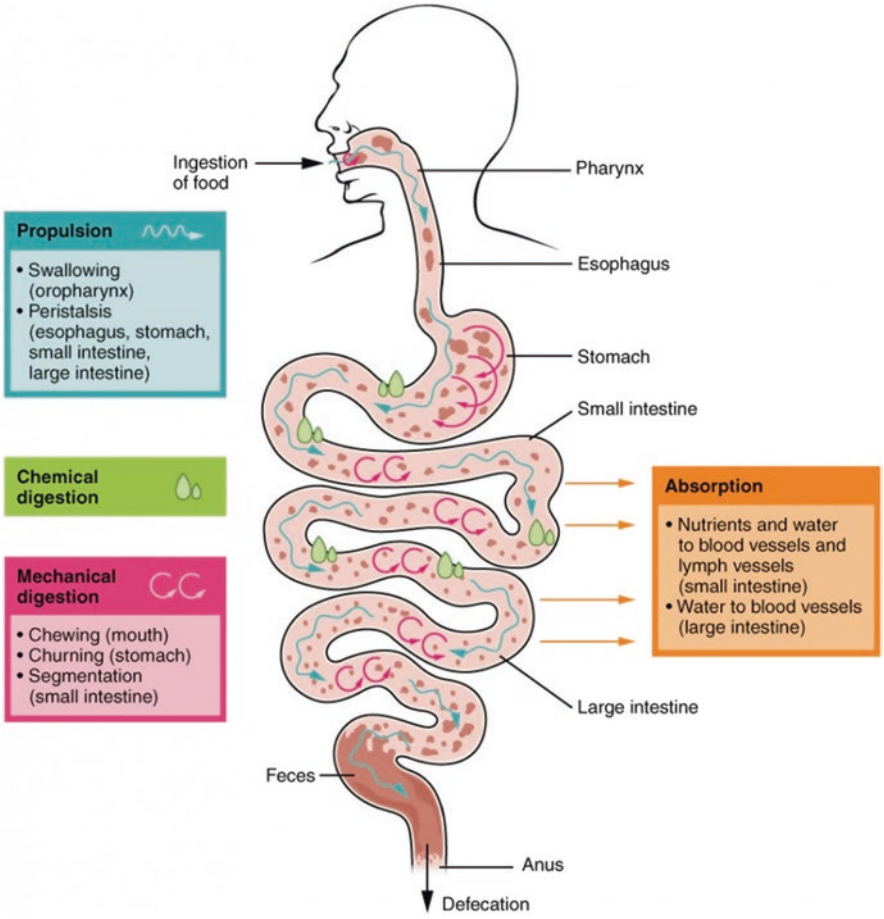


**Fig. 4.1** Illustration of how foods move through the gastrointestinal tract (Figure from OpenStax CNX™ available at: https://courses.lumenlearning.com/ap2/chapter/digestive-system-processes-and-regulation/)

## Intestinal Microbiota

The digestive tract is the most heavily colonized organ in humans with the colon alone estimated to contain more than 70 % of all human microbes [9]. The gut microbiome (microbiota, microflora, or flora) coexists with the host and influences the host's own metabolism, nutritional status, and immune function (Fig. 4.2). Four bacterial phyla are commonly found in humans: *Firmicutes* (e.g., *Streptococcus*, *Lactobacillus*, *Clostridia*), *Bacteroidetes* (e.g., *Prevotella*, *Bacteroides*), *Proteobacteria* (e.g., *Haemophilus*, *Escherichia*, *Salmonella*, *Oxalobacter*), and *Actinobacteria* (e.g., *Propionibacterium*, *Bifidobacteriales*) [11]. For more than 100 years, the existence of gastrointestinal microbes and their beneficial effect on

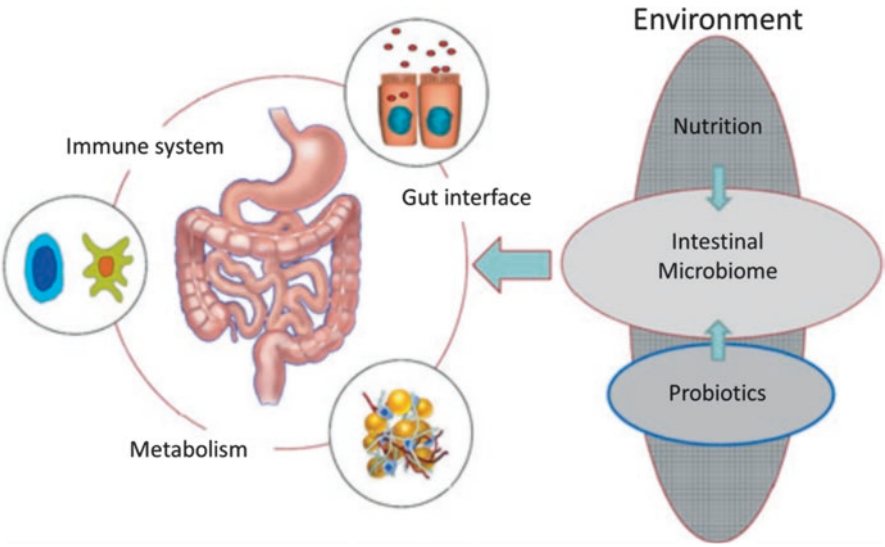


**Fig. 4.2** The interactions of nutritional factors and the intestinal microbiome on gut-associated metabolic activities, barrier function and the immune system (Published in: Thomas and Ockhuizen [10])

health have been known [7]. The use of kefir by people in the Bulgarian area was attributed to their notably longer life expectancy at the turn of the twentieth century than that of other Europeans [12]. Indeed, a species of lactic acid bacteria – *Lactobacillus bulgaricus* – owes its name to this observation. The gastrointestinal tract normally contains more than 1,000 known different species of bacteria [11], many of which are pathogenic if allowed to overgrow but many others of which are beneficial and thus known as probiotics. The definition of a probiotic has changed and continues to change over time but is most commonly and basically defined as a live microorganism that confers a health benefit to the host [13, 14] (Table 4.1).

As bacteria ferment undigested food material passing into the colon, metabolites are created, many of which are increasingly recognized as beneficial to the host [9]. There are two main types of bacterial fermentation in the gut, saccharolytic and proteolytic. Saccharolytic fermentation is carbohydrate based and gives rise to beneficial metabolites such as the short chain fatty acids propionate and acetate [19]. Short chain fatty acids are integral to the health of the colonic epithelium and have a myriad of other benefits, including anti-inflammatory properties [7, 8, 11]. Proteolytic bacterial fermentation is protein based and is a source of a number of toxic metabolites, particularly uremic toxins (e.g., indoxyl sulfate and p-cresyl sulfate) [8, 20].

Bacterial populations differ depending on location in the digestive tract. Bacteria in the mouth are dominated by *Streptococcus*, which exist in biofilms on the surface of teeth [9]. The stomach, despite its low pH, also has a rich microbiota under normal physiologic conditions. But the highest density of gut microorganisms appears

**Table 4.1** Definitions for probiotics and prebiotics

| Definition | Examples | Food sources | Examples of proposed effects |
|---|---|---|---|
| Probiotics | | | |
| Live, nonpathogenic microorganisms that inhabit the gastrointestinal tract and confer a health benefit on the host when consumed and/or administered in sufficient amounts or when colonized in the gastrointestinal tract in sufficient concentrations and within conditions that optimize their activity | Certain strains of: | Yogurts, kefir and other fermented dairy products, breast milk, cheeses, fermented foods (e.g., soy, vegetables), over-the-counter supplements, supplemented infant formulas, fortified foods | Effects are direct and include: |
| | *Lactobacillus* | | Prevention/reduction of duration and severity of certain virus- or antibiotic-induced diarrhea |
| | *Bifidobacterium* | | Attenuation of effects of lactose intolerance |
| | *Escherichia* | | Decreased expression and concentration of putrefactive bacterial metabolites |
| | *Enterococcus* | | Alleviation or prevention of irritable or disordered bowel activity |
| | *Streptococcus* | | Prevention of overgrowth of pathogenic bacteria |
| | *Bacillus* | | Prevention of certain infections |
| | Certain yeasts | | Treatment of some urogenital infections |
| Prebiotics | | | |
| Nondigestible but fermentable dietary components that allow for specific changes in the gastrointestinal microflora that confers benefits upon the host | Inulin | Fruits, vegetables, whole grains, honey, extraction of chicory root, over-the-counter supplements, fortified foods | Effects are indirect, i.e., mediated by intestinal microflora, by way of providing substrate for the colonization of probiotics (*see above definition*) that produce beneficial metabolites or exert other effects (*see above*) |
| | Some oligosaccharides (e.g., fructo-oligosaccharide, galacto-oligosaccharide) | | |
| | Lactulose | | |
| | Lactitol | | |
| | Resveratrol | | |
| | Gum arabic | | |
| | Fructan | | |
| | Some pyrodextrins | | |
| | Resistant starches | | |

References: (1) deVrese and Schrezenmeir [15]; (2) Hill et al. [16]; (3) Valcheva and Dieleman [17]; (4) Laurell and Sjöberg [18]

in the lower intestinal tract and is dominated by two bacterial phyla, *Bacteroidetes* and *Firmicutes* [11]. The primary gut microbial profile is thought to be fairly stable throughout a person's life once established, but external factors can dramatically affect it [19], including the intake of substrate for bacteria [17]. Many studies have documented the effect of antibiotics on gut bacteria and their ability to induce

dysbiosis [21]. In one study, antibiotic exposure was associated with an enrichment and stabilization of resistant *Bacteroides* strains [22]. Other studies have documented the role of antibiotics in the overgrowth of pathogenic gut bacteria such as *Clostridium difficile* [23]. Aging may also affect gut microbiota. The composition of the gut microbiome in people >65 years of age is distinct from that of younger adults [24].

Diet patterns and dietary changes also seem to influence the types of bacteria in the microbiome [19]. In one study, elderly adults living independently in the community had a reduction in the diversity of their gut flora after moving to assisted living, and these differences were associated with dietary changes incurred while in assisted living [25]. Differences in gut microbiome profiles have been observed in lean vs. obese individuals. Mouse studies have shown that obesity is associated with changes in the relative abundance of two dominant bacterial divisions, *Bacteroidetes* and *Firmicutes* [26]. Overweight and obese humans have been shown to have a higher relative *Firmicutes* abundance than lean individuals [27]. High-fat vs. low-fat diets have been shown to associate with distinct differences in gut microbial profiles [28]. High-protein diets are associated with increased levels of uremic toxins, metabolites produced by proteolytic bacteria, such as trimethylamine-N-oxide (TMO) [29], a microbial-generated metabolite of choline and phosphatidylcholine. High TMO blood levels have been linked to increased cardiovascular risk [29, 30]. In a study comparing the gut microbiome of people eating an entirely animal-based diet (high protein) to one that was completely plant based (lower in protein and higher in fiber), those eating the animal-based diet had higher levels of *Proteobacteria* and fewer *Firmicutes* than those eating the plant-based diet. Interestingly, the investigators discovered that 1 day on either diet was sufficient to shift the gut microbiome profile [19]. Higher- vs. lower-fiber diets in general are associated with changes in gut microbiota. Studies tend to show a higher proportion of *Firmicutes* with higher-fiber diets in addition to lower numbers of *Lactobacillus* [14].

In addition to macronutrients, dietary micronutrients and other plant-derived compounds have been found to influence the microbiome, and these effects are currently an area of heightened interest, if not debate, among biomedical researchers. For example, while a gluten-free diet in patients with celiac disease promoted the growth of *Bifidobacterium* populations in one study [31], it was associated with lower levels in another [32]. Bifidobacteria are thought to reduce intestinal inflammation, so understanding of their modulation by gluten and/or other plant-derived components is important for many patients with intestinal disorders not limited to celiac. In patients with generalized irritable and/or inflammatory bowel problems, a dietary strategy used with increasing clinical prevalence is a diet low for fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs), touted for its purported ability to reduce symptoms associated with these bowel disorders (e.g., bloating, abdominal pain, diarrhea, constipation) [33]. By default, this diet is frequently low in fiber. But its effect on healthy gut bacteria, such as *Bifidobacterium* and other species, is controversial. Inulin and fructo-oligosaccharides, which are typically limited in the low FODMAP diet, have been shown to increase *Bifidobacterium* populations; their restriction may reduce it [34].

But other evidence suggests that long-term restrictive diets, especially those lower for carbohydrates such as low FODMAPs, detrimentally alters gut microbiota and contributes to dysbiosis [35], which could actually worsen symptoms related to irritating bowel symptoms.

Certain gut microbiota is being investigated as a source of systemic inflammation in various disease states, including chronic kidney disease [36]. Patients with kidney disease frequently have a predominance of bacteria that possess urease-, uricase-, indole-, and p-cresol-forming enzymes. The presence of these bacteria can cause increased bacterial metabolism of urease to ammonia [37], which erodes the epithelial barrier. In patients with kidney stones, much attention has been placed on *Oxalobacter formigenes* (*O. formigenes*) [38], an obligate oxalate user that resides in the colon. Studies have shown that many people who form kidney stones do not have high levels of this bacterium in their digestive tract [39, 40]. Whether this is diet related has not yet been clarified, but antibiotics appear to have a major effect on *O. formigenes* [41, 42]. Indeed, reduced recolonization rates after antibiotic therapy are noted [43]. A few other species of intestinal bacteria, including strains of *Lactobacillus* and *Bifidobacterium* [44, 45], are also capable of consuming oxalate and have recently been shown to carry the same oxalate-degrading genes as *O. formigenes* [46]. Dietary patterns that enhance these bacterial species may thus be beneficial for patients who form calcium oxalate stones; studies are needed to confirm this.

## Disorders of Digestion and Absorption Relevant to Kidney Stones

*Irritable Bowel Syndrome and Inflammatory Bowel Disease* Irritable bowel syndrome (IBS) and inflammatory bowel disease (IBD) are common gastrointestinal tract disorders with symptoms including abdominal discomfort, distension, bloating, diarrhea, and/or constipation [47]. IBS is by definition a diagnosis of exclusion [48]. It is characterized by pain and altered bowel function in the absence of any organic or physiological cause. While the exact cause of IBS is not clear, it is thought to be multifactorial and possibly related, at least in part, to a dysregulation of the brain-gut axis resulting in spasms or inappropriate muscle activity [49]. Dysbiosis is also thought to play a role [50], and dietary triggers that promote dysbiosis are described. IBD is largely an idiopathic disease characterized by chronic, T-cell-mediated inflammation of the digestive tract [51, 52], though a genetic basis has been proposed [53]. Other theories suggest that one contributing factor may be an altered or inappropriate immune response to microflora in the digestive tract [54]. Two common types of IBD are ulcerative colitis, which mainly affects the colon and rectum [55], and Crohn's disease [56], which may occur anywhere in the digestive tract.

IBS is associated with bacterial overgrowth [57], bile salt malabsorption, fat malabsorption, calcium malabsorption, and lactose malabsorption. Bowel surgery can induce IBS symptoms [58, 59]. Dietary treatments for IBS have typically been diets that exclude or limit fat, sugar (simple carbohydrates), and individual "trigger"

foods [51]. New evidence implicates certain types of carbohydrates, specifically fermentable oligo-, di-, and monosaccharides and polyols (FODMAPs). FODMAPs draw water into the digestive tract, which could promote bloating in people prone to IBS. But studies of patients who restrict dietary FODMAPs are inconclusive in showing efficacy; individual variations and responses to treatment appear common [35, 60].

Patients with IBS have a higher risk for urinary stone disease [61, 62]. The fat malabsorption that often accompanies IBS and conditions causing IBS-like symptoms (e.g., celiac sprue, cystic fibrosis) is associated with an increased risk for calcium oxalate stones due to the binding of calcium with fats [63], rendering calcium less available to bind with oxalate and to lower its absorption. Additionally, patients with IBS have been found to have lower levels of *Bifidobacterium* [64]. As some species of *Bifidobacterium* are known to degrade oxalate, therapeutic interventions to enhance their presence in the gut are being considered [65].

IBD is associated with increased intestinal permeability which triggers inflammatory responses [47, 52]. With this chronic inflammation, normal gut tissue may be replaced with scar tissue and ultimately cease to function. Bowel resections are not uncommon in patients with IBD [58, 59]. The prevalence of urolithiasis is higher in patients with IBD [63, 66], and this is potentiated as patients undergo multiple bowel resections. Risk factors for renal stone development include malabsorption and dysbiosis, both of which can lead to excessive oxalate absorption and urinary excretion [61]. Additionally, patients with IBD characterized by frequent or chronic diarrhea often experience bicarbonate wasting, and this can lead to lower urinary citrate excretion and higher risk for calcium stone formation and also to uric acid stones if urine pH is low [61, 63].

*Short Bowel Syndrome (SBS)* Small intestine resections involving the loss of more than 100 cm can lead to compromised nutritional status due to macronutrient malabsorption (fat, carbohydrate, and protein) and micronutrient malabsorption (vitamins and trace elements) [58, 59]. Problems with diarrhea are common in patients with SBS due to increased gastric motility, unabsorbed bile salts entering the colon, and excess water losses in stool [67]. Treatment for SBS is aimed at controlling diarrhea and fluid losses and repletion of minerals and vitamins [51, 67]. Late complications of SBS include cholelithiasis due to the fact that bile losses exceed the liver's capacity to synthesize the bile. Small bowel bacterial overgrowth (SBBO) and d-lactic acidosis are also complications with SBS [57]. SBBO results in inflammatory changes in the intestinal mucosa causing fluid losses, fat malabsorption, and subsequent fat-soluble vitamin deficiency. With d-lactic acidosis, there is a malabsorption of carbohydrates (especially refined sugars) [67].

Patients with SBS have an increased risk for calcium oxalate kidney stones due to increased absorption of oxalate from the colon [58, 61]. In the setting of fat malabsorption (steatorrhea), increased intraluminal free fatty acids sequester and bind to calcium, resulting in increased oxalate absorption. Other factors contributing to increased stone risk include higher fecal fluid losses and reduced urine output, lower urinary magnesium (due to lower magnesium absorption) causing reduced capacity

to keep oxalate soluble in urine, and bicarbonate wasting from diarrhea causing higher renal citrate reabsorption and lower urine citrate [63]. Acidic urine has also been observed in patients with SBS, and this may promote the precipitation of uric acid in urine.

*Gastric Bypass Surgery* Bariatric surgery for obesity is increasing. Malabsorption of macronutrients, essential vitamins, and minerals occurs along with substantial weight loss. An increased incidence of kidney stones related to bariatric surgery has been observed similar to risks listed above for SBS [68–70]. Increased incidence of oxalate nephropathy has also been observed [71, 72]. In patients with bariatric surgery and nephrolithiasis, urinary oxalate was found to be directly related to fat malabsorption and the concomitant reduced availability of free calcium to bind oxalate in the gut [73]. When patients were placed on a low-fat diet after bypass, urinary oxalate levels were lower [74]. Vitamin deficiencies due to malabsorption may include pyridoxine (vitamin B6), a cofactor in hepatic metabolism of glyoxylate [75, 76]. Impaired function of the enzyme participating in this reaction leads to increased oxalate biosynthesis and urinary excretion. Whether and how bariatric surgery affects the gut microbiome are not fully characterized [77]. However, decreased intestinal colonization with oxalate-degrading bacteria in patients after gastric bypass has been described [78].

*Diarrhea* Patients with gastrointestinal tract conditions characterized by diarrhea, which may be idiopathic, antibiotic induced, or associated with any of the digestive conditions described above, must compensate for extrarenal fluid losses in order to promote suitably ample urine and maintain lower supersaturation. Low urine volume increases the concentration of urine and thus raises the risk of all types of stone formation. Diarrhea also promotes malabsorption, which increases the risk for bicarbonate wasting [63]. The rapid transit of gut materials associated with diarrhea reduces the time required for bacterial oxalate fermentation and potentially to altered microbial populations that are overall less effective in degrading oxalate. Strategies to control diarrhea are therefore helpful in mitigating the effects of low urine volume, malabsorption, dysbiosis, and bicarbonate wasting [61].

*Oxalate Absorption and Transport* Patients with any type of digestive tract disorder are potentially at risk for dysbiosis which may lead to higher oxalate absorption. Patients with gastrointestinal conditions may avoid certain foods, such as fiber or fructo-oligosaccharides. As these food-derived compounds provide substrate for many bacteria, dietary changes that eliminate or reduce these could affect the health of the gut microbiome. For example, a restriction of dietary oxalate may reduce the presence of *O. formigenes* as its only food source is limited [79]. In other digestive tract disorders, non-functioning or necrotic gut tissue could alter oxalate absorption and/or transport. For example, some patients with IBD and/or other bowel disorders have increased colonic mucosal permeability due to inflammation and potentially also to autoimmune activities [73]. This is thought to lead to excess free oxalate absorption as some oxalate is absorbed before binding to calcium or magnesium and prior to

bacterial degradation. Patients with delayed stomach emptying, such as in gastroparesis, may also be at risk for enteric hyperoxaluria. The stomach is a site of oxalate uptake [80]; transport is presumed to be via a transcellular mechanism. Increased oxalate absorption is observed when transit time through the stomach is slow.

Genetic variations in oxalate transporters in the gut have been proposed as a mechanism for enteric hyperoxaluria [81]. Oxalate transport is both paracellular and transcellular. Paracellular transport is passive, whereas transcellular transport is coupled with other processes independent of the electrochemical gradient. Epithelial oxalate transporters called solute-linked carrier 26 (SLC26) anion exchangers were identified in the kidney, liver, and gastrointestinal tract. There are 11 such carriers; they differ in location and also have differences in requirements for substrate (e.g., sulfate, chloride, bicarbonate, formate, and oxalate) [82]. Additional anion exchangers, such as those that transport chloride, may be involved in oxalate transport. While not completely characterized nor fully understood, genetic variations in these transport systems may account for some cases of enteric hyperoxaluria. Studies to identify how to affect these processes such that the transport of oxalate from the gut is reduced are needed.

## Summary

Digestion, which begins in the mouth and continues lower in the digestive tract, is the mechanical and chemical degradation of food into its smallest constituents. Absorption is the transit of these small molecules across the intestinal membrane into circulation. Each macronutrient – fats, proteins, and carbohydrates – is handled differently in the gastrointestinal tract with respect to how it is degraded and absorbed. Micronutrients, vitamins and minerals, are also handled differently depending on whether they require processing prior to absorption or whether they are fat or water soluble. Intestinal microorganisms benefit the host by degrading (fermenting) undigested carbohydrate material, largely in the colon. This degradation results in the production of short chain fatty acids, which are important in maintaining colonic health, the synthesis of new compounds that benefit the host, and the removal of other compounds. An imbalance in the profile of gut microbiota can lead to, or can be a result of, disordered digestion and absorption.

There is an association between gastrointestinal disorders and kidney stones, particularly those that induce diarrhea, malabsorption, steatorrhea, or surgical manipulation or resection. These conditions can lead to extrarenal fluid losses; loss of bicarbonate, calcium, and magnesium; and higher oxalate absorption. While the risk for all types of stones is higher with reduced urine output, loss of bicarbonate increases the risk for both calcium oxalate and calcium phosphate stones due to reduced urinary citrate excretion. Metabolic acidosis induced by bicarbonate loss may also lead to acidic urine, which increases the risk for uric acid stone formation. Malabsorption leads to a higher risk for calcium oxalate stones specifically both because of higher oxalate absorption and urinary excretion as well as reduced urinary magnesium excretion.

Finally, alterations in the gut microbiome can lead to dysbiosis. Dysbiosis in the form of reduced oxalate-degrading bacteria may lead to higher oxalate absorption and urinary excretion. There may be other effects of dysbiosis on kidney stone formation and growth that have yet to be characterized.

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# Energy and Nutrient Balance: Focus on Kidney Stones

5

Kristina L. Penniston

## Introduction and Background

To maintain life, humans must consume adequate energy and nutrients, including some that provide no energy but perform or assist in essential bodily functions. In optimizing the health of an individual, adaptations to energy and nutrient intake may be required due to changes in life stage or health status (e.g., growth, pregnancy, illness), age, physical activity, and exposure to environmental factors. Energy balance is achieved when the input of energy (intake) is equal to the output of energy (expenditure). In this scenario, a steady state – or homeostasis – is achieved. During periods of growth, such as childhood or pregnancy, energy balance as well as nutrient balance must shift into the positive as a higher energy intake is required for weight gain, tissue generation, and increased fat stores. When in negative energy balance, energy expenditure is greater than intake, leading to weight loss as well as losses of structural tissue, such as muscle and bone. Negative nutrient balance (deficiency or insufficiency) is caused by the insufficient intake of nutrients, be they macronutrients or micronutrients, such that normal or optimal physiologic functioning and/or metabolism is altered. The effects of both deficient and excessive nutrient intakes are illustrated (Fig. 5.1).

*Definitions* Terms related to the assessment and estimation of nutrient needs are defined below.

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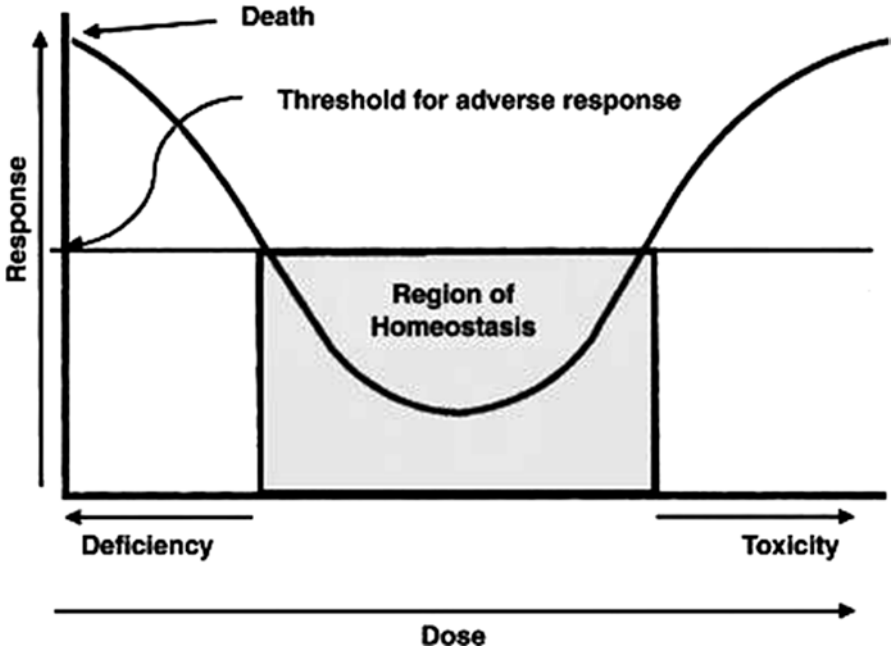


**Fig. 5.1** Dose-response relations for nutrients. Both deficient and excessive intake of a single nutrient or total energy result in adverse effects as illustrated in the u-shape of the curve. The region of homeostasis or steady state status is shown within the intersections of lower and higher doses as they cross the adverse response threshold (Figure from Hayes [51])

- *Energy.* Provided by foods in the form of chemicals which, through metabolism, are converted to small, biologically active molecules.
- *Calorie.* A measure of energy supplied by food and also of energy used by the body. 1,000 calories equals 1 kilocalorie (kcal). Food energy, as well as energy expenditure, is typically measured in kcals (in the USA) due to the convenience achieved from using fewer digits. The word "calorie" is often used to mean "kilocalorie."
- *Nutrient.* A biologically active substance obtained from foods that provides energy or a structural or functional component to humans. Nutrients include water, carbohydrates, amino acids (obtained from food sources of dietary protein), fats, vitamins, and minerals. Nutrients can be "essential" or "nonessential" (see below).
- *Essential nutrient.* Substance that must be obtained from the diet because of its inability to be synthesized at all or in sufficient quantities to maintain life through all life stages.
- *Non-nutrient.* Diet-derived substances that are not strictly necessary for life. Examples of non-nutrients that confer health benefits to humans include fiber and many plant pigments which function in the body as antioxidants.
- *Macronutrient.* Carbohydrates, protein, fats; all of these provide energy.

- *Micronutrient.* Vitamins, minerals; these provide no energy.
- *Basal metabolic rate (BMR)* also known as *basal energy expenditure (BEE).* Minimal amount of energy expenditure required to maintain homeostasis. BMR is usually expressed as energy per some unit of time and is measured in a resting and fasted state.
- *Resting metabolic rate (RMR),* also known as *resting energy expenditure (REE).* Commonly used interchangeably with BMR, RMR does not require a person to be in a complete resting or fasted state. RMR is usually fairly close to BMR; but technically, the terms are different.
- *Energy requirement.* Amount of food-derived energy required to afford the needs of BMR plus that required to maintain or achieve appropriate body size and composition, support physical activity, and allow for growth and development (such as bone growth, deposition of tissues during pregnancy, secretion of milk during lactation). Certain diseases and events (e.g., surgery, wound healing) are known to raise or alter the energy requirements of humans. As such, medical nutrition therapy provided by a registered dietitian nutritionist can be designed to meet these altered needs [1].
- *Total energy expenditure (TEE).* Energy spent in a typical 24-h period and usually reflects an average.
- *Thermic effect of foods (TEF),* also known as *diet-induced thermogenesis (DIT).* Energy spent above BMR for the processing, metabolism, and storage of diet-derived energy.
- *Physical activity level (PAL),* also known as *activity factor (AF).* A value to express the energy expenditure of movement which is multiplied by BMR to estimate TEE and energy requirements.

In addition to physical activity, there are disease-specific factors to account for the additional energy requirements conferred by fever, burn, infection, surgery, and trauma [2].

*Calculating energy requirements* There are several formulas used in the clinic setting to estimate a person's total energy (caloric) requirements [2]. These are based largely on a person's height, weight, gender, and age. The result can then be multiplied by a factor depending on a person's usual energy expenditure. But there is much debate about which formula is superior and about the selection of formulas to be used in specific medical conditions. A few of the most important models for estimating energy requirements in healthy individuals are shown (Appendix 4). However it is calculated, the estimated energy requirement is helpful in determining how much food – and in what composition – is required to best meet needs. The Dietary Reference Intakes (DRIs), nutrient intake goals set by the Institute of Medicine (IOM) [3], include recommended intake ranges for total energy (Appendix 5). These ranges are known as acceptable macronutrient distribution ranges (AMDRs) and represent the acceptable range of macronutrient intake that is considered healthy. AMDRs are expressed as percentages of recommended total energy intake.

*Calculating nutrient requirements: dietary reference intakes* The estimation of nutrient requirements, particularly of micronutrients (vitamins and minerals), is a complex and methodical process based on the available scientific and biomedical evidence. From 1941 to 1989, nutrient requirements were expressed as Recommended Dietary Allowances (RDAs) and were based on conclusions reached from studies that assessed the minimum amount of each essential nutrient required for life [3, 4]. Usually these were balance studies; in other cases, data were derived simply from identifying the average intake of a population. In the 1990s, the DRIs were developed to replace the RDAs (although they still include RDAs) [4]. Over time, increasing attention has been placed on the nutrient intake levels that optimize health vs. those that merely prevent deficiency. DRIs are an umbrella term that consists, in addition to the AMDRs addressed earlier, of five categories of reference values:

1. *The Estimated Average Requirement (EAR)* for a nutrient is the value that is estimated to meet the needs of 50% of a population. The EAR is used as a basis for establishing a RDA.
2. *The Recommended Dietary Allowance (RDA)* is the amount of a nutrient that prevents deficiency in 97.5% of a population. It is established when sufficient data are available for deficiency, saturation of relevant tissues or adequacy of molecular function, and toxicity. If the standard deviation (SD) of the EAR is available, and if the requirement for the nutrient is normally distributed (based on epidemiologic and other data supporting adequate nutrient intake), the EAR plus 2 SDs of the EAR equals the RDA. If data about variability in requirements are insufficient to set a SD, the EAR is multiplied by 1.2 to assume a 10% variability in intake.
3. *The Adequate Intake (AI)* is the goal intake for micronutrients about which insufficient data are available to calculate an EAR or RDA.
4. *The Estimated Safe and Adequate Daily Dietary Intake (ESADDI)* category was created for micronutrients for which insufficient data are available for developing EARs and RDAs but for which toxic upper levels are known.
5. *The Tolerable Upper Intake Level (UL)* is the highest level of a nutrient that, based on evidence, is unlikely to cause adverse effects in 97.5 % of the population. The use of these different reference categories in planning and assessing nutrition interventions and diets is shown (Table 5.1).

*Sources of nutrients* Nonessential nutrients are required for life but can, under normal conditions, be synthesized in the body from molecules provided from the metabolism of essential nutrients and other compounds. These include ten amino acids and two pro-hormones. Amino acids required for life but considered nonessential because they can be synthesized if sufficient precursors exist include alanine, asparagine, aspartamine, cysteine, glutamine, glycine, ornithine, proline, serine, and tyrosine. Pro-hormones synthesized in the body include vitamin A and vitamin D; but these are produced in amounts insufficient to meet needs, so dietary sources are required. This is why vitamin A and vitamin D are considered essential nutrients. The ten amino acids considered essential (must be obtained from the diet) are phe-

**Table 5.1** Categories of Dietary Reference Intakes (DRIs) for healthy individuals and groups of individuals and their uses in planning and assessing diets (Dietary Reference Intakes: A Risk Assessment Model for Establishing Upper Intake Levels for Nutrients. National Academies Press, available at https://www.ncbi.nlm.nih.gov/books/NBK45182/). Categories of the DRIs shown in the table are Recommended Dietary Allowance (RDA), Estimated Average Requirement (EAR), Adequate Intake (AI), Tolerable Upper Intake Level (UL), and the Estimated Safe and Adequate Daily Dietary Intake (ESADDI)

| Use | For an individual | For groups or populations |
|---|---|---|
| Planning and intervention | RDA: aim for this intake | EAR: used in conjunction with a measure of variability of a group's intake to set goals for a specific population's or group's mean intake |
| | AI: used as a goal for certain micronutrients when insufficient data for setting a RDA were available | |
| | ESADDI: used as a goal for certain micronutrients when insufficient data for setting a RDA were available | |
| | UL: upper limit of safe intake; chronic intake of amounts higher than the UL increases risk of adverse effects | |
| Assessment of intake | EAR: in the absence of clinical, biochemical, or anthropometric data, can be used to examine the possibility of inadequate intake | EAR: used to assess the prevalence of inadequate intakes within a population or group |
| | UL: in the absence of clinical, biochemical, or anthropometric data, can be used to identify and estimate a person's risk for excessive intake | |

nylalanine, valine, threonine, tryptophan, isoleucine, methionine, histidine, arginine, leucine, and lysine; these are conveniently recalled using the mnemonic "Pvt Tim Hall," wherein each letter stands for one of the essential amino acids. Essential nutrients – both macro- and micronutrients – as well as their common food sources are identified (Table 5.2).

## Role of Specific Nutrients Related to Kidney Stones

Nutritional factors are not always implicated in the formation and growth of kidney stones. Furthermore, the presence of a dietary contributor to stones (dietary risk factor) does not necessarily mean an individual will form a stone. In these events, nutritional solutions to reduce the risk of stones are not possible. The next chapter addresses the assessment of a patient's diet to determine if dietary risk factors exist. In the remainder of this chapter, some of the most common dietary contributors to stone formation are reviewed as well as their contributions to stone formation or prevention.

*Calcium* Many adults, including patients who form calcium stones, consume suboptimal calcium [5], i.e., less than the recommended 1,000 mg per day (1,200 mg

**Table 5.2** Dietary sources of the major essential nutrients for humans. The table lists general categories of foods that supply the major macronutrients and micronutrients. Over-the-counter supplements or medications are not included. Also not included are trace elements that are required in very low quantities (<1 mg/day)

| Nutrient | Food sources |
|---|---|
| *Macronutrients* | |
| Carbohydrates | Fruits |
| | Starchy vegetables (e.g., potatoes, beans, squash, peas) |
| | Breads and wheat-based foods (pasta) |
| | Grains of all types (e.g., rice, wheat, oats, corn, barley) |
| | Cereals |
| | Sugar cane, honey |
| Protein (source of amino acids) | Muscle tissue of mammals, fowl, poultry, game, fish, seafood |
| | Eggs |
| | Dairy |
| | Nuts and seeds |
| | Legumes |
| Fats | Meats |
| | Dairy |
| | Nuts and seeds and their butters |
| | Certain fruits (avocado, coconut) |
| | Cooking oils |
| | Foods made or processed with above |
| Fiber | Grains in their whole form (i.e., not refined or processed) |
| | Vegetables (especially starchy vegetables and those with edible skins) |
| | Fruits (especially those with edible peels and seeds) |
| | Nuts and seeds |
| *Micronutrients: vitamins* | |
| Vitamin A | |
| Preformed | Fortified foods (e.g., dairy milk, nondairy milks, cereals) |
| Provitamin | Organ meats of animals/fowl/fish |
| | Carotenoid-rich fruits (e.g., cantaloupe, apricots, pink grapefruit) |
| | Carotenoid-rich vegetables (e.g., spinach, chard, kale, carrots, sweet potatoes, squash, broccoli) |
| Vitamin D | Fortified foods, irradiated foods |
| Vitamin E | Vegetable oils (e.g., corn, sunflower) |
| | Wheat germ |
| | Nuts and seeds |
| | Certain green leafy vegetables (e.g., spinach, kale, mustard greens) |
| Vitamin K[a] | Green leafy vegetables (including broccoli, Brussels sprouts, cabbage) |
| | Fermented soy |
| | Fruits |
| | Cereals |
| | Dairy (especially fermented) |

(continued)

**Table 5.2** (continued)

| Nutrient | Food sources |
|---|---|
| Vitamin C | Most fruits (especially citrus, tomato, mango) |
| | Many vegetables (e.g., potato, peppers, cabbage) |
| B vitamins[b, c] | Grains |
| | Cereals |
| | Breads and baked products |
| | Fortified foods |
| | Vegetables |
| | Meats, fish, poultry (especially vitamins B6 and B12) |
| *Micronutrients: minerals*[d] | |
| Potassium | Fruits (especially dried fruits, avocado, bananas) |
| | Vegetables (especially potatoes, legumes, leafy greens, squash) |
| | Milk, yogurt, kefir |
| | Whole grains |
| | Meats of all kinds (especially fish) |
| Calcium | Dairy milks, yogurt, kefir |
| | Calcium-fortified nondairy milks |
| | Calcium-fortified fruit juices |
| | Kale and other leafy greens (e.g., collards, okra, bok choy, seaweed, broccoli) |
| | Fish with edible bones (e.g., canned salmon, sardines) |
| | Calcium-fortified cereals |
| | Dried figs |
| | Tofu processed with calcium |
| Sodium | Table salt, sea salt |
| | Breads and baked goods |
| | Luncheon meats packaged and/or processed with salt |
| | Cheeses and foods made with cheese |
| | Salty snacks (chips, pretzels, popcorn, salted nuts/seeds) |
| | Processed and packaged foods |
| | Frozen foods |
| | Canned foods |
| Chloride | Found with sodium; see above |
| Phosphorus | Milk and milk products |
| | Cheeses and foods made with cheese |
| | Some vegetables (especially beans, potatoes) |
| | Seeds (e.g., pumpkin, squash) |
| | Nuts |
| | Meats, fish, and seafood |
| | Whole grains |
| | Processed foods |

(continued)

**Table 5.2** (continued)

| Nutrient | Food sources |
|---|---|
| Magnesium | Dark leafy greens |
| | Nuts and seeds |
| | Fish |
| | Whole grains |
| | Legumes |
| | Chocolate |
| | Dried fruits |
| Sulfur | Foods containing methionine and/or cysteine in their protein portion, i.e., meats, poultry, fish, eggs, dairy, legumes, nuts, seeds |
| Iron | |
| Heme | Animal tissue (meats, fish, seafood, poultry, organ meats) |
| Nonheme | Egg yolks |
| | Dried peas and lentils, legumes |
| | Leafy greens |
| | Fortified foods |
| | Seeds (especially squash and pumpkin seeds) |
| Zinc | Animal tissue (meats of all kinds, poultry, seafood – especially oysters) |
| | Whole grains |
| | Fortified foods |
| | Nuts |
| | Cheeses |
| Iodine | Iodized salt and foods made or processed with salt |
| | Seafood |
| | Plant foods grown in iodine-rich soil |
| Selenium | Whole grains |
| | Meats of all kinds, seafood |
| Copper | Nuts and seeds |
| | Legumes |
| | Whole grains |
| Manganese | Whole grains |
| | Nuts and seeds |
| | Leafy vegetables |
| | Beans |
| Fluoride | Fluoridated drinking water |
| | Fish |

[a]Diet-derived vitamin K is in the form of K3 (phylloquinone); vitamin K2 (menaquinone) is synthesized by bacteria in the gastrointestinal tract

[b]The B vitamins include thiamin (B1), riboflavin (B2), niacin (B3), pantothenic acid (B5), pyridoxine (B6), cobalamin (cyanocobalamin, B12), and folate (folic acid, sometimes referred to as vitamin B9). Biotin and choline are also considered B vitamins

[c]Vitamin B12 is produced only by bacteria as neither humans nor plants have the enzymes to synthesize it. Vitamin B12 is, however, consumed when eating animal foods and fish because it is stored in their tissue. Thus, good food sources of vitamin B12 include many fish and meats

[d]Other essential minerals not listed here are required in much smaller quantities, less than 1 mg, and include molybdenum, chromium, nickel, silicon, cobalt, and vanadium

per day is recommended for men >70 years and for women >50 years). A balanced intake of calcium, i.e., neither too low nor too high, is critical. Low calcium intake and/or that which is not distributed at meals results in lower oxalate binding potential in the gastrointestinal tract and contributes to hyperoxaluria in susceptible individuals [6], and this is why dietary calcium with meals is recommended for the control oxalate absorption and urinary excretion [7, 8]. Conversely, a high calcium intake, especially from supplemental sources, may result in increased intestinal calcium absorption and hypercalciuria [9]. Usually, excessive calcium intake is not possible without some amount of calcium supplementation. Unfortunately, many individuals supplement with the total amount of calcium recommended in a day [10]. But because their diets provide some calcium, even without eating calcium-rich foods, these individuals are highly likely to approach or even exceed the UL for calcium, which was recently lowered and is 2,000 mg/day for adult men and adult nonpregnant women [3, 4]. The use of supraphysiologic doses of calcium in patients with calcium malabsorption and hyperoxaluria is addressed in a later chapter. Appendix 8 lists foods relatively rich in calcium.

*Magnesium* Commonly consumed at lower levels than recommended (420 and 320 mg/day for adult men and women, respectively) [11, 12], magnesium can bind oxalate in the gastrointestinal tract and reduce its absorption [12]. Via a different mechanism, low magnesium status leads to suboptimal urinary magnesium excretion and contributes to higher urinary calcium oxalate supersaturation due to the increased potential for oxalate to complex with calcium forming an insoluble complex [13]. For these reasons, supplemental magnesium, above and beyond that which is obtained in the diet, has been a suggested therapeutic strategy for patients with malabsorption and/or hyperoxaluria [14] (if the latter is thought to be due to higher oxalate absorption). Magnesium supplementation can be designed either to raise a person's intake to the values set in the DRIs or to provide excess magnesium to promote oxalate binding. Appendix 9 lists foods relatively rich in magnesium.

*Sodium Chloride (Salt)* Most Americans consume double, if not more, salt in the form of sodium chloride than required. The AI for sodium (no RDA is available) is 1,500 mg/day. Dietary salt is well known to influence calciuria [15]. High intake results in expansion of extracellular volume and decreased renal calcium resorption, contributing to hypercalciuria in susceptible individuals. High intake also increases cystine excretion in urine [16, 17] and is therefore a concern for those with cystinuria. Appendix 10 lists foods relatively rich in sodium.

*Vitamin D* Dietary vitamin D is frequently limiting in adults, and this is especially problematic in northern latitudes and during winter months as dermal vitamin D synthesis is reduced [18]. Research has revealed a relatively high prevalence of lower vitamin D status among patients with recurrent kidney stones [19]. It is unknown whether vitamin D insufficiency or deficiency promotes kidney stone recurrence or is merely associated with it. Vitamin D enhances gastrointestinal calcium absorption and reduces renal calcium excretion with the net effect of inducing

incorporation of calcium in bone. If vitamin D intake is excessive, it could contribute indirectly to hypercalciuria due to hyperstimulation of gastrointestinal calcium absorption [20]. An intake of vitamin D that ensures adequate stores without overstimulating calcium absorption is thus important.

*Oxalate* In the USA, less than 25% of patients who form kidney stones have hyperoxaluria, whereas the prevalence in other regions of the world appears higher [21]. Dietary oxalate is nonetheless a risk factor for calcium oxalate stones. When intake is not opposed by appropriate amount of dietary calcium, more oxalate is absorbed in the gastrointestinal tract [22]. Oxalate is not a nutrient and so there is no "recommended" intake value. Urinary oxalate excretion is generally considered below the risk cutoff at around 40 mg/day. Though it varies between individuals due to differences in food and nutrient intake and also in gastrointestinal physiology, approximately 50% of dietary oxalate may be absorbed [23]. Foods with oxalate content in the realm of 20–755 mg per serving include spinach, rhubarb, almonds, potatoes, bulgur, beets, navy beans, cashews, and cocoa power (see Appendix 6 for details). As humans have no use for oxalate, the sum total of absorbed dietary oxalate and oxalate synthesis must be excreted in urine, leading to the potential for hyperoxaluria.

*Oxalate precursors* Excessive supplementation with ascorbic acid or with certain over-the-counter plant-derived supplements, such as cranberry, turmeric, and cinnamon, may increase urinary oxalate excretion [24–26]. Some other over-the-counter supplements have been shown to be high in oxalate [27], including *Aloe vera* with cactus, green tea extract, and nettle [28], but these have not been shown to induce hyperoxaluria. There is no evidence that the intake of foods rich in vitamin C causes hyperoxaluria.

*Phytate* Higher intakes are associated with higher urinary phytate excretion [29], which results in reduced calcium availability to bind with oxalate and/or phosphorus in urine. Phytate is thus an inhibitor of calcium stone formation in urine. As with oxalate, phytate is not a nutrient, and there is thus no recommended or estimated daily requirement. Phytate usually accompanies foods higher in fiber; Appendix 11 lists foods relatively rich in phytate.

*Dietary acid load* A diet higher for acid load enhances renal citrate resorption [30], reducing its excretion and removing it as a calcium stone inhibitor in urine. A high dietary acid load may also lead to a reduction in urine pH [30], making conditions more favorable for the formation of uric acid or cystine stones. Dietary acid load is higher with the relative absence of dietary potassium and the alkali precursors to which it is frequently bound in foods. Fruits, vegetables, and dairy (milk and yogurt) are rich sources of potassium-bound organic acids such as malic acid, citric acid, and tartaric acid [31]. Appendix 12 lists food groups rich in potassium. These foods exert either a negative or near neutral effect on the potential renal acid load of the diet, thereby opposing the effect of foods with acidogenic potential [32]. When their intake is lower, especially in the context of a relatively high intake of foods with acidogenic potential (those with sulfur-containing amino acids in their protein

structures), the excess $H^+$ secretion causes a higher need for citrate delivered (i.e., resorbed) by the kidneys [33]. Foods highest for acid load per typical serving are meats (fowl, mammal, and marine), egg yolks, and all types of grains and foods made from grain (e.g., cereal, pasta, flour) [32]. Appendix 13 lists food groups and their estimated potential renal acid load. Although meats and grains contain ample potassium, as do fruits and vegetables, their organic acid content is negligible. Potassium that is not complexed with bicarbonate precursor organic acids does not exert an alkaline effect. Appendix 14 lists food groups rich in other organic acids with bicarbonate-generating potential.

*Uric acid precursors* The consumption of flesh from any animal (including marine-derived) may contribute to uric acid biosynthesis [34]. In susceptible individuals, excessive uric acid is thus excreted in urine. Foods with a relatively high purine content (>100 mg/100 g) include fish, meats, and liver [35]. Some plants have purines, although at much lower concentrations than animal foods, but these exert a different effect on uric acid metabolism and are not thought to contribute to uric acid biosynthesis [36]. Alcohol and fructose are thought to be uric acid precursors; biological mechanisms and clinical presentations have been reviewed [37, 38].

*Fluids* Low intake results in suboptimal urine volume, contributing to urine supersaturation and increased risk for precipitation of calcium and other relatively insoluble complexes [39].

*Fruits and vegetables* The 2015–2020 version of the US Dietary Guidelines for Americans (Appendix 2) recommends the equivalent of 2.5 cups of fruits and vegetables (combined) for a person consuming 2,000 kcals/day. This amounts to approximately five servings/day. As discussed earlier, a suboptimal intake of fruits and vegetables could contribute to low urinary citrate excretion and acidic urine. In addition, a low intake is thought to contribute to the potential for higher urinary oxalate excretion due to the intake of prebiotic material (substrate) insufficient to colonize and sustain optimal oxalate-degrading bacteria in the gastrointestinal tract [40, 41]. Due to their high fiber content, fruits and vegetables are a major source of prebiotic potential. Without sufficient prebiotics, a healthy gastrointestinal microbial profile that includes oxalate-degrading bacteria may be less likely. Also due to a lower fiber intake, the risk for higher urinary calcium excretion exists as less fiber in the gastrointestinal tract means less inhibition of calcium absorption [42]. A diet high in fiber was shown to reduce urinary calcium excretion [43]. Its use as a means to regulate the gastrointestinal absorption of dietary calcium, assuming calcium balance, has been proposed [44].

*Other factors* The excessive intake of other dietary compounds may contribute to the development of various urinary stone risk factors and/or stones. These include foods and beverages containing refined (processed or "simple") carbohydrates [45, 46], caffeine [47, 48], and fructose [38, 49], a monosaccharide naturally expressed in many fruits and some vegetables and found also in many sweetened and processed foods and beverages.

Table 5.3 provides a condensed description of the common dietary contributors to stones addressed above and their mechanisms of action that increase stone risk.

**Table 5.3** Major dietary risk factors related to the risk for kidney stone formation and growth. Information shown includes the source (column 1), mechanism of action (column 2), and the urinary derangement (column 3) for each risk factor

| Dietary risk factor | Mechanism for risk | Urinary outcome |
|---|---|---|
| Suboptimal fluids [39] | Increases urine saturation | High urine supersaturation indices for certain measured crystalloid(s) |
| Excessive sodium chloride [15–17] | (1) Expands extracellular volume, reducing renal calcium reabsorption, resulting in more excreted | (1) Hypercalciuria |
| | (2) Increases urinary cystine excretion | (2) Cystinuria |
| High potential renal acid load of diet [30–33] | (1) May increase calcium bone resorption, resulting in higher renal filtered load and more calcium excreted | (1) Hypercalciuria |
| | (2) Increases renal citrate reabsorption, resulting in less citrate excreted | (2) Hypocitraturia |
| Excessive intake of refined carbohydrates, caffeine, alcohol [45–49] | (1) Carbohydrates – increases gastrointestinal calcium absorption; increases plasma insulin, reducing renal calcium reabsorption; fructose may increase uric acid biosynthesis | (1) Hypercalciuria; hyperuricosuria (from fructose) |
| | (2) Caffeine – adenosine antagonism | (2) Hypercalciuria |
| High intake of uric acid precursors (fructose, alcohol) and/or purines [34–38] | (1) Increases uric acid biosynthesis, resulting in more uric acid excreted | (1) Hyperuricosuria |
| | (2) Reduces urine pH, decreasing urinary uric acid solubility | (2) Urine pH <5.6 |
| Low calcium (also magnesium) intake and/or intake not timed with meals [7, 8, 12–14] | Decreases gastrointestinal binding potential for oxalate, resulting in more oxalate absorbed | Hyperoxaluria |
| High intake of high-oxalate foods unopposed by ample calcium or magnesium [22, 23] | Increases renal oxalate load | Hyperoxaluria |
| High intake of oxalate precursors [24–28] | Increases oxalate biosynthesis | Hyperoxaluria |
| Lower intake of prebiotics and/or probiotics [41, 50] | Decreases gastrointestinal oxalate-degrading potential via dysbiosis (also referred to as dys-symbiosis) | Hyperoxaluria |

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# Dietary Assessment of Patients Who Form Kidney Stones

6

Kristina L. Penniston

**Synopsis**

1. Assessment of a patient's habitual dietary pattern and intake of specific foods and beverages is important in identifying whether diet is contributory to stone formation. Registered dietitian nutritionists are experts at obtaining patients' diet histories and generating assessments of their habitual intake.
2. The 24-h urine analysis and the stone composition report, part of the usual metabolic work-up of patients with urinary tract stones, are not surrogates for dietary assessment as food-derived compounds that may appear in urine or renal calculi are subject to multiple metabolic processes after ingestion, during circulation, and prior to excretion.
3. If diet is not contributing to stone formation, or if a patient is already eating according to a dietary recommendation aimed at controlling a specific stone risk factor, then the assessment of the patient's diet will reveal this.
4. The results of dietary assessment for stone prevention will guide the development of a nutrition intervention, i.e., specific dietary changes, if any are warranted.
5. Dietary changes should be implemented according to the available evidence for the role of diet in stone prevention and targeted to a specific dietary risk factor(s). Strategies to accomplish the changes are tailored to each patient based on his/her nutritional needs; the presence of other medical conditions requiring integration

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of dietary recommendations; use of medications with nutrient interactions; food knowledge, beliefs, and attitudes; lifestyle; and other patient-specific factors.

## Introduction

By multiple mechanisms, diet can influence the formation and growth of many types of kidney stones. Diet, however, is only one of several factors that predisposes an individual to form stones. Underlying medical conditions, certain medications, genetic heritability, altered anatomy, and some non-dietary lifestyle factors are other factors that influence stone formation. It is therefore important to evaluate whether diet is causative to an individual's stone formation and recurrence risk prior to providing dietary recommendations or, in the case of the registered dietitian nutritionist (RDN), medical nutrition therapy.

Diet contributes to many medical conditions, including type 2 diabetes, osteoporosis, cardiovascular disease, and urolithiasis. In these conditions, clinicians may prescribe pharmacologic agents or – if diet is deemed contributory – recommend dietary changes and/or refer to an RDN for consultation and follow-up (see Appendix 1 for referral form); frequently, both strategies are employed. Dietary changes are not needed, however, in patients whose diets already embrace preventive guidelines or in those whose condition is not caused by diet. In a broad scale, general healthy diet recommendations may be considered appropriate for all patients and are useful for patients in whom no lithogenic risk factors are identified. But, when possible, it makes sense that the priority for disease-specific dietary recommendations should be on those most likely to affect disease pathology [1]. Misplaced priority on useless dietary changes could falsely elevate patients' hopes about prevention or interfere with their adherence to more important aspects of their therapy.

Patients frequently request for dietary approaches to prevent stones, often hoping to avoid medication. Our response to such requests should be to investigate whether diet is causative in the same way as we explore non-dietary factors (e.g., anatomical or physiological abnormalities, underlying medical conditions, use of certain medications) for their contribution to stone recurrence risk. Determining whether diet plays a role in stone risk is important for many reasons, including (1) if there is no nutritional risk factor or cause for a patient's stone formation, there will likely be no nutritional cure; (2) in the absence of any dietary contributor to stone recurrence, patients can form unfounded expectations about the ability of dietary change to alter their stone risk; and (3) the ability of patients to implement dietary changes, if indicated, may be dependent on the number of recommendations provided [2] and on whether they actually address an existing risk factor.

## Assessing the Diet

*What is dietary assessment?* Just as biochemical tests, imaging studies, and the physical exam are tools used to rule in or out non-dietary contributors to stones, a diet assessment is the tool for determining whether diet is contributory [3]. Dietary

assessment is the comprehensive evaluation of an individual's usual food intake and pattern of intake in the context of (1) anthropometrics (e.g., height, weight, weight-to-height ratio); (2) medical history and medications; and (3) relevant, disease-specific biochemical indices, which vary depending on the condition for which a patient is being evaluated [4]. In the case of urolithiasis, these would include, but not be limited to, stone composition and stone-related urinary parameters (Table 6.1). The dietary assessment is the appraisal of the habitual intake of foods and nutritional supplements (i.e., nonprescriptive, over-the-counter vitamins, minerals, herbals, etc.). The period of time for which diet is assessed, as well as whether or not to focus only on specific food or supplement factors, varies by the reason for consultation or evaluation. The dietary assessment is usually done after completing steps 1–3 above, though data for any of these areas may be obtained during the dietary assessment. Different methods for assessing diet are briefly reviewed (Table 6.2).
There is no evidence-based, validated dietary "risk profile" for assessing lithogenic risk factors in the diet. A 24-h urine collection or "risk profile," though useful in identifying lithogenic risk related to renal function and handling [19], may only *suggest* the presence of dietary excesses or inadequacies; it is not a surrogate for dietary assessment as many urinary parameters are subject to metabolic control prior to renal handling, such as during digestion, absorption, circulation, and storage. Some stone risk factors that appear in urine are synthesized in vivo by precursors that may or may not be consumed in the diet. By any means – be it by 24-h diet recall, diet history, food frequency questionnaire or screener, weighed diet records, or any other of a number of alternatives – dietary assessment is uniquely subjective and controlled in most ways by the patient. The patient's willingness and ability to provide accurate information depend on a number of both patient and provider factors, not the least of which include how accepting the patient perceives the provider to be, how well the patient describes his/her intake, and how accurately the provider interprets the information.

People's dietary habits are inherently personal and frequently linked to cultural and ethnic identity. Patients feel most comfortable providing dietary information in a nonjudgmental, culturally aware, and understanding environment [20, 21]. RDNs and similarly trained nutrition experts are skilled in dietary assessment yet are not widely distributed among urology clinics, where the majority of patients are seen for stone prevention [22]. Thus, non-dietitian providers often include diet in their evaluation. But urologists and others frequently lack the time (which may require >30 min per patient if both assessment and intervention are done) and detailed knowledge about foods, digestion, and absorption to conduct a thorough and meaningful diet assessment. Because of this, urologists have expressed a desire for greater access to dietitians [23].

*General dietary assessment* A general dietary assessment may begin by asking the patient if he or she follows any special diet. The words patients use to describe their overall dietary patterns, whether accurate or not, can be useful in interpreting the data obtained. Patients may then be queried about their appetite and whether any changes have occurred recently and about their weight history. Other information

**Table 6.1** Dietary indicators for stone formation and growth and their link to derangements in the 24-h urine collection

| Dietary risk | Indication(s) for assessing risk | Mechanism for dietary risk |
|---|---|---|
| Suboptimal fluid intake | Assess as needed, especially when: | Low fluid intake results in concentrated (less dilute) urine and high urine supersaturation for specific crystalloid(s) |
| | Urine output less than 2 L or some other output target | |
| Excessive dietary salt (NaCl) intake | Assess as needed, driven by presence of: | Dietary sodium chloride expands extracellular volume and increases urinary calcium and cysteine excretion |
| | Hypercalciuria | |
| | Higher urinary sodium or chloride excretion | |
| | Patient is prescribed a thiazide diuretic for hypercalciuria | |
| | Cystinuria [5] | |
| Higher intake of refined or simple carbohydrates [6], caffeine [7], alcohol [8, 9] | Assess as needed, driven by presence of: | Carbohydrates may: |
| | Hypercalciuria (refined or simple carbohydrates, caffeine, alcohol) | Increase calcium absorption from GI tract |
| | Hyperuricosuria (fructose, alcohol) | Increase plasma insulin, reducing renal calcium reabsorption |
| | | Increase uric acid biosynthesis (fructose in particular) |
| | | Caffeine may: |
| | | Block c-AMP and thus reduce renal calcium reabsorption |
| | | Alcohol may: |
| | | Increase osteoclast activity |
| | | Increase uric acid biosynthesis |
| Higher acid load of diet [10] | Assess as needed, driven by presence of: | Unbalanced consumption of alkaline/neutral vs. acid-ash foods can lead to: |
| | Acidic urine | Systemic acidosis and low urine pH |
| | Hypercalciuria | Increased calcium resorption from bone |
| | Hypocitraturia | Increased renal citrate reabsorption |

(continued)

**Table 6.1** (continued)

| Dietary risk | Indication(s) for assessing risk | Mechanism for dietary risk |
|---|---|---|
| Higher intake of uric acid precursors (fructose, alcohol, purines from animal/marine flesh foods) [9, 11, 12] | Assess as needed, driven by presence of: | Dietary purines (animal-derived), fructose, and alcohol provide substrate for uric acid biosynthesis |
| | Hyperuricosuria | |
| | Precipitation of uric acid crystals in sample (important to note if urinary uric acid excretion is unusually low) | |
| Suboptimal calcium and/or magnesium intake; intake timed apart from meals (especially if from supplements) | Assess in the presence of: | Insufficient calcium intake leads to higher oxalate solubility and absorption from GI tract |
| | Higher oxalate excretion | |
| | Lower magnesium excretion | |
| High intake of high-oxalate foods relative to consumption of calcium and/or magnesium | Assess in presence of hyperoxaluria and when oxalate consumption occurs: | High oxalate intake without sufficient calcium leads to higher oxalate content and solubility in GI tract and higher oxalate absorption |
| | In absence of (unopposed by) calcium and/or magnesium sources | |
| | By patients prone to malabsorption | |
| | By patients with primary hyperoxaluria | |
| Intake of herbal over-the-counter supplements and/or ascorbic acid [13–16] | Assess in presence of hyperoxaluria | Ascorbic acid is metabolized to oxalate |
| | | Some plant-derived dietary supplements provide high-oxalate load |
| Dysbiosis (dys-symbiosis) [17, 18] | Assess if: | Antibiotics: |
| | Frequent antibiotic use | Target beneficial gut bacteria, including those that may degrade oxalate |
| | Chronic diarrhea | Diarrhea: |
| | Suboptimal intake of prebiotic material | Reduces colonization of beneficial gut bacteria, including those that may degrade oxalate |
| | | Low intake of prebiotics (contained largely in the fiber of fruits, vegetables, and whole grains): |
| | | Provides insufficient substrate for oxalate-degrading bacteria in GI tract |

**Table 6.2** Methods for assessing patients' diets

| Method | Description | Advantages | Disadvantages |
|---|---|---|---|
| Usual intake/diet history | Qualitative method in which patient is asked to recall a typical daily intake pattern, including specific foods and beverages, frequency of consumption, methods of preparation, and portion sizes consumed | Easily obtained | Depends on patient's ability to provide details |
| | Patient is usually asked to run through a typical day in chronological order | Accomplished relatively quickly if done by dietitian or other trained professional | Can be challenging for patients whose intake varies significantly from day to day or week to week or whose memory is questionable |
| | | Identifies longer-term, habitual dietary habits | Portion sizes may be inaccurately described |
| | Reveals lifestyle and other factors related to food intake | Information can be used to quantify usual intakes of specific macro- and micronutrients and food groups | Requires assessor to be able to correctly interpret patient-reported information |
| | | Relatively low patient burden | |
| 24-h recall | Qualitative method in which patient recalls all foods and beverages consumed in the last 24 hours, including quantities, portion sizes, and methods of preparation | Easily obtained | Limited data obtained; may not reflect usual or habitual intake |
| | Can be completed in person or over the telephone; some nutrient analysis software programs provide modules specifically designed for 24-h recalls | Requires limited memory | Portion sizes may be inaccurately described |
| | | Information can be used to quantify last 24-h intake of specific macro- and micronutrients and food groups | Requires expertise by assessor to correctly interpret data provided |
| | | Low patient burden | |

(continued)

**Table 6.2** (continued)

| Method | Description | Advantages | Disadvantages |
|---|---|---|---|
| Food frequency questionnaire (or food screener) | Written or computerized checklist of foods and beverages which patients complete, usually on their own | Questionnaires for specific medical conditions, groups of patients (e.g., children, adults, racial/ethnic groups), and time frames (e.g., month, year) exist; many are validated against more rigorous diet assessment methods | Depending on length of questionnaire (some are several pages long), patient burden may be quite high |
| | Foods are usually listed in categories; frequencies are usually listed for patient to identify "daily," "weekly," or other consumption | Can be used to quantify intake of specific macro- and micronutrients and food groups | Patient error in completing questionnaire, such as in estimating frequency of intake over a year's time, is well documented |
| | | | Usually no way to identify food preparation methods |
| | Useful in determining general dietary patterns and trends | | Not all questionnaires query about specific portion sizes, resulting in over- or underestimation of intake |
| | | | Questionnaires designed for specific medical conditions or populations are not reliable when used out of context |
| Food log, diet record or journal | Patient records all food and beverage consumption for a variable length of time (a day, multiple days, a week) in as much detail as possible | Patient records information as soon as possible after consumption, eliminating errors due to faulty memory | As with other methods, depends on patient's honesty and ability to accurately record data |
| | Food scales may be provided to aid in accurately recording amounts prepared and consumed | Data provided can be extremely accurate, so much so that weighed food records are considered as close to a "gold standard" as currently exists | Patient burden is relatively high, especially when food scales are used |
| | Data is typically entered into a nutrient analysis software program to obtain detailed information about macro- and micronutrient consumption | | Patients may err in recording food quantities |
| | | | Quality of data may decline in relation to the number of days recorded |
| | | | Patients may not eat the way they normally eat during the documentation period |

obtained during a general dietary assessment may include the extent to which patients eat more or less the same things every day, eat at the same times of day, eat out or bring home take-out foods, use condiments, participate in food preparation, skip meals, snack between meals, use alcohol, and avoid certain foods (and if so, why). Information obtained during the course of the assessment includes: details about where foods are consumed (e.g., home, work, school), portion sizes, methods of preparation, grocery shopping habits, food likes and dislikes, swallowing and dentition issues, food insecurity, knowledge of nutrition, and use of nutritional supplements. If quantification of intake is desired, data may be entered later into a nutrient analysis software program. Alternatively, a RDN may quantify in the clinic the foods and nutrients of interest by estimation, using his/her knowledge of nutritional composition and food tables that provide nutrient content.

*Targeted dietary assessment* Assessment may be targeted to the condition under evaluation and is always aimed at identifying the specific dietary mechanism(s) contributing to disease etiology, exacerbation, or risk of recurrence. The following is an analogy of a targeted assessment using the physical therapist (PT) as an example. A patient referred for a specific physical or muscular derangement is not typically assessed by the PT for his/her entire body and musculature as he or she might be if undergoing a general physical assessment. Rather, in the interest of time and efficiency and to address an acute injury or chronic problem, the PT will focus on body areas near to and involved in the problem of interest. In the area of urolithiasis, a targeted dietary assessment by the RDN or other person conducting it may be similarly indicated and should focus around the most common dietary risk factors, driven or informed by the presence of biochemical aberrations (Table 6.1).

*Common pitfalls during dietary assessment* Depending on how comprehensive and if targeted to certain foods or not, dietary assessment is frequently not accomplished in a couple of minutes. Without ample time, it is therefore understandable that shortcuts are taken. However, some shortcuts can lead to inaccurate assessment. A common problem in assessing the diets of patients is to ask leading questions, such as, "You don't eat a lot of salt, do you?" or "Tell me which of these foods (provider hands the patient a list) you eat." The appearance of judgment or expectation on the assessor's part could lead to withholding or otherwise inaccurate patient reporting [20]. Thus, open-ended questions about specific foods of interest are best. Another problem is the inaccurate assessment of portion sizes. A patient might say, "I eat a lot of peanuts," but his/her interpretation of "a lot" – or the assessor's – could differ vastly from another who uses the same verbiage. Strategies to elicit accurate portion size estimations are widely employed by dietitians and include pictures or photos; synthetic ("fake") foods; household measuring utensils; plates, bowls, and cups; food packages; and/or follow-up questions that result in the reasonable assurance of correct sizing [24]. Information about frequency of intake is also important. The frequent vs. infrequent intake of "high-risk" foods should be discerned. The patient who "loves spinach" but who only eats it once a month or so is likely to benefit little – if at all – from a restriction of spinach to address her risk of calcium oxalate

stones. Yet another mistake is to ask only about meals. Rather than asking what the patient typically eats for breakfast, lunch, and dinner, use open-ended questions, such as, "Tell me about the first time in your day that you eat or drink anything." This avoids the potential to miss between- and/or after-meal food and beverage intake, which could be significant. Moreover, some patients may follow a "grazing" dietary pattern and not identify with discrete "meals" when queried about them.

*Quantification of foods and nutrients* Beyond usual servings per day of certain foods – such as fruits and vegetables, meats, breads and baked goods, calcium-rich foods, and beverages – it is usually also desirable to quantify the intakes of specific nutrients, such as sodium and calcium, in milligrams or grams consumed per day. This requires detailed knowledge of the sources of foods that express these nutrients as well as the amounts they contain. While some may wish to quantify the amount of oxalate consumed, this is problematic due to the extensive variability in the reported oxalate content of foods, to the variable bioavailability of food oxalate, and to variations in human gastrointestinal tract physiology leading to significant differences in oxalate absorption [25]. Although these same problems exist to some degree in quantifying sodium and calcium, food values for these minerals are quite stable across multiple data sets.

## Link Lithogenic Risk Factors to Results of the Diet Assessment

There is no standard diet or eating plan that is universally effective for all stone formers. Even when patients form the same type of stone, risk factors (i.e., causes) frequently differ, if not in the specific risk factor, then in its magnitude of severity. Targeted nutrition therapy is therefore appropriate. While it might be tempting to address each and every dietary "indiscretion" uncovered in dietary assessment, this may result in overwhelming the patient or providing useless recommendations. The goal of the diet assessment is to provide recommendation(s) with the greatest possible impact on stone disease. Dietary risk factors should be linked directly to biochemical or other evidence exposing stone risk. For example, high sodium intake revealed from the diet assessment would be linked to high urinary calcium excretion (if observed), and lower salt intake would be a priority. However, high sodium intake in the absence of high urinary calcium excretion would have lower priority for intervention and would warrant only a comment, perhaps, about future risk. Plenty of patients have high sodium intake by standard definitions (e.g., Dietary Reference Intakes [26] – see Appendix 5) but have normal urinary calcium excretion, even in repeated 24-h urine collections. This could be due to a regular exercise regimen that induces ample dermal sodium excretion, to the presence of chronic calcium malabsorption, or to higher fecal sodium excretion. Focusing on sodium reduction in such scenarios could diminish the patient's enthusiasm for other dietary changes that are capable of real risk reduction or for dietary stone prevention as a whole. Moreover, reducing sodium intake in these situations would not reduce the patient's stone risk. This could deflate patients' expectations for the potential of diet

to reduce stone risk. Below, common urinary risk factors for stones and links to dietary risk factors are reviewed.

## Aim Recommendations at Specific Stone Risk Factors in the Diet

After dietary assessment and the identification of dietary risk factors for stone recurrence, nutrition intervention in the form of recommendations (or nutrition therapy if guided by a RDN) is provided. Of the different types of urinary tract stones, calcium oxalate, mixed calcium, and uric acid stones are most likely to have a nutritional influence. Cystine and struvite stones are generally affected by diet to a lesser degree. The discussion below addresses major dietary factors related to calcium and uric acid stones. These dietary factors are further described in Table 6.1.

*High urinary calcium excretion: calcium intake* The dietary assessment of patients with normal urinary calcium excretion may not include an extensive accounting of calcium intake. Conversely, patients with high urinary calcium excretion should be assessed for food and supplement contributors to calcium in order to rule out diet as a contributor. Evidence suggests that most adults, including (and perhaps especially) calcium stone formers, consume suboptimal calcium [27], i.e., <1,200 or so mg/day. In these cases, other explanations for hypercalciuria are identified. Nonetheless, there are those who supplement with large amounts of calcium. Patients whose calcium intake – either from diet alone or from diet plus supplements – is deemed excessive and therefore contributory to high urinary calcium excretion should be directed to decrease/normalize their intake per appropriate reference standard (age and gender specific) [26]. Usually, excessive calcium intake is not possible without some amount of calcium supplementation. Especially in cases where patients are supplementing calcium in the total amount required in a day [28], excessive calcium intake from supplements should be ruled out as a contributor to hypercalciuria. Note that this concern may not apply to patients who supplement with supraphysiologic doses of calcium due to malabsorption and concomitant hyperoxaluria.

*High urinary calcium excretion: sodium chloride intake* Dietary sodium chloride (commonly referred to as salt) is well known to influence calciuria [29]. In individuals with high urinary calcium excretion, salt intake should be assessed (see Appendix 10 for a list of foods high for salt). Without high urinary calcium excretion, the exhaustive assessment of dietary salt may be a lower priority, especially if there are multiple other risk factors to address. But because salt intake may vary on a day-to-day basis, calcium stone-forming patients with seemingly well-controlled sodium as judged solely by their 24-h urinary sodium excretion should be assessed for intake. If high, strategies to reduce added salt and reliance on higher-sodium foods should be suggested with a goal of reducing current intake. Helping patients reduce their current salt intake to less than whatever it is now, monitoring its effect on cal-

ciuria in the next 24-h urine collection, and then recommending lower intake as needed thereafter may be a more successful approach than simply admonishing the patient to consume "no more than" a certain number of milligrams or milliequivalents of sodium or salt daily.

*High urinary calcium excretion: vitamin D intake* Usually, vitamin D is limiting in adults, especially in northern latitudes and during winter months [30]. Vitamin D enhances gastrointestinal calcium absorption and also reduces renal calcium excretion with the net effect of inducing incorporation of calcium in bone. In theory, the effect on urinary calcium excretion of dietary vitamin D (cholecalciferol) in the setting of normal vitamin D status is non-pathologic. Even high-dose vitamin D repletion, such as for insufficiency or deficiency, has not been linked with hypercalciuria [31]. Nonetheless, if vitamin D status is high, and if hypercalciuria is present, excessive vitamin D intake may be suspected; this would be revealed in the dietary assessment. Caution in recommending lower vitamin D intake is warranted, however, even in the setting of hypercalciuria as likely only a small percentage of hypercalciuria is explained by excessive vitamin D intake.

*High urinary calcium excretion: phytate intake* While understudied, phytate in urine is a potent inhibitor of calcium stone formation as phytate binds with calcium and remains soluble [32]. Unfortunately, the analysis of urine for phytate is limited to a few laboratories, none of which provide commercial analytical services to clinicians acquiring 24-h urine collections from their patients. But dietary phytate is quantifiable (see Appendix 11 for foods rich in phytate) and is known to relate directly to urinary phytate excretion [33, 34]. Historically known as an "antinutrient" because of its ability to reduce the absorption of dietary zinc, iron, calcium, and other divalent cations, phytate is commonly found in foods rich in fiber and, coincidentally, oxalate. Nutrient deficiency due to a high phytate intake and relatively low intake of essential minerals is a problem among people in developing nations, causing impaired growth, hypogonadism, and altered immune and cognitive function. Dietary phytate could also be a problem in patients prone to higher oxalate absorption as phytate is able to complex calcium and thereby reduce its availability to bind with oxalate. Nonetheless, the use of phytate as a calcium stone inhibitor is attractive. Data from an observational study showed an inverse association of phytate intake with risk of incident kidney stones in younger women [35]; this association was not, however, apparent in men [36].

*High urinary oxalate excretion: calcium intake* Patients with low calcium intake and high urinary oxalate excretion should be advised to normalize calcium intake using appropriate cultural-/national-, age-, and gender-specific guidelines [26] (see Appendix 8 for a list of foods and beverages relatively high for calcium). It should be noted that both dairy (animal-derived) and nondairy calcium sources are abundant. Calcium intake should be distributed at meals and snacks in an effort to maximize the availability at all times of calcium in the gastrointestinal tract. Patients whose high urinary oxalate excretion coexists with malabsorption have been found

to benefit from a combination of higher calcium intake from a combination of foods and supplements [37], each titrated as needed over time using urinary oxalate excretion as the primary outcome measure.

*High urinary oxalate excretion: oxalate intake* The intake of oxalate by patients with urinary oxalate excretion under adequate control is not usually a concern. As only a minority of patients who form calcium oxalate stones have hyperoxaluria [38], the assessment of oxalate should be reserved for these individuals. The intake of oxalate is difficult to quantify as many nutrient databases either do not include oxalate values from foods or have values with questionable validity [25]. Moreover, the amount of oxalate in a given food matters little. Rather, the oxalate bioavailability of the food or, more importantly, the meal in which foods are consumed is the determining factor for oxalate absorption and urinary oxalate excretion [25, 37]. Reduced oxalate intake, if deemed necessary, should be limited to those with demonstrated hyperoxaluria that is unresponsive to normalized calcium intake and limited only to the foods highest in oxalate (Appendix 6) and consumed frequently. Wholescale elimination of high-oxalate foods, however, should be avoided as they are typically healthy, low-calorie foods that are ample for stone inhibitors, such as phytate, magnesium, fiber, prebiotics, bicarbonate precursors, and antioxidants – all of which inhibit stone formation by various mechanisms.

*Low urinary citrate excretion: dietary acid load* A dietary acid load unopposed by dietary alkaline sources enhances renal citrate reabsorption and reduces its excretion. The acid load of the diet is higher with the relative absence of potassium and the dietary alkali precursors to which it is bound compared to the presence of organic sulfur. Stated conversely, dietary acid load is higher with the relative abundance of dietary organic sulfur compared to the intake of alkali precursors. Lower alkali intake increases $H^+$ secretion, which increases citrate reabsorption [39]. Potassium is considered a marker for dietary alkali potential as it is frequently complexed with organic acids that serve as bicarbonate precursors. Many adults consume less potassium than recommended [40, 41]. Potassium-rich foods include most all fruits and vegetables, legumes, yogurt, milk, and many varieties of cold water fish (though the sulfur-containing amino acid contribution of fish may outweigh its potassium contribution – see below). Appendix 12 provides a list of foods relatively rich in potassium. The alkali precursors typically accompanied in foods by potassium (or alternatively by other minerals) include citric acid, malic acid, and tartaric acid (Appendix 14 lists foods rich in these organic acids). Foods rich in these acids are most all fruits and vegetables and their juices. In patients whose intake of fruits and vegetables averages <5 servings/day and whose urinary citrate excretion is suboptimal, increased fruits and vegetables is a good start to correcting low excretion [40]. In addition, if the relative intake of acidogenic foods – those with sulfur in their amino acids (methionine and cysteine) – is excessive, concomitant reduced intake of these foods is required in order to obtain a favorable net effect. Foods highest for acid load per typically consumed serving are all meats (fowl, mammal, and marine), egg yolks, and all types of grains and foods made

from grain (e.g., cereal, pasta, flour); see Appendix 13 [41]. Because the need for methionine and cysteine, which are essential amino acids (meaning they must be obtained from diet), differ with respect to age, life stage, and body habitus, it is usually most useful to recommend lower-than-current intake. This may be accomplished by advising smaller portion sizes or fewer servings of meats and grains in a day or throughout the week. Follow-up effects on urinary citrate excretion will indicate whether more restriction is required. In some cases, simply increasing fruit and vegetable intake may elicit a response in the desired direction without the need for restriction(s). As dietary strategies may be able to raise urinary citrate excretion by only 200 mg or so, adjunct pharmacologic therapies are needed in many.

*High urinary uric acid excretion: purine intake* Dietary changes are not likely to substantially reduce urinary uric acid caused by uric acid overproduction, such as is the case with gout [42]. Both a complete medical history and dietary assessment are required in the patient with hyperuricosuria in order to evaluate the role of diet. If indeed diet is contributory, focus on animal purine sources, such as seafood, fish, and organ or muscle tissue of any animal (including fowl). Some plants have purines, although at much lower concentrations than animal foods, but these exert a different effect on uric acid metabolism and are not thought to contribute to uric acid biosynthesis [43]. Thus, they need not be restricted. Unwarranted restriction of plant foods because of their reported purine content could reduce urine pH, which would make urinary uric acid less soluble and increase the risk for uric acid precipitation and stone formation.

*Low urine volume: fluid intake* As much has been written elsewhere about the primary effect of fluid intake on urine output and stone risk (see chapter on low fluid intake), and as evidence is very strong that fluid intake affects kidney stone risk [44–50], little will be said here. Strategies that patients may find helpful as they work on increasing intake are provided (Table 6.3).

*Multiple urinary risk factors: fruit and vegetable intake* A low intake could contribute to multiple urinary derangements and stone risk factors, including (1) low urinary citrate excretion due to high dietary acid load from suboptimal intake of bicarbonate precursors, (2) high urinary oxalate excretion due to an intake of prebiotic material insufficient to colonize and sustain optimal oxalate-degrading bacteria in the gastrointestinal tract, or (3) higher urinary calcium excretion due to unregulated/higher calcium absorption from a low or suboptimal fiber intake. If diet is suspected to contribute to any of the above sequelae, recommend a higher intake, usually at least five servings or cups/day, of a wide variety of fruits and vegetables. Patients with less experience in eating fruits and vegetables may need information to help them understand what a serving of a fruit or vegetable is, how to shop for and store them, and how to prepare them. There are multiple healthy eating patterns that are rich in fruits and vegetables that could be suggested as a dietary pattern. These include the 2015 Dietary Guidelines for Americans (Appendix 2), the Dietary Approaches to Stop Hypertension diet, and the Mediterranean diet (Appendix 3), all of which have been suggested at one time or another as suitable, perhaps with minor modifications, for stone prevention.

**Table 6.3** Strategies for helping patients increase their fluid intake

| Strategy | Rationale | Specific tactic |
|---|---|---|
| Encourage a diversity of fluids | Unnecessary restrictions of certain beverages may discourage overall fluid intake or dampen enthusiasm for the fluid intake goal | Emphasize lower-calorie, low-sugar beverages, including water, flavored waters, coffee, tea, vegetable juices, fruit juices, milk (including nondairy milks), kefir; recommend beer, wine, soda, sweetened drinks (in moderation if at all) |
| Encourage patient to track ins and outs | Knowledge of what is needed to produce the target volume of urine in a day may help patients understand the relationship of their fluid intake to urine output | Use household measuring cups and/or containers with visible volume markings to assess and track fluid intake in a day while also totaling total urine output (e.g., by keeping a log and pencil handy when toileting) |
| Have options ready and available for all situations | Carrying around a refillable beverage container is a trigger to drinking | Keep refillable, ready-to-use fluid containers at home, work, school, in vehicles, at the gym, etc. |
| Distribute fluid intake throughout the day, schedule if needed | A patient's thirst mechanism may not be an appropriate cue to his/her need for fluids | Divide the day into 3 or 4 equal sections and assign a fluid intake goal to each section; use cell phone or watch timers as needed to remember to meet goals |
| Develop healthy daily "drinking habits" | The conscious formation of healthy habits is a mainstay of medical nutrition therapy for stone prevention and is linked to effectiveness | Suggest always drinking a glass of water or other beverage: (1) upon waking, (2) before leaving home for the day, (3) after lunch, (4) immediately upon coming home for the day, and (5) before bed |
| Modify and individualize fluid intake goals to each patient | Some patients require fluid restrictions, have periods of time during which they cannot drink (e.g., in certain working situations), suffer from urinary incontinence or urgency, or have nocturia that disrupts good sleep | Schedule the majority of fluid intake during times of day and in situations that are most favorable for drinking; increased vigilance against other stone risk factors is warranted if unable to increase fluids to completely meet goal |

Dietary factors related to urolithiasis not discussed herein include fish oil, pyridoxine (vitamin B6), magnesium, excessive energy intake, obesity/overweight, alcohol, and fructose (though some are addressed in Table 6.1). Roles for the increased or decreased intake of these factors are supported in the literature and have been reviewed [44–50].

## Conclusion

The assessment of the diet drives the prescription of medical nutrition therapy or dietary intervention much like prescription of physical therapy, which is similarly preceded by the assessment of the physical therapist. In the case of nutrition

therapy, the specific contributing dietary mechanism(s) to stone disease etiology or risk factor is identified by a RDN, and therapy aimed at that mechanism(s) is provided. While dietary recommendations can be provided by non-dietitians and may not require an assessment of each patient's diet, they may not address a dietary risk factor. Along with biochemical and urinary risk factors, dietary assessment can shed light on aspects of the diet that contribute to stone formation and growth and can point the way to specific recommendations for change.

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# Part III

# Nutrition Therapy for Specific Lithogenic Risk Factors

# Nutrition Therapy for Low Urine Volume

7

Marawan M. El Tayeb

Kidney stones result from a complex process; however, the two main opposing processes are urinary supersaturation (providing a driving force) and urinary inhibitors (providing protective effects) [1, 2]. High urine output decreases supersaturation of various stone components and, therefore, decreases stone episodes [3]. Low urine volume is considered an important risk factor for both onset and relapse of stone disease [4–6]. Curhan et al. in two large series, recognized the importance of high fluid intake and its effect on urine output [7, 8].

Reasons for low urine volume can be classified into habitual and environmental factors including low fluid intake, patients living in hot climate, seasonal variation during summer time related to an increase temperature, or working in sun-exposed areas leading to fluid losses from perspiration [9]. Pathological factors include fluid loss due to enteric and chronic diarrheal diseases. Geography also plays an important role in stone formation. Multiple studies reported a higher incidence of stone episodes in hot, dry areas such as mountains and deserts. Interestingly, the highest prevalence of stone episodes was found in the southeast areas of the United States [10, 11].

## Risk Assessment

First time, low-risk stone formers should be offered empiric fluid and dietary manipulation recommendations without extensive metabolic workup [12]. However, patients at higher risk for repeat episodes should be offered an extensive metabolic evaluation, including those with a family history of stones, obesity, intestinal disease (particularly when causing chronic diarrheal states), prior gastric bypass

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surgery or other bowel resection, pathologic skeletal fractures, osteoporosis, recurrent urinary tract infections, or gout [3, 12].

Confirmation of low urine output in a stone-forming patient (less than 0.5–1 l/day) can be easily measured by the collection of two separate 24-h urine specimens [13, 14], although some authors recommend empiric fluid manipulation in low-risk stone formers without metabolic evaluation. The same authors reported 60% decrease in stone incidence for more than 5 years [15]. These data are similar to the later reports that suggested that hydration is effective in preventing stone formation [16].

Although 24-h urine volume measurement is unequivocal for measuring urine output, spot specific gravity measurement predicts total urine volume (cite). Seven subjects measured their spot specific gravity using both a handheld hydrometer and a urine dipstick. Concurrent 24-h urine measurement was obtained. Specific gravity of <1.020 predicts urine volume of >2,000 cc.

Increasing fluid intake and subsequently increasing urine output is the mainstay of conservative management to prevent further stone events, and satisfactory daily urine output should be between 2 and 2.5 l/day, perhaps even 3 l/day for cystine stone formers [6, 17]. The 2014 AUA Guidelines for the Medical Management of kidney stones point out that while no study has pinpointed a defined threshold for urine output above which risk is decreased, an accepted goal is 2.5 l/day [12].

The first step is appropriate counselling of patients regarding increased fluid intake and subsequently urine output [4]. While the concept is simple, patient compliance is hard to achieve. Parks et al. reported in large series that the average increase in urine output after counselling was only 0.3 l/day [18]. For those who are not compliant with fluid recommendations, Strauss et al. found that patients who are unable to increase their urine output are very likely to have recurrent stones [6]. Perceived barriers by patients to ingestion of adequate amounts of fluid were identified in three stages. Primary barriers include patients not being clearly informed of the benefits of fluid intake. Secondary barriers involved problems with availability of water, patients not feeling thirsty, or not liking the taste of water. Tertiary barriers included workplace issues related to drinking fluid or frequent bathroom use.

## Therapeutic Considerations

*Amount of fluid* Increasing fluid intake can be achieved by setting a goal of the amount of fluid required per day to maintain a urine output around 2.5 l/day. Most literature recommends 2–3 l/day [12], and in the author's experience, fluid intake should be divided into six times per day, recognizing the need to potentially decrease intake 3–4 h before bedtime if nocturia becomes a problem. Follow-up can be done by assessing the urine output 2–3 days before the follow-up visit or in more devoted patients by fluid charts.

Technology can be utilized in motivating patients to set their goals. Several "smart" water bottles have been developed in the last few years which provide feedback to the patient on how much fluid they have consumed per day. These bottles

range from a simple digital timer on the bottle to a more sophisticated device that synchronizes with smartphones to alert patients when fluid intake is suboptimal.

*Hardness of water* Water hardness has been the topic of many conflicting articles. Early studies found a lower incidence of stone disease in areas with a hard water supply [20, 21]. In contrast, a more recent reports found no association between the hardness of water and stone incidence [22]. However, most authors believe that the hardness of water is of low concern and should not affect the overall incidence of stone formation.

*Type of fluid intake* Most literature supports that the amount of fluid consumed is more important than the type of the beverage. Multiple studies reported that carbonated beverages offer a protective effect against stone formation. However, these studies focused primarily on beverages that increase urinary citrate levels [23, 24]. Interestingly, Shuster et al. reported that patients whom mostly consumed drinks were acidified by phosphoric acid but not citric acid and had a 15% higher 3-year recurrence-free rate than controls [25].

Alcoholic beverages, wine, and citrus juices like lemonade and orange juice provide a protective effect against stone formation in observational studies, particularly in the hypocitraturic patients [8, 26, 27]. In contrast, grapefruit juice has been found to increase stone risk; however, these results have been debated by Goldfarb and Coe [5].

Multiple studies reported that caffeinated beverages offer a protective effect [8]; however, Massey and Sutton et al. recently reported that caffeine increases the stone risk in calcium oxalate stone formers by increasing the excretion of calcium [28]. Ferraro et al. found that sugar-sweetened beverages demonstrated an increased risk. However, these findings were observational, and these beverages have not been evaluated in randomized trials [29].

## Providing Fluid Recommendations

Although fluid recommendations are fairly simple instructions and can be easily given by general urologist, a survey conducted by the Endourology Society revealed that only 87% of endourologists are interested in nutritional recommendations. Most providers (88%) provide recommendations themselves, but 76% of urologists prefer that other staff members provide these dietary instructions [30]. Most literature supports the fact that registered dietitians (RDs) are helpful in providing this information. RDs are especially helpful when dealing with challenging patients such as those with diabetes, Crohn disease, and cardiovascular disease. These patients already have dietary restrictions and need detailed, extended counselling requiring time that most urologists don't have [31, 32].

For complex patients, tailored dietary and fluid manipulation is favorable and can avoid pitfalls. Penniston and Nakada provided a scheme of the appropriate tailored metabolic assessment and management for patients requiring stone prevention and the RDs' role [32] (Fig. 7.1).

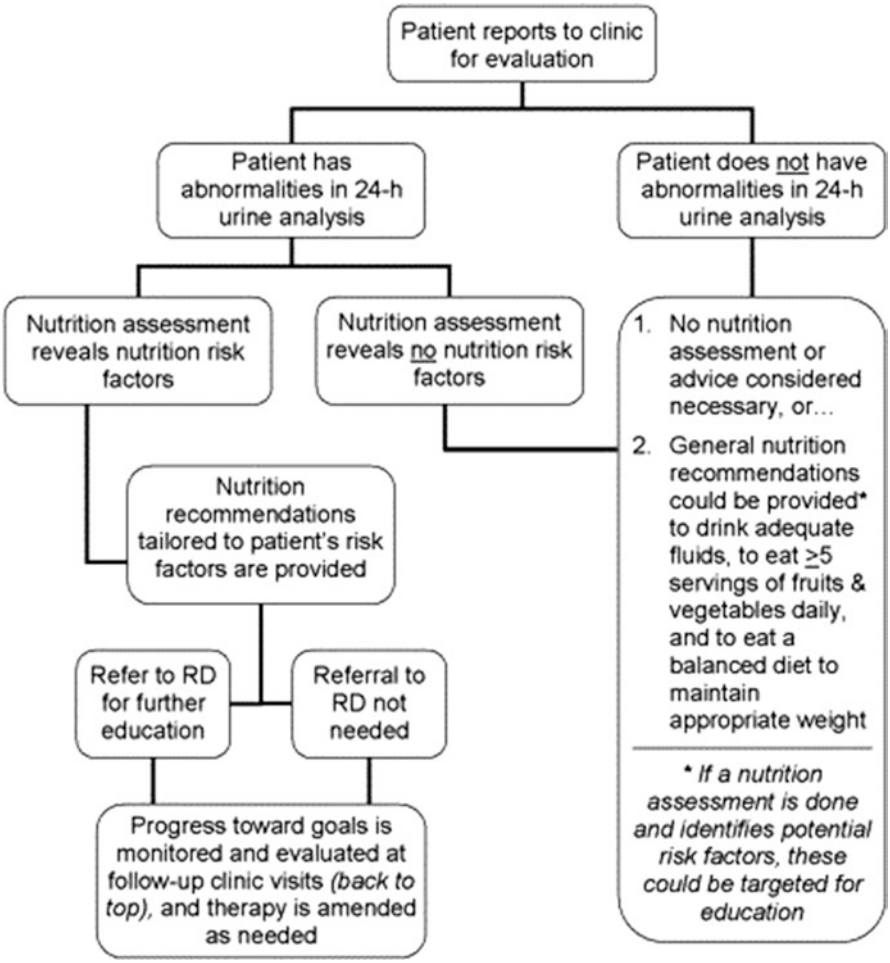


**Fig. 7.1** Tailored nutrition therapy (From Penniston and Nakada [32])

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# Nutrition Therapy for Specific Lithogenic Risk Factors: High Urine Calcium, High Urine Oxalate

8

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## Hypercalciuria

The most common component of kidney stones is calcium – a major constituent of over 75% of urinary calculi [1]. Hypercalciuria, found in 10–15% of the general population and 35–65% of stone-forming population, is the most common metabolic abnormality found in these patients [2–4].

High urinary calcium and high urinary oxalate are both significant risk factors for stone formation. Overlap exists for the nutrition therapy of these two conditions, so they will be presented together in this section. Not every patient will need each of these dietary changes. Individual therapy should be based on 24-h urine studies, response to therapy, continued stone formation, etc.

Hypercalciuria has been defined as greater than 200 mg of urinary calcium/day [5]. Definitions, however, have been somewhat variable; Parks and Coe defined hypercalciuria as excretion of greater than 4 mg/kg/day or greater than 7 mmol/day in men and 6 mmol/day in women [6]. If no etiology can be discovered on metabolic testing, hypercalciuria is classified as idiopathic hypercalciuria. Secondary hypercalciuria describes an underlying cause of the hypercalciuria and may be further categorized as absorptive, renal leak, and resorptive hypercalciuria [7].

After diagnosing hypercalciuria in a stone-forming patient, and after excluding resorptive hypercalciuria (which necessitates a different approach), the first step in management is dietary modification. Potential strategies include protein restriction,

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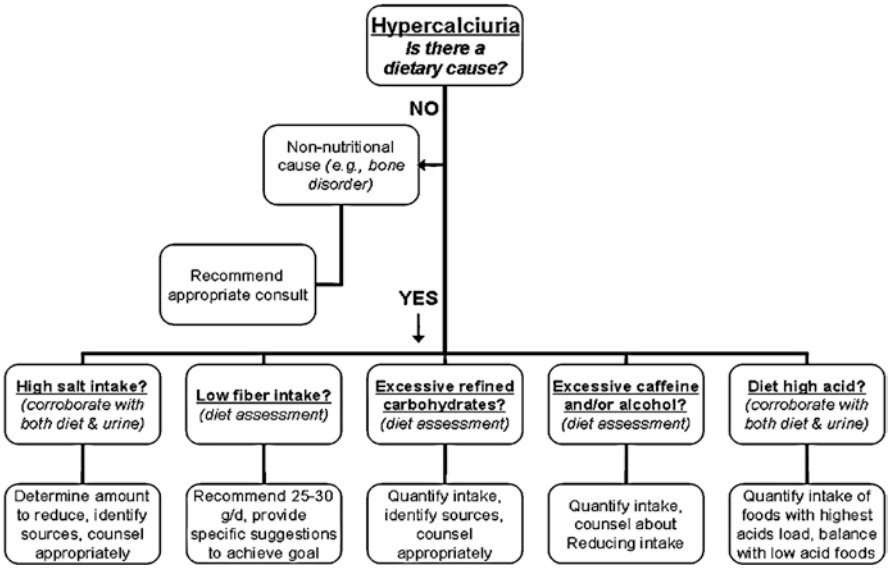


**Fig. 8.1** Hypercalciuria: Nutritional Contributors and Goal Oriented Management. Data from Penniston [26] (Current Websites with oxalate content of foods. http://www.wakehealth.edu/Urology/Kidney-Stones/Oxalate-Content-of-Foods.htm)

salt restriction, moderate calcium intake, and increased citrate intake. Penniston et al. recommend a detailed assessment for nutritional contributors and goal-oriented management (Fig. 8.1).

## Animal Protein

Increased animal protein consumption is associated with a higher renal stone incidence [8–10]. High protein intake causes an increase in calciuria and uricosuria, with a decrease in urine citrate and urine pH [11, 12]. Studies reveal that in both stone formers and non-stone formers, high animal protein intake results not only in higher urinary excretion of calcium, oxalate, and uric acid but also lower excretion of urinary citrate [13, 14]. Animal flesh protein contains sulfur-containing amino acids which produce sulfate as they are metabolized, causing a metabolic acidosis. In this state, calcium resorption from bone is increased, and with the increased urine acidity, calcium reabsorption in the renal tubules is decreased, which combine to increase urinary calcium. In addition to decreasing the tubular calcium reabsorption, the acid load *increases* reabsorption of urinary citrate, concurrently lowering the urinary citrate level. For every 25 g increase in animal protein intake, the urinary calcium will rise by approximately 32 mg [15]. This holds true for all animal flesh proteins. When compared directly to red meat, fish and poultry have been shown to increase the acid load by similar amounts, leading to similar changes in urine [14].

Studies of populations with particularly high or low protein intake further support these findings. In oil-rich Middle Eastern countries, people generally eat animal protein (red meat, fish, poultry) at all three daily meals, with a higher average protein intake even than Americans. This high level of animal protein intake results in high levels of urinary uric acid, acidic urine pH, and low urinary citrate. These factors contribute to an increase stone formation, and lifetime prevalence of stone formation in this population is >20%, compared to 8–15% in Western industrialized nations [16–18]. Another well-characterized population with increased animal protein intake includes patients on the "Atkin's diet." This is an obese population who eat a diet rich in protein and fat, but very low in carbohydrates. One study evaluated a cohort whose animal protein intake was increased to 170 g/day; after 6 weeks the urinary calcium increased by 90 mg/day and the urine uric acid increased by 130 mg/day. Simultaneously, the urine citrate decreased by 180 mg/day and the pH fell from 6.09 to 5.67 [19]. Vegetarian diets have the opposite effects. A study compared the effects of different proteins on urinary risk factors by starting with 75 g animal protein, which was first replaced with ovo-vegetable protein, and finally with solely vegetable protein. The vegetarian-only diet resulted in urine with decreased calcium, decreased acid excretion, and increased citrate, indicating that decreasing animal protein lowers the urinary risk factors for stone formation [20].

Currently, no recommendation exists for specific quantity of protein to be considered an upper limit or a safe range for daily intake. Consider that the studies cited above had protein intake ranging from 75 to 170 g (or 2.6–6 oz), which in many industrialized nations may be less than a serving of meat at only one meal. For hypercalciuric patients, rather than focusing on a specific upper limit of animal protein intake, perhaps efforts should be focused on significantly reducing their current intake, which should reduce urinary calcium excretion.

## Sodium

Excess sodium intake can increase urinary calcium levels. A high sodium intake increases the amount of sodium traveling through the distal tubule, where sodium and calcium compete for a reabsorptive transport mechanism. This competition inhibits the reabsorption of calcium, leading to increased urinary calcium levels. Additionally, high sodium intake decreases the effectiveness of thiazides for lowering the urinary calcium levels in hypercalciuric patients [21]. Current AUA guidelines suggest that daily sodium intake should not exceed 100 mEq (2,300 mg) [17].

A review of salt loading studies found that in normal subjects, urinary calcium excretion rose approximately 40 mg for each 100 mEq (2,300 mg) increase in dietary sodium, but subjects who are calcium stone formers with hypercalciuria appeared to have even more significant increases in urinary calcium (approximately 80 g) per 100 mEq increase in salt intake [23].

The primary dietary source for sodium source is not the added salt via the salt shaker. Penniston et al. evaluated diet records from stone-forming patients and found the source of salt was spread out across numerous foods, including processed meats, bread and baked, added salt and spices containing salt, canned vegetables/soups/pickles, condiments, salty snacks, cheese, pizza and fast food, and meal starters such as rice and pasta mixes. The aforementioned foods range in their contribution to the daily sodium from 14% to 7% in a descending manner [24, 26]. Some foods that may not be particularly high in sodium may contribute more to the overall sodium intake load if they are eaten regularly or in high quantities. The sodium content in bread, for example, may add up since bread is commonly eaten several times a day as breakfast toast, breakfast bagel, part of a sandwich, or dinner rolls. Sodium-containing foods must be recognized for the amount of sodium content as well as the pattern of intake to properly counsel a patient on decreasing sodium intake.

Additionally, although the mechanism is unknown, increased dietary sodium intake is associated with decreased urinary citrate [25].

Keeping daily sodium intake below 100 mEq (2,300 mg) will allow better control of urinary calcium levels.

## Calcium

Previously, calcium restriction was prescribed as a method to decrease stone episodes. Unfortunately, a low calcium diet decreases oxalate binding by calcium in the gut resulting in increased intestinal absorption of oxalate and subsequent increased levels of urinary oxalate [27]. Calcium restriction in patients can cause a negative calcium balance in patients who excrete more calcium than normal (hypercalciuria), which in the long term may result in osteoporosis [28–30]. Current guidelines recommend calcium intake of 1,000–1,200 mg in hypercalciuric patients with calcium stones [22].

Normalizing calcium intake to 1,200 g is based on a randomized clinical trial in which hypercalciuric men were placed on a diet of either low calcium (400 mg) or normal calcium (1,200 mg) daily. Both groups were told to limit oxalate, drink proper fluids, and were placed on an animal protein restriction of 52 g and a sodium restriction of 2,900 mg. After 5 years, the low calcium group formed 23 stones in 60 subjects, while the normal calcium group formed only 12 stones. Compared to the low calcium diet cohort, the relative risk for forming a stone for the normal calcium intake group was 0.49 [12].

If patients are unable to take adequate amounts of daily calcium (food allergies, intolerances, etc.) calcium supplements may be beneficial, and conflicting reports exist throughout the literature. The Women's Health Initiative study looked at a large population of subjects randomized to 100 mg Ca carbonate or placebo, and the calcium supplement cohort had a higher risk of stone formation; however, the calcium supplement cohort had a daily calcium intake higher than recommended,

which may have affected the findings [31]. Other studies suggest that calcium supplementation can also be safe. Studies in postmenopausal women that were placed on calcium and estrogen for osteoporosis showed no significant increase in urinary calcium or oxalate [32]. The type of calcium preparation may be important. Over-the-counter calcium citrate (950 mg calcium citrate – 200 mg elemental calcium/tablet) did not have a significant impact on kidney stone episode [14, 33]. Additionally, the timing of calcium supplement intake may also have a role. Domrongkitchaiporn et al. reported that calcium supplements in any preparation are not associated with an increase in urinary calcium if taken with meals [34]. Breaking the calcium tablet into two to three portions to be taken with each meal may be further beneficial. In summary, the risk of calcium supplements is not conclusively characterized. For patient safety, the AUA guidelines suggest obtaining a 24-h urine sample before and after beginning calcium supplements to insure that no increase in urinary calcium risk occurs [22].

Hypercalciuric patients should be counseled to have a goal of taking in 1,000–1,200 mg of calcium daily, preferably split up so that calcium-containing foods are taken with each meal.

## Potential Renal Acid Load

As dietary acid load increases, urinary calcium and uric acid increases while urinary citrate decreases. This concept was discussed in the Animal Protein section above since animal flesh protein also raises the acid load. A scale has been developed to estimate the potential renal acid load (PRAL) effect of diet on renal net acid excretion [35].

Acid load in diet is believed to increase the risk of kidney stones by inhibiting tubular calcium reabsorption and increasing bone mineral mobilization to buffer the acid load [35]. In addition to animal protein, foods that increase the net acid load due to their sulfur-containing amino acids include cheese, eggs, and grains and grain products (flour, pasta) [36]. Notably, fats are neutral; milk and yogurt have minimal acid effect. Vegetables and fruits and their juices give an alkali load and should usually be increased to lower stone risk.

By altering the intake of high PRAL foods such as animal flesh protein, eggs, cheese, and grain products so that they are eaten in moderation and increasing low PRAL foods such as fruit, vegetables, milk, and yogurt, hypercalciuric patients will decrease their renal net acid excretion and consequently lower their urinary calcium levels.

## Dietary Fiber

Fiber intake reduces gastrointestinal calcium absorption if at the recommended levels (25–30 g/day) [36]. However, oxalate levels may rise, so one may choose not to utilize this therapy in patients with hyperoxaluria.

Fifteen healthy women were given a standardized calcium-rich diet (1,800 mg calcium/day) with or without 36 g bran for 5 days. A similar study was also carried out with rice, soy, and wheat bran. Urine samples were also collected 24 h. With all brans renal calcium excretion decreased slightly and renal oxalic acid excretion increased slightly. However, the effect of rice bran was statistically significant. After 5 days of consuming 36 g rice bran/day, 14 of 15 subjects showed significant decreases in calcium excretion, but concomitant increases in oxalic acid excretion. Relative supersaturation with calcium oxalate, as a measure for the risk of calcium stone formation, increased after addition of all forms of bran [36].

For the purpose of decreasing calcium excretion, increased fiber may be an effective option in patients with normal urinary oxalate.

## Miscellaneous

Carbohydrate, alcohol, and caffeine may slightly increase urinary calcium excretion. However, the effect is transient and does not necessitate limitation or restriction and should be assessed on case to case basis [37–39].

## Citrate

Citrate is a potent natural inhibitor of calcium stone formation [40]. Citrate binds to calcium in the renal tubule, resulting in a complex with increased solubility [41]. Additionally, citrate binds to existing stone crystals, preventing further crystal growth. For calcium stone formers with 24-h urine testing that reveals low citrate, current AUA guidelines recommend supplementation by increasing the consumption of fruits and vegetables [22]. A study including both stone formers and non-stone formers clearly reinforces this recommendation. In the group of non-stone-forming subjects, the removal of all fruits and vegetables from the diet resulted in significant decreases in urinary citrate (44%) and potassium (62%). Conversely, in a cohort of calcium stone formers with hypocitraturia, supplementing the diet with fruits and vegetables (100 g orange juice, 400 g fresh fruit, 300 g fresh vegetables) caused a significant increase in urinary citrate (68%) and potassium (68%) and additionally raised urine volume from 1,231 to 2,024 ml/day, a 64% increase [42].

Normal levels of citrate are difficult to characterize, but since most non-stone-forming people excrete 600 or more mg of citrate daily, the AUA guidelines suggest 600 mg as a minimum goal for stone-forming patients.

In order to maintain high levels of urinary citrate, adequate potassium levels must be maintained. Hypocitraturia results in intracellular acidosis and decreases tubular pH [43]. Decreased tubular pH stimulates reabsorption of citrate, and intracellular acidosis has been shown to increase mitochondrial transport and metabolism of citrate. Consequently, low 24-h potassium levels must be supplemented to allow for adequate citrate excretion.

**Take Home Points: Hypercalciuria**

1. Increased intake of animal flesh protein of all types (fish, poultry, red meat) causes an increase in urinary calcium and uric acid and a decrease in urinary citrate and urine pH. **Patients with hypercalciuria should limit the intake of animal flesh protein**.
2. Patients with hypercalciuria should be counseled to have a daily sodium intake below 100 mEq (2,300 mg).
3. Patients with hypercalciuria should be counseled to have a daily calcium intake of 1,000–1,200 mg, preferably allocated so that calcium-containing foods are eaten with each meal.
4. Hypercalciuric patients should also limit the intake of animal protein, cheese, eggs, and grains and grain products, as these foods have a high potential renal acid load (PRAL). Increased consumption of vegetables and fruits is recommended as they have an alkali effect on the PRAL.
5. Patients with hypercalciuria should increase their intake of citrate-containing foods, with a goal of excreting 600 mg of citrate daily.

## Hyperoxaluria

Hyperoxaluria presents a challenging scenario for both practitioners and patients. Treatment would be straightforward if we could simply give patients a simple, short list of high oxalate foods to avoid in order to bring their urinary oxalate levels down to within normal limits. And while dietary restriction of oxalate is a mainstay of treatment, other approaches exist that can be utilized in addition to dietary restriction to lower oxalate excretion. Evidence-based studies are lacking for treatment of hyperoxaluria, and the current AUA guidelines only have one statement for hyperoxaluria, with a strength of evidence only noted to be "expert opinion."

Hyperoxaluria is defined as urinary oxalate higher than 40 mg/24 h, leading to increased urinary calcium oxalate supersaturation (SS) and subsequently formation of kidney stones. There are multiple causes of hyperoxaluria including primary hyperoxaluria (disorders in biosynthetic pathways), intestinal malabsorptive states associated with inflammatory bowel disease, celiac sprue, or intestinal resection (enteric hyperoxaluria), and excessive dietary intake or high substrate levels (vitamin C) (dietary hyperoxaluria) [44].

## Etiologies of Hyperoxaluria

Primary hyperoxaluria comes from one of two different autosomal recessive genetic disorders, both of which are characterized by an endogenous overproduction of oxalate. These patients generally present in childhood with oxalosis, stone disease, and often renal failure.

Primary hyperoxaluria 1 (PH1) is caused by an autosomal recessive defect in the enzyme alanine glyoxylate aminotransferase (AGT). This deficiency results in an

inability to detoxify glyoxylate in the peroxisomes. PH1 patients with renal failure require a hepatectomy prior to a combined liver/kidney transplant. PH2 is caused by a defect in glyoxylate reductase, also an autosomal recessive defect. Urine parameters are characterized by high urine oxalate excretion [45]. Primary hyperoxaluria of either type should be referred to gastroenterology for management.

Enteric hyperoxaluria stems from an intestinal malabsorptive state such as bowel resection or inflammatory bowel disease. Enteric hyperoxaluria is characterized by high urine oxalate more than 50 mg/day and is often associated with chronic diarrheal states in which fat malabsorption causes saponification of calcium and magnesium with fatty acids. This decreases the calcium and magnesium available to bind oxalate, resulting in much more free oxalate which is easily absorbed. The chronic diarrhea also results in dehydration, bicarbonate fluid loss, low urine PH, and hypocitraturia, all of which further increase stone risk [46, 47].

Dietary hyperoxaluria is either due to the deficiency of *Oxalobacter formigenes* or an increased intake of oxalate-containing foods [48], [49]. Since a small increase in urinary oxalate affects calcium oxalate supersaturation, perhaps patients with only mild or borderline hyperoxaluria may benefit from low oxalate diet [60].

## Sources of Dietary Oxalate

Commonly, patients are placed on some arbitrary dietary combination of "low green vegetables, no coffee/tea/soda, no nuts or nut butter" type of diet without regard for what the patient actually eats on a daily basis. Penniston et al. examined food diaries from patients in a metabolic stone clinic to evaluate oxalate intake in stone formers. This study revealed that nuts, seeds, and nut butters offer the highest contribution to the total oxalate intake by 26%; spinach and flours and baked goods come next with 12% share. Cereals, potatoes, and french fries offer 7% and other foods less [50]. Note that these are averages, and individual intake may be much different for unique stone patients. Only a thorough dietary assessment will identify which foods place different individual patients at risk. Additionally, practitioners must take care to avoid examining only the intake of high oxalate foods, as low oxalate-containing foods eaten regularly or in large amounts may add up to yield large quantities of oxaluria even though the food may not seem like a particularly high oxalate food type. Again, this type of information would be identified through a dietary assessment.

## Oxalate Restriction

A conundrum exists when we wish to stringently restrict oxalate-containing foods. Since oxalates are obtained almost solely from plants, these foods are healthy fruits and vegetables. Indiscriminate restriction could decrease the health benefits derived from the variety of nutrients that come from these foods, as well as restrict some of the important stone-inhibiting food products such as citrate, magnesium, potassium, fiber, phytate, etc. [26].

A detailed list of oxalate-containing food can be found in many research articles, and excellent, detailed lists may be found on several websites, as well as through Internet search engines (Appendix 6) (Fig. 8.1). These lists are important for practitioners and patients to review, as they will not only guide meal planning but will also dispel certain myths about which foods may or may not be high in oxalate. For example, these show most leafy green vegetables (with the notable exceptions of spinach or collard greens) are not high in oxalate, and coffee is also shown to have low content.

The Harvard website is particularly detailed with over 600 foods categorized as fast foods, fruit, vegetables, breakfast foods, beverages, dairy, nuts and grains, cereals by manufacturer (many of which have very high content), etc. These foods have the oxalate content listed by milligrams and grouped by very high, high, moderate, low, and very low oxalate content.

## Variability of Oxalate

Oxalate content of food may vary depending on conditions such as the time of year, soil composition, amount of sunlight, and geographic location of the plant [51]. This suggests that the oxalate content of a particular plant grown in the northwest United States maybe significantly different from that same species of plant grown in Florida. Additionally, a particular species of plant grown in the same exact location may have different oxalate content if grown in the spring versus the fall. Consequently, oxalate content lists are certainly useful, but have precise measurements only for that particular food which was measured on a particular day.

## Bioavailability of Oxalate

Oxalate is found in plant storage cells and exists in both soluble and insoluble salts. Insoluble oxalate passes through the intestine without being absorbed and comes out in the stool. The soluble oxalate may be absorbed in the intestines and is subsequently excreted through the urinary tract. Currently, no reliable measure exists to discern between the two types of food oxalate. More research will allow more accurate nutrition counseling on more relevant oxalate content when we can identify which foods are higher in soluble oxalate.

## Dietary Management

The first step in the dietary management of hyperoxaluria is to assess for a dietary cause. If the patient has a genetic disorder, they require an appropriate referral for medical therapy. If a patient has chronic diarrhea from antibiotic use, perhaps probiotics after the cessation of the antibiotic course will reverse an iatrogenic hyperoxaluria. Additionally, insure that a dietary assessment results in the treatment of

the identified risk factor. For example, if a patient has a profoundly low calcium intake, they may only need a normalization of dietary calcium without need for restricting oxalate.

Most calcium oxalate stone-forming patients with hyperoxaluria, however, will benefit from both limiting consumption of oxalate-rich foods (without being overly restrictive) and maintaining normal calcium intake of 1,000–1,200 mg daily; ideally the calcium is evenly divided between meals [22]. This strategy follows the recommendation of the current AUA guidelines (statement #10).

Since 40% of excreted urinary oxalate comes from dietary intake, the potential exists through dietary manipulation to lower the urinary oxalate to normal levels, decreasing stone risk. However, care must be taken with oxalate restrictive diets. As mentioned, most of the oxalate-containing foods are healthy, and overly strict constraints on fruit and vegetable intake have the potential to cause more harm than good [26]. Additionally, the DASH (Dietary Approaches to Stop Hypertension) diet, which consists of high fruit and vegetable intake without oxalate restriction, has been shown to reduce the risk of kidney stones [52] (Appendix 3). Furthermore, vegetarians, especially when watching out for particularly high oxalate foods, have lower levels of urinary calcium and oxalate compared to non-vegetarians [53]. One population study in Great Britain found a decreased prevalence of stones by 66% in the vegetarian population [9]. Patients should be encouraged to consume calcium-containing food with meals to enhance the binding of calcium with oxalate in the gastrointestinal tract, decreasing oxalate absorption in the gut. A randomized controlled trial showed a decreased stone occurrence rate in calcium oxalate stone formers who consumed 1,200 mg of calcium daily divided between meals and followed a diet of moderate oxalate restriction, decreased animal protein intake, and decreased sodium intake [12].

However, patients with enteric hyperoxaluria from malabsorptive conditions such as inflammatory bowel disease or postgastric bypass may benefit from more a more rigid dietary oxalate restriction and significantly higher calcium intake with meals [22, 46]. These patients will benefit from 24-h urine surveillance to insure they do not become hypercalciuric from too much calcium supplementation.

## Oxalobacter Formigenes

Oxalate-degrading bacteria are another potential source for the control of oxalate absorption in the intestine and may someday be a mainstay of intervention to lower oxalate. *Oxalobacter formigenes* is an anaerobe normally inhabiting the colon. *O. formigenes* has an obligate need for oxalate as its only source of energy and is thought to help decrease stone risk by metabolizing oxalate prior to intestinal absorption. *O. formigenes* colonizes the colon flora of approximately 30–40% of the population, but only 15–20% of stone-forming patients are colonized. Additionally, those not colonized with *O. formigenes* have a rate of stone occurrence 70% higher

than patients who are colonized. Currently, no treatment exists with *O. formigenes*. However, other bacteria metabolize oxalate and hyperoxaluria patients may benefit from the use of probiotics to promote a healthy colon flora to maximize the potential for oxalate metabolism [61]. However, no trials have been performed to confirm a stone risk benefit for probiotics. Nonetheless, this is a reasonable treatment with minimal potential ill effects, especially for patients failing therapy. With the current explosion of research into the human microbiome, more information will certainly be forthcoming into this exciting potential area of treatment.

For patients who utilize probiotics, they will have more benefit if they also take in adequate prebiotics. Prebiotics are nondigestible food components that have beneficial effects on the host through effects on the microbiome. In this case, the nondigestible carbohydrates (fiber, inulin, polysaccharides, etc.) found in fruits, vegetables, and whole grains provide a favorable environment for a diverse gut flora [26, 61].

## Pyridoxine

Pyridoxine (vitamin B6) has been utilized as an adjunct for patients with elevated urinary oxalate levels. Alvarado et al. looked retrospectively at 95 subjects with idiopathic hyperoxaluria. Forty-four patients were managed with dietary recommendations alone, and 51 managed with diet and pyridoxine. The two groups were not identical, as the pyridoxine group started with a significantly higher mean oxalate level (47 vs 58.2). Both groups responded well with decreases in mean oxalate of 32% in each group. In patients with significant hyperoxaluria not responding to dietary manipulation, pyridoxine may offer a supplemental option for treatment in addition to dietary recommendations. Pyridoxine must be used with caution and should be slowly titrated up to a maximum of 300 mg. While increasing the dose, one must follow urinary oxalate levels to evaluate treatment response and, more importantly, carefully monitor for side effects, specifically sensory neuropathy [59].

## Magnesium

Magnesium binds oxalate in the intestine, thereby reducing the amount of oxalate that may be absorbed [54]. Hypothetically, treatment with magnesium seems to be an attractive option. However, in a randomized clinical trial, magnesium hydroxide did not decrease the incidence of stone formation [55]. Patients with hyperoxaluria and low urinary magnesium may be safely and easily treated, but no consensus exists to suggest effectiveness or dosing.

## Vitamin C

Ascorbic acid is broken down in the liver into oxalate, which is subsequently excreted into the urine. Currently, the US recommended dietary allowance (RDA) is 90 mg for men and 75 mg for women. At these levels, and probably up to 500 mg, no additional risk for kidney stones would be noted. However, at the massive, supraphysiologic doses (initially recommended without evidence of effectiveness by Nobel Laureate Linus Pauling,) stone risk increases. In both normal and stone-forming subjects, after intake of 1,000 mg of vitamin C daily, urinary oxalate increased by a moderate, but statistically significant, amount [56]. Consequently, large dose vitamin C ingestion is not recommended for patients at risk of calcium stone formation.

Other supplements that may lead to an increase in urinary oxalate are turmeric and cranberry [57, 58]. Within supplements available at health food stores and pharmacies, extracts may contain very large amounts of turmeric which contains oxalate. The amount of turmeric concentrated into various supplements is not always well characterized, but has been shown to increase urinary oxalate levels [36]. However, turmeric or other spices used in simply the amount to provide spice for cooking food are acceptable. Supplements containing cinnamon were not shown to significantly increase urinary oxalate levels.

However, perhaps all hyperoxaluric and calcium oxalate-stone forming patients should be cautious with all supplements that contain vegetable extracts since their oxalate content is unknown.

In summary, patients with hyperoxaluria require a complete dietary assessment to determine the etiology of their oxaluria. The first-line treatments are a moderate oxalate restriction and normalization of calcium in the diet.

### Take-Home Points: Hyperoxaluria

1. Hyperoxaluric patients should decrease the intake of foods containing high amounts of oxalate.
2. Hyperoxaluric patients should consume 1,000–1,200 mg calcium/day divided between the three meals.
3. Hyperoxaluric patients should limit vitamin C consumption.
4. Hyperoxaluric patients should consider magnesium supplementation in patients who do not respond to treatment.
5. Hyperoxaluric patients should consider pyridoxine in patients who do not respond to treatment, but take care with dosing.
6. Hyperoxaluric patients should consider probiotics in patients who do not respond to treatment.
7. Hyperoxaluric patients should beware of certain supplements due to the possibility of having large amounts of oxalate in their extract.

Assessment of nutritional contributors is described in Fig. 8.2.

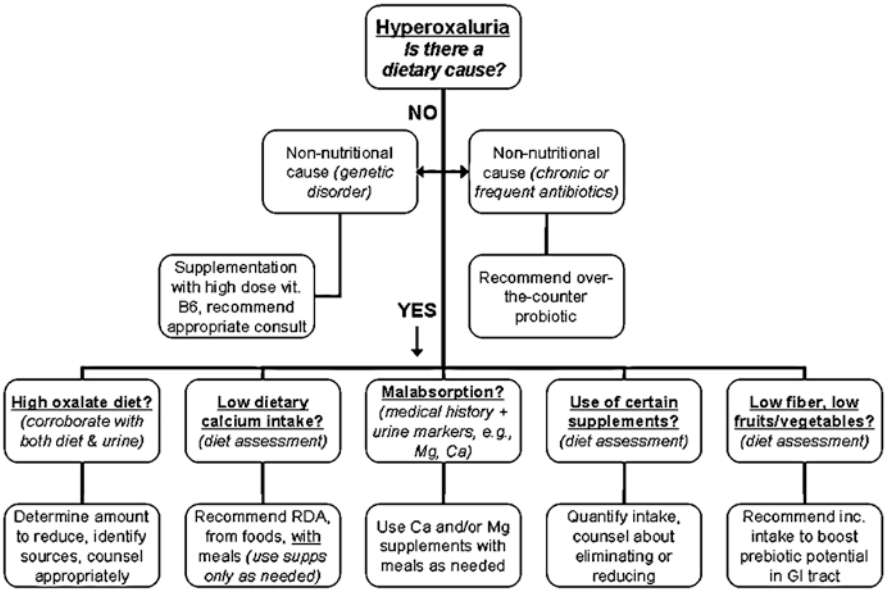


**Fig. 8.2** Hyperoxaluria: Nutritional Contributors and Goal Oriented Management. Data from Penniston and Nakada [26] Hyperoxaluria: Nutritional Contributors and Goal Oriented Management (citations [13, 14–15] not needed?)

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# Low Urine Citrate/Magnesium/Potassium

9

Fysal AlBaalbaki and Mohanram Narayanan

## Hypocitraturia

Citrate is the most abundant organic ion in urine and a potent natural inhibitor of calcium oxalate and calcium phosphate nucleation. Most of the orally ingested citrate gets converted to bicarbonate conferring an alkali load which may result in increased urine pH depending on concomitant acid load [1].

Whereas acid loads and acidosis increase kidney tubule reabsorption of citrate, alkali loads and alkalosis reduce it, hence increasing urinary citrate excretion. In addition, the systemic alkalization that occurs with citrate supplementation reduces calcium excretion. This effect is also important in increasing urine pH, thus reducing the risk of uric acid and cystine-based calculi [2].

There is some controversy regarding the definition of normal urinary citrate excretion. Women tend to have higher urinary citrate measurements than men, particularly before menopause [3]. Despite gender differences, some consider normal urine citrate as greater than 320 mg for both genders [3]. Others consider higher limits of normal with men being more than 450 mg and women at more than 550 mg daily [4].

Hypocitraturia is considered one of the more common metabolic diagnoses, probably second only to hypercalciuria. Five of the major causes of hypocitraturia are reviewed [5]:

1. Distal renal tubular acidosis (RTA; type 1): Patients in this disorder have impaired distal tubular excretion of hydrogen ions with non-anion gap metabolic acidosis and alkaline urine. The acidosis causes calcium and phosphate to be released

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from bone with an ensuing increase in renal excretion of these ions, all of which increase the propensity of calcium phosphate precipitation. The acidosis also leads to an increase of citrate reabsorption by the proximal tubule. Up to 70% of adults with distal RTA have kidney stones [6]. Approximately 80% of RTA patients are women. These patients may progress to renal insufficiency. The laboratory hallmark of this disease is a low urine citrate (24-h urine citrate less than 100 mg/day) with an inappropriately high urine pH (6.5 or above). Patients with RTA will be unable to acidify their urine overnight and should have a urine pH no lower than 5.5. Hypokalemia, hyperchloremia, and non-anion gap acidosis are often evident on the serum studies. Serum bicarbonate usually stays in the mid-teens [7].

2. Chronic diarrheal states: The laboratory findings in a patient with a chronic diarrheal disorder are similar to the patients with enteric hyperoxaluria. Bicarbonate reabsorption occurs in the colon; and since diarrhea shortens the transit time through the colon, bicarbonate is not effectively absorbed. This bicarbonate wasting leads to a chronic metabolic acidosis and a subsequent decrease in urinary citrate excretion. Consequently, these patients will likely demonstrate moderate decreases in urinary citrate excretion with associated low urine volumes due to the fluid losses associated with diarrhea [7].
3. Thiazide-induced hypocitraturia: One of the side effects of thiazide therapy is the development of hypocitraturia. This defect is presumably secondary to the hypokalemia and resultant intracellular acidosis that may develop after prolonged therapy with thiazides [8]. Thus stone formers treated with thiazides should be screened for hypocitraturia.
4. Idiopathic hypocitraturia: Patients with idiopathic hypocitraturia include all those with 24-h urine citrate less than 550 mg (males) or 450 mg (female) in the absence of any of the previously noted disease states.
5. Medication induced: Carbonic anhydrase inhibitors, such as topiramate and acetazolamide, reduce urinary citrate excretion because they induce metabolic acidosis in some patients [9]. This results in higher citrate reabsorption and less excretion.

## Nutrition Therapy for Hypocitraturia

A number of conditions reduce urinary citrate excretion, predisposing to stone formation. Hypokalemia, metabolic acidosis, a diet high for acid load, extreme exercise, hypomagnesemia, infections, androgens, starvation, and carbonic anhydrase inhibitors have been implicated in decreased urinary citrate excretion. Therapy in general involves treatment of the underlying condition (distal RTA, chronic diarrheal disease, etc.) and administering citrate salts.

Distal RTA: Potassium citrate therapy can correct the metabolic acidosis and hypokalemia found in patients with distal RTA [6]. Potassium citrate is capable of restoring normal urinary citrate, lowering the urinary saturation and inhibiting crystallization of calcium salts. It typically produces a sustained decline in the urinary

saturation of calcium oxalate (from reduction in urinary calcium and in citrate complexation of calcium).

Citrus juices have long been considered to have anti-lithogenic potential, as they are an excellent source of dietary citrate. Diets rich in citrus fruits and juices are common practice prescriptions for "stone prevention." Lemon and lime juices contain the highest concentration of citric acid (1.44 g/oz and 1.38 g/oz, respectively), grapefruit juice intermediate (0.75 g/oz), and orange juice the least (0.27 g/oz) [10]. Fresh tomato juice is also reported to contain a considerable amount of citrate [20]. However, despite being richer in citrate, lime, lemon, or lemonade generally does not increase urinary pH (0.1 point increase), whereas orange juice does by 0.6–0.8 points, similar to potassium citrate [1]. Most studies consistently indicate increased urinary citrate with ingestion of studied citrus fruits (lemon, orange, grapefruit), consumed in large amount. Large amounts of orange juice, however, are not routinely recommended due to its relatively high caloric load and fructose content. Interestingly, prospective-observational epidemiological studies have found paradoxical results, e.g., "minimal protective" effect of orange juice and "lithogenic" effect of grapefruit juice [1, 11, 12]. For reasons yet unexplained, stone risk increased up to 44% for each 240-mL serving of grapefruit juice consumed daily in men and women [13, 14].

An additional benefit of citrus juice, particularly if low-sugar, low-calorie formulations are consumed, is the requisite increase in overall fluid consumption, thus increasing daily urine volume and reducing urine supersaturation [2]. Because any organic anion that causes a systemic alkalosis increases citrate excretion, malate may also increase urinary citrate [15].

Most recently the American Urological Association (AUA) published guidelines regarding the medical management of kidney stones (see Table 9.1). They recommended encouraging patients with calcium stones and relatively low urinary citrate to increase their intake of fruits and vegetables and limit nondairy animal foods [16]. There was, however, no recommended preference of type of fruit or vegetable nor mention of suggested amount. Patients whose self-assigned diets more closely resembled the Dietary Approaches to Stop Hypertension (DASH)-style diet, which is rich in fruits and vegetables, had a marked decrease in kidney stone risk [17].

Non-citrus fruits such as pineapple and cranberry may also be rich in citrate. However, the effect of cranberry extracts on urine citrate excretion is variable and may increase oxalate excretion, either because of the presence of oxalate or conversion of ascorbic acid to oxalate in vivo [18, 19]. Finally, various melons (non-citrus alkaline fruits rich in potassium, citrate, and malate) yield increase in urinary citrate excretion similar to those provided by orange, hence representing another dietary alternative for the treatment of hypocitraturic stone formers [21].

Some of the commercial oral rehydration solutions contain a higher pH and citrate concentration and have led to an increase in citraturia and urinary pH [22]. However, these sports drinks may contain too many calories and fructose to be preferred beverages for stone prevention. The amount of vitamin C added to juices is also a concern because of its conversion to oxalate, although the amount is not high if compared with vitamin C supplements [19].

**Table 9.1** Evidence related to the role of citrate, magnesium, and potassium in nephrolithiasis. Results from a review of the epidemiologic evidence [12]

| | Cross-sectional data | Prospective data | Prospective interventional data | AUA guidelines | Grade |
|---|---|---|---|---|---|
| Citrus fruits/juices | Mixed | Mixed | None | Adequate fruits and vegetables; ample intake especially of those containing citrate | B |
| Potassium | Favorable | Favorable | Favorable (supplementation) | Encourage diet rich in potassium, especially from fruits and vegetables; must use caution in patients with renal failure | B |
| Magnesium | No effect | Favorable | Favorable | Consume diet rich in magnesium; supplementation may be permissible in recurrent stone formers | B |

Adapted from Agarwal et al. [1]

## Hypomagnesemia

Magnesium (Mg) is the second most abundant cation in the intracellular fluid (ICF). It is involved in the majority of metabolic processes. In addition, it plays a part in DNA and protein synthesis. Magnesium is involved in the regulation of mitochondrial function, in inflammatory processes and immune defense, allergy, growth, and stress, and the control of neuronal activity, cardiac excitability, neuromuscular transmission, vasomotor tone, and blood pressure.

The intestinal absorption of dietary Mg occurs mainly in the distal small intestine and the colon. Various factors modify intestinal Mg absorption. In addition to high magnesium intake, high dietary phosphate intake is inhibitory, as is high phytate consumption. Magnesium is mainly eliminated by the kidney. Losses through intestinal secretion and sweat are negligible under normal conditions.

Magnesium deficiency is defined as a decrease in total body magnesium content. Poor dietary intake of magnesium is usually not associated with marked magnesium deficiency because of the ability of the intestine to increase Mg absorption and the kidney to conserve Mg. However, prolonged and severe dietary magnesium restriction of less than 0.5 mmol/day can produce symptomatic magnesium deficiency. Underlying causes are usually GI diseases, in particular malabsorption syndromes and massive resection of the small intestine. Hypomagnesemia can also be induced by prolonged tube feeding without magnesium supplements and excessive use of non-magnesium-containing laxatives. Renal losses mostly happened due to diuretic use (Fig. 9.1).

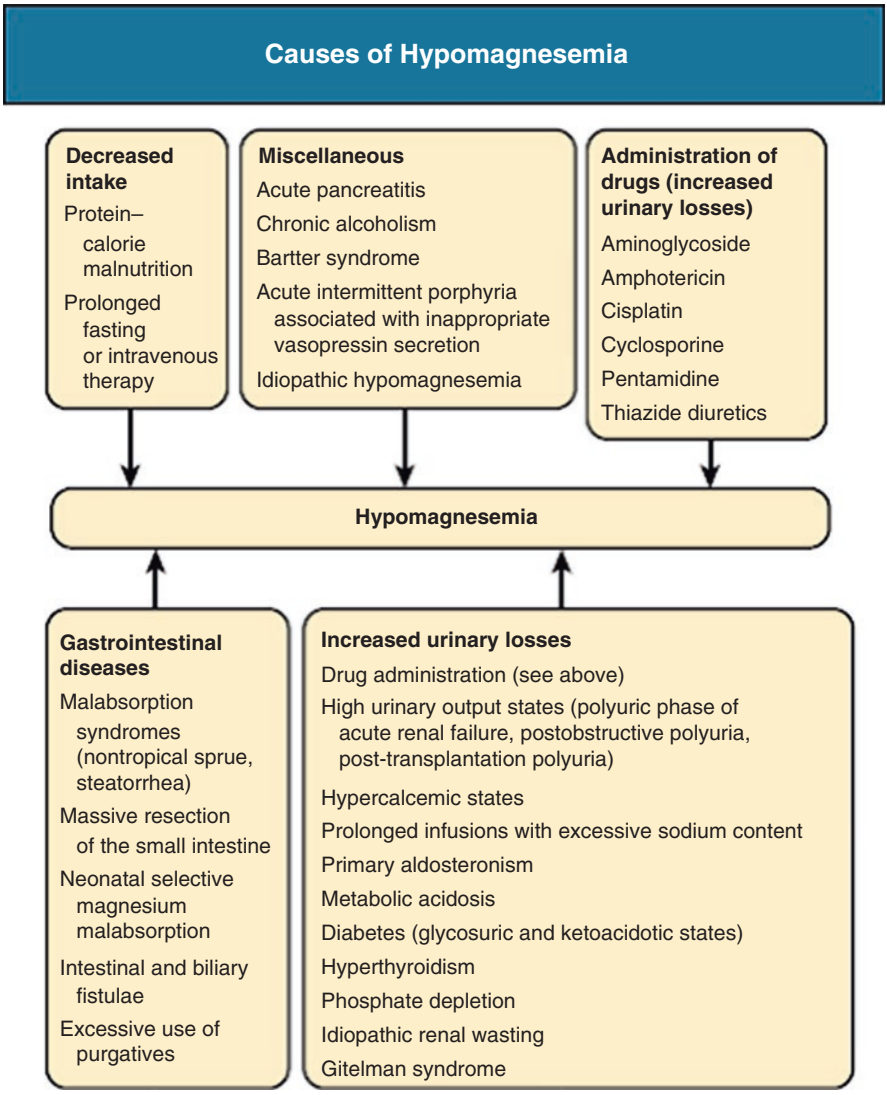


**Fig. 9.1** Causes of hypomagnesemia

Hypomagnesuria (defined variably as 24-h urine Mg <60 mg) may result from hypomagnesemia. Other clinical manifestations of moderate to severe magnesium depletion include generalized weakness and neuromuscular hyperexcitability with hyperreflexia, carpopedal spasm, seizure, tremor, and rarely tetany. Cardiac findings include a prolonged QT interval and ST depression. Magnesium deficiency can also be associated with hypocalcemia (decreased parathyroid hormone (PTH) release and end-organ responsiveness) and hypokalemia (urinary loss).

## Hypomagnesuric Calcium Nephrolithiasis

Hypomagnesuric calcium nephrolithiasis is characterized by low urinary magnesium, hypocitraturia, and low urine volume. Mg acts as a competitor to calcium in oxalate binding. However, Mg oxalate (MgOx) is more soluble than calcium oxalate (CaOx), 0.07 g/100 mL versus 0.0007 g/100 mL, respectively; so MgOx does not form stones at physiological urine concentrations. Because Mg competes with Ca in binding oxalate, both in the gut and urine, the ratio of Mg/Ca in the urine has been used as an estimate of stone risk [23].

Also Mg in combination with citrate, another inhibitor, is more effective than either alone. Mg citrate slowed crystal growth rate, nucleation rate, and supersaturation [24]. Another study found Mg supplements alone had no effect, but Mg with citrate increased pH and lowered the relative saturation of brushite in urine [25]. Recently a mixture of Mg and phytate shows a synergistic effect of delaying calcium oxalate crystallization [26].

A second way Mg may reduce the CaOx stone risk is through its effect on oxalate absorption. Even though MgOx is 100 times more soluble than CaOx, it is still relatively insoluble. Because of this property, Mg binds oxalate in the gut and reduces its absorption [27, 28].

## Nutrition Therapy for Hypomagnesuria

Several benefits supporting the use of oral magnesium (Mg) salts have been suggested. First, higher urinary Mg excretion may reduce the availability of oxalate to complex with calcium as Mg binds with oxalate to form a relatively soluble complex in urine. Second, higher urinary Mg concentration results in a more favorable magnesium-to-calcium ratio, a condition that offers relative protection against stone formation. Finally, Mg decreases renal tubular citrate resorption through the chelation of citrate and thus increases urinary citrate excretion [5].

Several Mg salts have been used for the treatment of stone disease. Magnesium oxide (MgOx) and magnesium hydroxide are poorly absorbed and produce only a slight decrease in urinary oxalate and a modest increase in urinary magnesium [29]. Additionally, urinary calcium levels are increased during magnesium oxide supplementation [31, 32], and thus urinary saturation of calcium oxalate is not significantly lowered with magnesium oxide. The more soluble forms of Mg are chloride, gluconate, aspartate, and citrate. Mg citrate doubled the Mg/Cr ratio 2–4 h after oral loading, while MgOx only increased the ratio by 3% [30].

A new magnesium preparation (potassium-magnesium citrate) has been developed. It provides both magnesium and citrate in the same tablet. This formulation of potassium-magnesium citrate has been shown to provide as much bioavailable potassium as other preparations. Ettinger reported results from a randomized, double-blind trial of potassium-magnesium citrate versus placebo. In this study, 64 recurrent stone formers were randomly assigned to receive placebo or potassium-magnesium citrate (42 mEq potassium, 21 mEq magnesium, and 63 mEq citrate)

daily for up to 3 years. The result was new calculi formed in 63.6% of subjects receiving placebo and in 12.9% of subjects receiving potassium-magnesium citrate [33]. When compared with placebo, the relative risk of treatment failure for potassium-magnesium citrate was 0.16. He concluded that potassium-magnesium citrate effectively prevented recurrent calcium oxalate stones and could be depended on to provide up to 85% protection over 3 years.

Several limitations of using magnesium salts to prevent nephrolithiasis are as follows:

(a) GI intolerance – a potential side effect of magnesium therapy is diarrhea, but Mg in tablet form rarely promotes diarrhea.
(b) Mg deficiency is relatively rare in stone formers. Even if Mg salts are well absorbed and increase urinary Mg, most patients already have sufficient urinary Mg to decrease crystallization to its minimum potential [23]. Patients with Mg deficiency are identified with 24-h urine testing, and subsequent testing can evaluate the adequacy of treatment.
(c) Dietary Mg is less likely to be deficient if the diet includes green leafy vegetables and whole grains, as Mg is a major mineral in chlorophyll. Additional dietary sources of dietary Mg include chocolate and nuts.

Regardless of conflicting clinical and laboratory data regarding the benefits of Mg salts, epidemiological evidence supports the probable effectiveness of increased magnesium in preventing symptomatic kidney stones. Taylor et al. followed 45,619 men for 14 years, with dietary assessments every 4 years [40]. After multivariate adjustment, the relative risk of stone formation for subjects with the highest quintile of magnesium intake (over 450 mg/day) compared to the lowest quintile (less than 314 mg/day) was 0.71. Consequently, this decreased risk supports Mg supplementation for those with Mg deficiency.

## Role of Potassium in Hypocitraturia

Over 50 years ago, Fourman et al. linked potassium deficiency to a decrease in urinary citrate levels [35]. Potassium depletion results in intracellular acidosis, which in turn decreases the pH of the tubular lumen [36]. Decreasing tubular pH increases reabsorption of citrate, thereby decreasing the urinary concentration of citrate [37, 38].

There is epidemiologic evidence that higher potassium intake is associated with lower incidence of urolithiasis (RR 0.49–0.54) [39]. It has been estimated that every 20 meq/day increase in urinary potassium is associated with 17 mg/day decrease in urinary calcium [40]. Another potential benefit is that foods high in potassium content usually are replete with alkali, which may further stimulate urinary citrate excretion. Moreover, stone formers are considered to have an adversely raised sodium-to-potassium ratio [41]. Lastly, markedly beneficial effect of alkaline citrates (especially potassium salts) in prevention of recurrent urolithiasis is well

established. Several studies have confirmed this, and their results justify these dietary recommendations which are included in several guidelines for prevention of nephrolithiasis [1, 16, 42].

## Conclusion

Citrate is a potent inhibitor of the formation of calcium kidney stones. Hypocitraturia may be the most common risk factor for recurring calcium stone formation, and dietary citrate supplementation can increase urinary citrate levels, helping to offset this risk.

Potassium depletion leads to hypocitraturia. In patients with low potassium levels (serum or 24-h urine), correction of the low potassium will help with correcting hypocitraturia.

Increased urinary magnesium levels are correlated with increase urinary citrate levels. In hypocitraturic patients, magnesium supplementation can raise citrate levels.

Citrate metabolism is affected by magnesium and potassium. Normalization of potassium and magnesium, through supplementation is needed, is an important adjunct in the treatment of hypocitraturia.

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# Nutrition Therapy for Specific Lithogenic Risk Factors: High Urine Uric Acid/Acid Urine

10

Robert Marcovich

## Introduction

High urinary uric acid is a common finding on 24-h urine testing and can contribute to both uric acid and calcium oxalate stone formation. With the increasing prevalence of obesity and diabetes mellitus (DM), disorders both linked to derangement of uric acid metabolism and renal acid handling [1–3], it is imperative that practitioners gain awareness of the pathophysiology and treatment of high urinary uric acid and associated conditions. While pharmacologic therapy with alkali has proven successful in preventing stone recurrence related to acid urine, nutritional intervention must lay the foundation for any treatment strategy.

## Uric Acid Metabolism

In humans, uric acid (UA) is the end product of metabolism of the purines adenine and guanine, both of which are components of various nucleotides such as ATP, AMP, cAMP, cGMP, and others (Fig. 10.1) [4]. Purines are synthesized from precursors or can be obtained from the diet, with about 20% of the UA excreted by the kidneys originating from dietary sources. Humans typically excrete more than 600 mg of UA per day [5]. Figure 10.1 details the final catabolic pathways of the adenine- and guanine-related substrates as xanthine oxidase (XO) converts them to uric acid. While nondairy animal protein is the major source of dietary purine, high levels of fructose intake also stimulate production of UA by an indirect effect. The phosphorylation of fructose by the enzyme phosphofructokinase causes intracellular phosphate depletion,

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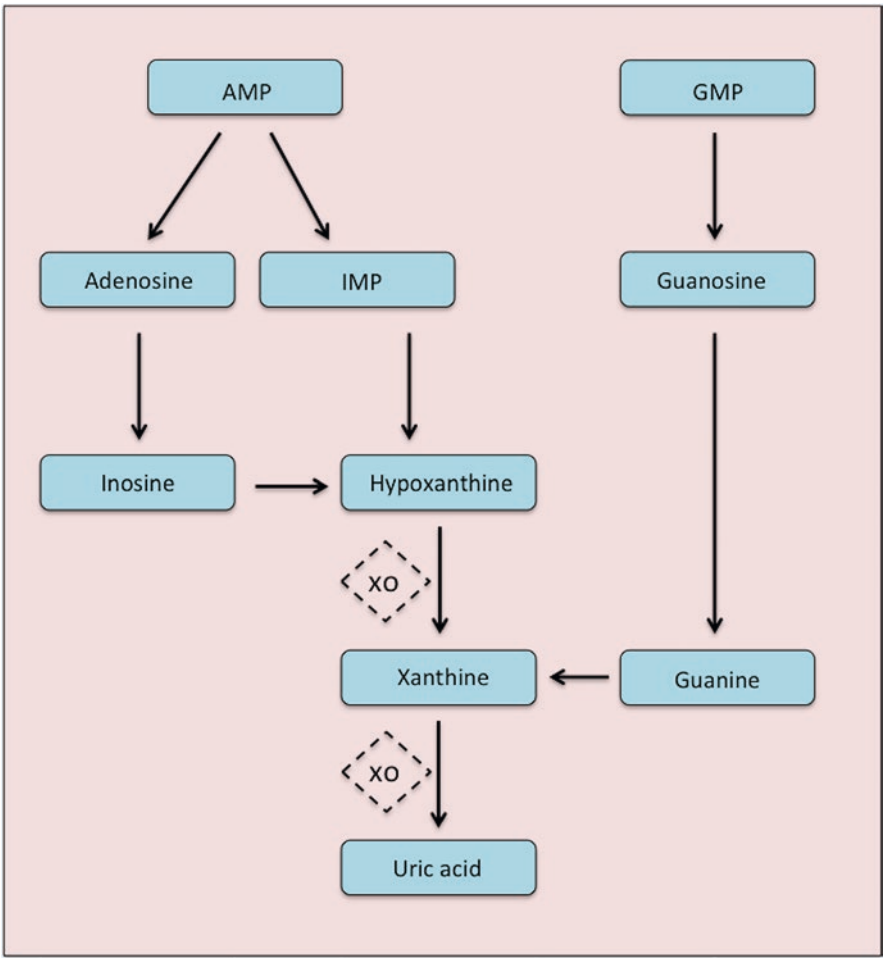


**Fig. 10.1** Metabolism of purines and uric acid. *AMP* adenosine monophosphate, *GMP* guanosine monophosphate, *IMP* inosine monophosphate, *XO* xanthine oxidase

which in turn disinhibits the enzymes that degrade AMP, increasing concentrations of inosine and promoting formation of UA from inosine via xanthine oxidase [6].

Uric acid is mainly excreted by the kidney, while the remainder is disposed of by intestinal bacteria. In the glomerulus, UA is freely filtered prior to being reabsorbed in the proximal tubule. While some secretion does occur in the distal tubule, the overall effect is retention of the majority of UA in the blood [4].

## Etiology of Uric Acid Nephrolithiasis

Uric acid nephrolithiasis is a condition long linked to prosperity and dietary excess, and a Western-type diet appears to promote its onset [7]. Metabolic syndrome is a major culprit in the development of UA stones [8–11], and it has recently been demonstrated

that total body fat and truncal obesity are strongly associated with 24-h urinary pH and UA supersaturation index [12]. Other clinical states conferring a higher risk of UA stones include chronic diarrhea, inflammatory bowel disease, and having an ileostomy [13, 14], all of which lead to a combination of fluid and bicarbonate loss in the stool and an acidic environment favoring UA precipitation.

The three main urinary risk factors for UA stones are *low urine pH*, *insufficient urine volume*, and *elevated urinary uric acid*. Low urine pH is by far the most important of these [15] because it increases the level of undissociated uric acid in the urine. Low urine pH can result from two mechanisms, reduced renal ammonium (RA) excretion and increased net acid excretion (NAE) [1, 3]. Obesity, DM, and metabolic syndrome are states of caloric imbalance wherein caloric intake exceeds caloric expenditure resulting in fat deposition in non-adipose tissue, including the kidney. Fat deposition in the kidney is thought to cause renal lipotoxicity [16, 17], and proximal renal tubule cells, which are the major contributors to the synthesis and secretion of ammonium [18], are injured, leading to impaired ammonium excretion [19]. Reduction in ammonium levels then requires buffering of secreted $H^+$ by titratable acid, thereby increasing the acidity of the urine and promoting uric acid precipitation.

In addition to impaired ammonium excretion, high net acid excretion also causes acidic urine and leads to increased risk of UA stones. Patients with UA stones have been shown to be similar in this regard to patients with type 2 DM, in terms of having significantly increased NAE [20]. The pathophysiology of this derangement has not yet been established but may involve net GI losses of alkali due to alterations in pancreatic exocrine function induced by pancreatic lipotoxicity or changes in the intestinal microbiome or increased colonic transit time that promote organic acid production via fermentation [20].

## Nutritional Strategies to Address the Risk Factors for Uric Acid Lithiasis

The three proximate factors leading to uric acid stone formation are inadequate urine volume, hyperuricosuria, and low urine pH, and all three must be addressed in a nutritional plan. Additional consideration should be given to fructose consumption.

### Low Urine Volume

Adequate daily fluid intake is equally important for uric acid stone formers as it is for patients with other stone compositions. Generating a daily urine output of over 2 liters (L) is the goal and typically cannot be achieved unless patients consume at least 3 L of fluid per 24-h period. While not complicated, this can be difficult to achieve. Initial dietary screening should include obtaining a history of estimated daily fluid intake (often overestimated by patients) as well as identification of barriers to hydration. These can include factors ranging from work schedules that do not allow the patient to drink enough or have sufficient access to a toilet to daily work

or recreational activities that lead to inordinate fluid losses such as working in a hot environment. Older patients with overactive bladder or prostatism may restrict their fluid intake to control symptoms of these syndromes. Systemic conditions leading to fluid loss such as chronic diarrhea or ileostomy status should be noted. A 24-h urine volume should be obtained to guide individual recommendations.

Counseling on fluid intake largely involves educating the patient on the role of fluid in preventing stones and on strategies to achieve a satisfactory amount of fluid, as well as which ones are desirable and which ones should be avoided. Tracking fluid intake is of paramount importance. This can be done by using a container of known volume or by advising the patient on the volumes of commonly used single-serve containers. In the United States, the latter include 16.9 oz (500 mL) bottles and 12 oz (354 mL) cans. Many patients find it easier to keep track if they know their daily goal of 3 L can be achieved by consuming six 16 oz bottles of water per day. The same can be achieved by drinking an 8 oz (236 ml) glass of water at the beginning and end of each meal and two glasses each in midmorning, midafternoon, and evening. Choices of fluid can include tap, bottled, and sparkling water, unsweetened lemonade, and nonsugar carbonated beverages, although noncaloric artificial sweeteners have recently been found to induce glucose intolerance by altering gut microflora [21]. Juices, sports or energy drinks, and sugared carbonated beverages should be avoided due to their carbohydrate load. Additionally, a recent analysis of data from the National Health and Nutrition Examination Survey found a 23% higher risk of kidney stone development in participants consuming sugar-sweetened cola, a 33% higher risk in those reporting intake of sugar-sweetened non-cola, and an 18% increased risk for those frequently consuming punch [22].

## Hyperuricosuria and Low Urine pH

Nutritional strategies geared to lowering urinary uric acid and raising urine pH overlap and will be considered together.

Due to high levels of purines, animal protein consumed in excess has long been known to confer an increased risk of both uric acid and calcium oxalate stones. Diets high in animal protein have been shown to increase net acid excretion – thus lowering urine pH – and also to contribute to hyperuricosuria and hypocitraturia. A short-term increase in dietary animal protein of 34 g/day, yielding 11 mmol of purine nitrogen/day, caused a 48% increase in uric acid excretion in normal male subjects [23], while in a comparison of serum and urine chemistry between omnivorous and vegetarian women, the former were found to have a significantly higher level of urinary titratable acid [24]. Similarly, urinary net acid excretion rose in a progressive manner in a cohort of healthy adults consuming 75 g protein/day derived from vegetarian, ovo-vegetarian, or animal protein sources [25].

A study of recurrent stone formers fed high and low animal protein diets for 2 weeks showed a 200% increase in urinary uric acid and reduction of urine pH by 0.9 in the former. This was accompanied by a significant increase in urinary uric acid supersaturation and an increased risk of forming uric acid crystals or stones in the urine [26]. All of these studies were relatively balanced in terms of nutrient

composition other than protein. The effects of a high protein diet combined with carbohydrate restriction (the so-called Atkins diet) were shown to include significant decreases in urine pH and doubling of urinary ammonium, titratable acidity, net acid excretion, and sulfate in both the initial "induction" phase and the maintenance phase. The level of undissociated uric acid also doubled [27]. A recent randomized, crossover metabolic study comparing the effect of different animal protein sources found that fish raised urinary uric acid and titratable acidity levels significantly higher than did beef or chicken [28]. Patients often have heard that they should lower their intake of red meat for health reasons, and patients with high urinary uric acid should be made aware of the effects of both chicken and fish on uric acid levels.

Given the effects of animal protein intake on urinary stone risk factors, limiting its intake may be a strategy to lower the risk of uric acid lithiasis. A study on the effects of moderate dietary protein restriction on idiopathic hypercalciuria and calcium nephrolithiasis demonstrated a significant reduction in 24-h urinary uric acid in addition to beneficial changes in urinary calcium, although urine pH levels were not reported [29]. Conversely, an increase in the proportion of dietary protein, when combined with a reduction in calories and carbohydrates, and replacement of refined carbohydrates with complex carbohydrates can lead to clinically significant reduction in serum uric acid, as well as weight loss [30]. Such a diet may be more palatable and therefore easier to comply with than a protein restricted diet.

### Fructose

Fructose has been implicated in the development of metabolic syndrome, obesity, and hypertension [31], and, as previously mentioned, high levels of fructose intake can stimulate uric acid production [6]. High fructose corn syrup (HFCS) has been shown to adversely affect lipid risk factors for cardiovascular disease such as postprandial triglyceride and fasting low density lipoprotein levels in a dose-dependent manner [32]. The same study also demonstrated an increase in serum uric acid level in men and women whose ad-lib diets were supplemented with HFCS-sweetened beverages at up to 25% daily energy requirement [32]. More provocatively, it has been demonstrated that mice fed a combination high-fructose/high-sodium diet had two- to four-fold increases in urinary uric acid, accompanied by substantial decreases in urinary stone inhibitors citrate and magnesium, when compared to standard diet [33]. Analysis of data from the Nurses' Health Studies I and II and the Health Professionals Follow-Up Study suggests that fructose intake is associated with an increased risk of kidney stones independent of age, body size, and other dietary factors [34].

## Specific Dietary Advice

In addition to maintaining a satisfactory fluid intake and avoiding HCFS-sweetened items, patients with high urinary uric acid can benefit from knowledge of the purine levels of various foods in order to design a meal plan. In a 2014 review, Kaneko and

**Table 10.1** Purine group level of common foods [Ref. 35]

| Food item | Group | Exception | Group |
|---|---|---|---|
| Cereals | 1–2 | | |
| Beans | 1–2 | | |
| Soybean products | 1–2 | Dried soybean, fermented soybean | 3 |
| Eggs | 1 | | |
| Dairy products | 1 | | |
| Mushrooms | 1–2 | Dried shiitake | 4 |
| Fruits | 1 | | |
| Vegetables | 1–2 | Broccoli sprouts, young leaf spinach, parsley | 3–4 |
| Meat (beef, chicken, pork) | 2–3 | Liver | 3–5 |
| Processed meat | 2–3 | | |
| Fish | 3 | Bonito, sardine | 4 |
| | | Monkfish, smelt | 2 |
| Shellfish | 2–4 | | |
| Dried fish | 4–5 | | |
| Canned tuna/salmon | 3 | | |
| Honey | 1 | | |
| Miso | 1–2 | | |
| Soy sauce | 1–2 | | |
| Beer yeast | 5 | | |

(1) Very low (<50 mg per 100 g food item). (2) Low (50–100 mg per 100 g food item). (3) Moderate (100–200 mg per 100 g food item). (4) High (200–300 mg per 100 g food item). (5) Very high (>300 mg per 100 g food item)

associates analyzed, tabulated, and published the purine content of over 270 common foods and calculated the amount of uric acid produced by ingestion of each item [35]. They classified the amount of total purines (as mg uric acid generated per 100 g of food item) into five groups (very low <50, low 50–100, moderate 100–200, high 200–300, and very high >300) (Table 10.1). For example, eggs, dairy, and fruit (banana and strawberry) contained almost no purine and were classified in the very low group. Seventy percent of the 38 vegetables analyzed were also classified in the very low group. Examples of vegetables with significant purine content were broccoli sprouts (moderate – 153 mg/100 g) and parsley (very high – 341 mg/100 g), although the latter is typically eaten in small quantities. Most cuts of beef, chicken, and pork, as well as fish, fell into the moderate category, whereas organ meats, particularly the liver, were typically high in purine. Interestingly, previous investigations have shown that all purines do not have equal effects on serum and urinary uric acid concentration, with hypoxanthine having the strongest effect [36] and guanine having negligible effects [36, 37]. They found that so-called "metallic" oily fishes, which have also been found to be beneficial in decreasing cardiovascular risk, had a high proportion of guanine and thus would not need to be limited in a low-purine diet.

The above data would indicate that the ideal diet for prevention of lithiasis related to high urinary uric acid and acidic urine is an ovo-lacto vegetarian (OLV) one. Patients who are not inclined to a vegetarian diet for religious, ethical, or other health reasons may find adhering to such a regimen difficult, if not impossible. A less extreme alternative is a DASH-style diet. DASH (Dietary Approaches

to Stop Hypertension) is a plan which is high in intake of vegetables and fruits, moderate in low-fat dairy products, and limited in animal protein and sweetened beverages [38]. The diet is lower in animal protein than the standard Western diet. It was designed with the aim of reducing blood pressure in hypertensive individuals. Hypertensive kidney stone formers have been found to have significantly lower urine pH and citrate and higher titratable acid and ammonium than normotensive stone formers [39]. Data from the Health Professionals Follow-Up Study and Nurses' Health Studies have shown an inverse association between age-, BMI-, and fluid-intake-adjusted risk of kidney stone formation and adherence to a DASH-style diet [40]. Examination of 24-h urines in these cohorts also revealed that those most closely following a DASH-style diet had higher urine pH, higher urinary citrate, and lower supersaturation of uric acid [38]. Additionally, DASH adherents had higher 24-h urine volume that was independent of fluid intake, thought to be due to the higher fluid composition in fruits and vegetables [38]. An advantage of this regimen is the ready availability of numerous commercial publications providing information on the diet in addition to meal plans and recipes.

## Effect of Weight Loss and Exercise

Weight loss as a consequence of reduced caloric intake can also have beneficial effects on serum and urinary uric acid. Plasma and urinary UA decreased significantly in obese patients placed on a reduced calorie diet and the change in plasma UA correlated with a fall in serum cholesterol [41]. In an intriguing rat model of metabolic syndrome, animals with restricted caloric intake as well as animals with both restricted calories and exercise training had significant decreases in plasma and urinary uric acid levels compared to control animals on standard diet and activity level. Addition of exercise to the dietary regimen further lowered serum and urinary uric acid. In animals that had overt type 2 DM, diet and exercise had no effect on urinary uric acid, but urinary pH significantly increased. Although uric acid supersaturation was not assessed in this study, it would be expected to decrease substantially, given the mean 1.0 unit pH increase seen [42].

**Take-Home Points**

Knowledge of the etiology and pathophysiology of uric acid stones as well as the risk factors associated with stone formation can give practitioners tools to counsel patients on nutritional prevention strategies. The following take-home points should be emphasized:

- *Uric acid is the end product of metabolism of the purines adenine and guanine.*
- *The primary dietary sources of uric acid are nondairy animal protein and fructose.*
- *The three main urinary risk factors for uric acid stones are low urine pH, insufficient urine volume, and elevated urinary uric acid. Low urine pH is the most important of these.*

- *Obesity, diabetes mellitus, and metabolic syndrome are states in which fat is deposited in the kidney, causing lipotoxicity. Lipotoxicity impairs renal acid handling, thereby increasing the acidity of the urine and promoting uric acid precipitation.*
- *Uric acid stone formers should drink sufficiently to generate at least 2 L urine output daily.*
- *Reduced dietary protein intake can lower urinary uric acid and make urine more alkaline.*
- *Fructose intake in the form of high-fructose corn syrup is associated with development of metabolic syndrome and can stimulate uric acid production. Thus excessive intake of fructose should be avoided.*
- *Dietary plans which are most suitable for prevention of elevated urinary uric acid and uric acid stone formation include vegetarian diets (vegan and ovo-lacto vegetarian) and DASH-style diets. These diets often have additional related health benefits.*
- *Weight loss through caloric limitation and exercise has been shown to lower urinary uric acid in both humans and animal models.*

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# Therapeutic Nutritional Strategies When No Risk Factors Are Apparent

11

Karen Doersch and Patrick Lowry

## Introduction

Recurrent urolithiasis are a significant cause of morbidity and discomfort. Not only are they painful, but they also result in repeated expensive and sometimes invasive medical interventions. In some patients, a treatable cause is diagnosed, which can result in a significant reduction in clinically significant urolithiasis. However, in roughly 15–20% of calcium oxalate stone formers, no specific cause can be identified [1, 2]. Given that kidney stones affect 0.5–1% of the population per year in the United states and that up to 80% of these are calcium oxalate stones, idiopathic stone formers comprise a significant portion of the population [3, 4]. Formulating a treatment plan for these patients, in whom no correctable cause is identified, presents a unique challenge.

In this chapter, risk factor identification for idiopathic stone formers (i.e. those with no identifiable risk factors on lab testing) will be discussed, as well as dietary strategies for avoiding stones in these patients.

## Diagnosis

In this patient population, a complete history and workup focused on stone risk factors presumably revealed no underlying cause, yet the patient continues to experience repeated episodes of stones [5–7]. Patients should also be questioned about professional and recreational activities that occur in a hot environment or are

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associated with excessive sweating and may decrease urine output even in the context of sufficient fluid intake [8]. Furthermore, a 7 day diet and fluid intake diary may reveal dietary risk factors impacting stone formation, which will be discussed later. Tracking their diet for 7 days has the added benefit of drawing patients' attention to their consumption of certain foods associated with stone formation or, more importantly, a paucity of fluid intake.

Patients who have repeated stones will have a workup including at least one 24 h urine collection [6]. However, a 24 h urine with normal values does not account for the possibility that stone risk may increase before levels of some metabolites cross the threshold into the abnormal range. Additionally, some patients may, either intentionally or unintentionally, be more adherent to their prescribed dietary interventions during their 24 h urine collection. For this reason, it is recommended that a urinalysis be done on a different day than the 24 h urine collection. The urinalysis osmolality can then be compared to the osmolality and volume collected during the 24 h urine collection. If these values do not correlate, a clinician can consider the possibility that the 24 h urine collection may not be representative of the patient's usual daily fluid intake or urine output. Urine Osmolality may not be easily obtainable, and urine specific gravity may be used instead. The laboratory test results should also be compared with the diet and fluid intake reported during the history. Together, these results may be used to further educate the patient and improve their chances of remaining stone-free.

It is important to individualize a patient's diet to improve their chances of remaining stone free [7]. Patient characteristics and diet can vary widely and because so many factors contribute to stone risk, it is important to determine what, if any dietary interventions might be beneficial. In attempting dietary remediation of urolithiasis, it is important to understand that dietary interventions can be challenging for patients to implement and can lead to expectations that might outweigh the benefits the patients receive. Thus, dietary interventions should be considered carefully and it is important to explain to patients the benefits that might reasonably be expected from each intervention. Additionally, dietary counseling that addresses too many issues at once may result in lifestyle changes that the patient perceives as complex, which may result in noncompliance. Rather than address every risk factor at once, we prefer to simplify patient instructions, and prioritize counseling the patient on only the most important factor or two, in order to maximize compliance. The remaining causes are addressed during follow up visits after additional 24 h urine testing is performed.

## Nutritional Strategies

Risk factors may be uncovered in a diet history or 24 h urine collection. Such risk factors include low fluid intake resulting in low urine volume, imbalances in calcium, oxalate, or other key nutrients. This section outlines and explains these risk factors and considers possible interventions to address them. Keep in mind that the subset of patients discussed in this section have no identifiable risk factors. We do not recommend nutrition therapy that is not warranted, but instead we

propose to maximize urinary parameters according to available evidence in order to minimize the risk of stone formation. The authors believe that although 24 h urine tests in these patients are within normal limits on the day of the evaluation, it is highly likely that the variability of food intake from day to day results in some days with low risk and other days with high risk of stone formation [9]. During these days of high risk, crystals may form, and propagate over time.

## Fluid Intake

Patients with a normal workup may still need to increase their fluid intake [5, 8, 10]. As mentioned previously, patients may behave differently on the day of their workup and may not maintain a sufficient fluid intake to prevent stones on a daily basis. Furthermore, there is evidence that patients who have a history of stone formation have a higher risk of forming stones at a given urine volume compared to individuals who do not form stones. Thus, patients with a normal workup and a propensity to form stones should still be advised to increase fluid intake. Evidence suggests that in stone formers, stone risk increases dramatically when urine volume drops below 1.6 L/day. To minimize stone risk according to the AUA guidelines, patients should drink sufficient liquid to excrete a urine volume of roughly 2.5 L/day [5]. If stones still recur at this urine volume, fluid intake may need to be increased further in order to increase urine output to 3 L/day, or even higher if stones continue to recur [8].

Individuals attempting to increase fluid consumption to diminish stone risk should also be counseled on the type of liquids that may best mitigate risk factors. Patients should focus on increasing fluid intake, while recognizing that the fluid of most beverages will lower risk more than the hypothetical increased risk of the contents of some beverages. Additionally, it may be worthwhile to counsel patients regarding the content of calcium and other minerals in the water a patient drinks. While there is insufficient evidence that individuals who drink hard water have a higher risk of stones, patients commonly ask about their water source and its potential effect. Rodgers showed that in stone formers, ingestion of a mineral water rich in calcium and magnesium showed beneficial parameters on a 24 h urine test compared to tap water [11]. Schwartz et al. reviewed 4,833 stone formers by zip code, and used the zip code to stratify patients by water hardness based on information provided by the Environmental Protection Agency. No difference on lifetime stone episodes was detected in regions with hard or soft water, although 24 h urine calcium, magnesium, and citrate levels were higher in the hard water regions [12].

Observational studies have shown a decreased risk of stone formation with increased consumption of tea, coffee, decaffeinated coffee, and alcoholic beverages [13, 14]. Curhan et al. demonstrated in a prospective trial a decreased risk of stone formation with intake of both caffeinated and decaf coffee (10%), tea (14%), beer (21%) and wine (39%). This information is important to share with patients as many practitioners incorrectly counsel that coffee and tea increase stone risk through their oxalate content. Finally, patients should be advised to avoid drinking fluids that may increase their risks of forming stones. Drinks associated with a higher risk of stones

include those flavored with high sugar content. Schuster et al. showed that stone formers who simply abstained from drinking sugar sweetened soft drinks decreased their incidence of stone formation by 7% [23]. Additionally, Ferraro revealed that patients who drank one or more sugar sweetened sodas per day had a 23% increased risk of stone formation, and those who ingested one or more sugar sweetened non soda beverages had an increased risk of 33% [14].

Patients may struggle to adhere to the recommendations for increased fluid intake. Some patients may have lifestyles or professions that make high-volume liquid consumption or frequent trips to the restroom difficult [8]. Additionally, patients with colitis, Crohn's disease, or other bowel disorders may have difficulty maintaining urine output due to gastrointestinal fluid losses, and often require input from Gastroenterology colleagues to better manage the chronic diarrhea [15].

Timing of fluid intake may help prevent stones. Although it may result in nocturia, drinking before bedtime prevents dehydration form the lack of fluid intake. Stone formers would not go 6–8 h without fluid intake in the daytime, so they need to drink enough to stay hydrated at night. Otherwise, the relative dehydration at night caused by poor fluid intake results in an increased risk of crystallization of stone forming constituents. If nocturia presents a barrier to nighttime fluid intake, patients may need further Urologic evaluation to improve this condition.

## Dietary Oxalate

High urine oxalate is a risk factor for the formation of calcium oxalate stones [5, 8, 16]. However, dietary intake of oxalate is a controversial risk factor for stone formation. There is some evidence that dietary oxalate contributes to stone formation, however there is limited evidence that limiting dietary oxalate decreases stone risk. This is because dietary oxalate may not be bioavailable and therefore may not be readily absorbed. Oxalate that is in crystal or precipitated forms, which is what is typically found in food, is less likely to be absorbed. In patients with normal 24 h urinary oxalate levels, restriction of dietary oxalate is unlikely to significantly affect stone risk. However, if the oxalate level is borderline high and the patient persists in forming calcium oxalate stones, per the AUA guidelines, a mild oxalate restriction combined with maintaining normal calcium may help decrease the risk of future stone formation [6]. In spite of the fact that dietary oxalate may not be bioavailable, there may be other dietary sources of urine oxalate. Several oxalate precursors, including hydroxyproline and ascorbic acid, may be found in the diet and could contribute to oxalate excretion.

## Dietary Calcium

Because high urinary calcium has been considered a significant risk factor for stone formation, dietary calcium has long been thought to contribute to stone risk [8, 17]. However, it may not be as simple as preventing stones by restricting calcium intake.

There is insufficient evidence to determine that diminishing urinary calcium excretion by means of a low-calcium diet impacts the risk of stone recurrence [3]. In fact, a low calcium diet has been shown not to impact urine calcium excretion in patients with normal urine calcium concentrations following a calcium load [18]. Thus, a low calcium diet may not impact the urine calcium content of all patients. Additionally, it has been shown that stone risk increases when dietary calcium intake drops below 720 mg/day [7]. It has been hypothesized that gastrointestinal calcium is capable of binding and precipitating oxalate, preventing the absorption of both ions. By keeping more calcium in the gut to bind available oxalate, stone risk may be diminished.

Despite the possibility that dietary calcium may not contribute to stones and may even assist in sequestering other stone-forming ions in the gut, few studies have specifically addressed calcium supplementation as a means to prevent stones [19, 20]. There have been, however, studies that assessed the impact of calcium supplementation on stone risk. Hess et al. showed that despite an extreme oxalate rich diet, calcium supplementation led to a decrease in urinary oxalate with minimal increases in urinary calcium. There have been a few trials that followed stones formers over time, but these studies have demonstrated conflicting results, with some demonstrating improvement with calcium supplementation and some demonstrating no change [8]. More research on this topic is needed to definitively determine how calcium would best be employed to prevent stone formation, but current recommendations suggest 1,000–1,200 of calcium spread in the meals throughout the day.

Another contributor to calcium metabolism and excretion is phosphate [8]. Phosphate contributes both to the excretion and precipitation of calcium in the urine, leading to stones. However, phosphate is also capable of trapping calcium in crystal form in the gut, and historically, was used for stone prevention. It is imperative to give phosphate in a basic formulation because acidic phosphate may increase urinary calcium. Phosphate supplementation is currently not used because it may contribute to a decrease in plasma calcium which stimulates the production of parathyroid hormone, ultimately increasing urinary calcium. Furthermore, patients with renal impairment are unable to tolerate this type of treatment. Thus, focusing on other aspects of calcium metabolism may better prevent stones without any harmful side effects.

Calcium-phosphate metabolism in the body is also impacted by vitamin D [8]. Vitamin D, which is absorbed from dietary sources and converted to its active form by the kidney, acts to increase blood calcium levels. Vitamin D promotes calcium absorption from the gastrointestinal tract, although this may not be true of calcium bound to oxalate. Calcium absorbed in the gut in response to vitamin D may ultimately end up in the urine. However, vitamin D deficiency is common among individuals that form stones, hinting that vitamin D may actually be helpful in stone prevention. Furthermore, there is some evidence that vitamin D promotes reclamation of calcium in the kidneys, which might mean that vitamin D could decrease the chance of forming calcium oxalate stones [5, 8]. These results may be explained by the fact that vitamin D is also thought to increase urinary phosphate levels both by

promoting gastrointestinal phosphate absorption and promoting its excretion in the urine. Thus, vitamin D may promote crystallization by phosphate in the urine, which may explain its relationship to increased stones and also explain why attempts to use vitamin D supplements to decrease stone risk have not been successful. Manipulation of dietary Vitamin D is not likely to affect stone risk, especially in patients with normal 24 h calcium levels.

Regarding calcium, we reiterate that patients with normal 24 h urinary calcium levels are not likely to have their stone risk affected by changes in dietary calcium, and current recommendations suggest 1,000–1,200 of calcium spread in the meals throughout the day [6].

## Protein

Individuals who consume significant animal meat in their diets may also be at risk for forming stones [5, 8]. Protein has a variety of effects on the content of urine, which may increase the risk of stone formation. For example, acidic urine is an established risk factor for urolithiasis. A diet high in proteins which contain acidic amino acids, such as the proteins found in animal meat, may contribute to urinary acidity. Additionally, the amino acids in meat are also metabolized to purines in the body, which increase uric acid levels and may contribute to stone formation as well. Furthermore, some individuals may have undiagnosed polymorphisms in enzymes that process purines or uric acid, and may thus form stones with meat consumption that is tolerated by individuals without these polymorphisms.

There is some evidence that a diet that controls animal-based proteins may help prevent stones [8]. The risk of stone formation in vegetarians is lower than that of people who eat meat. Additionally, some studies have demonstrated that following a vegetarian diet can increase likelihood of stone recurrence [10]. Furthermore, vegetarian diets are often difficult for patients to adhere to. For recurrent stone formers without risk factors, including purine gluttony on a 24-h urine (elevated uric acid, phosphate, sulfate), it is reasonable to recommend limiting the diet to 6–8 ounces of animal flesh protein daily to minimize stone risk.

## Sodium

Dietary sodium may contribute to high urinary calcium levels and lead to increased stone risk [7, 8, 10]. Sodium is reabsorbed at multiple points along the urinary tubule. Urinary sodium in the distal renal tubule is reclaimed via the sodium-calcium antiporter, leading to increased urinary calcium and possibly contributing to stone formation. Sodium is also exchanged for hydrogen ions in the proximal convoluted tubule via the sodium-hydrogen antiporter, meaning that high urinary sodium acidifies the urine, which leads to an increased urinary calcium. Restricting sodium is unnecessary in patients without diagnosed hypercalciuria, but might be a consideration in patients with persistent stone formation who have urinary calcium levels on the upper end of normal.

## Citrate/Magnesium

Urinary citrate has been described as an inhibitor of stone formation by forming a soluble complex with calcium, and by preventing the precipitation of the calcium salts that typically comprise stones [8].

Magnesium binds oxalate, which helps it remain soluble in the urine, and magnesium also inhibits the crystallization of calcium. Magnesium supplements in the form of tablets are well tolerated, and may be used for the purpose of preventing stones. Increasing dietary magnesium is possible by increasing consumption of whole grain breads, pastas, and rice.

The consumption of fruits and vegetables increases the urinary excretion of both citrate and magnesium. Additionally, a diet rich in fruits and vegetables increases excretion of potassium, which inhibits the tubular reabsorption of citrate, resulting in urinary citrate levels [21]. Finally, urine volume has been shown to increase significantly in a diet supplemented with fruits and vegetables [22].

## Probiotics

There is some evidence that probiotics may contribute to stone prevention [7]. One specific anaerobe found in the human digestive tract, *Oxalobacter formigenes,* is able to metabolize oxalate and may thus reduce absorption of dietary oxalate [8]. Thus, a low level of this bacteria in the large intestine may be a risk factor for stone formation. Additionally, exposure to antibiotics may increase the absorption of dietary oxalate by killing this bacteria species. There is some evidence that supplementation with lactic acid bacteria, which also metabolize oxalate, may decrease stone risk, however, these results are controversial.

## Fiber/Prebiotics

Fiber may contribute to stone prevention; however, fiber also binds and traps water in the gut, which may slightly affect the amount of water available to dilute the urine [7, 8, 10]. Certain dietary fibers ae capable of binding calcium in the gastrointestinal tract, thereby preventing its absorption. Additionally, fiber and other nondigestible dietary carbohydrates act as prebiotics, which selectively stimulate the growth or activity of probiotics, beneficial colonic bacteria food components. Thus, fiber appears to be a double-edged sword and warrants normalization but neither overconsumption or nor avoidance.

## Summary

It is difficult to determine the best strategies to address individuals who form stones in the absence of abnormal laboratory findings. In these patients, careful consideration of dietary risk factors and fluid status should be considered and the above-mentioned

dietary strategies may be tried. It is also important to consider the possibility that the patients' behavior on the day of their testing may differ from their typical behavior, and patients need to be counseled that consistency from day to day will go a long way to preventing stones in the long term. Furthermore, for some nutrients there is an increase in stone formation both above and below their ideal levels. More research is needed to further improve our understanding of stone risk factors and prevention, especially in patients with no obvious laboratory finding.

**Take Home Points**

1. In patients with normal laboratory test results and no diagnosable cause for their stones, a history with a focus on stone risk factors should be performed.
2. Dietary interventions should be tried with considerations of the patients' life style and individual risk factors.
3. If the oxalate level is borderline high and the patient persists in forming calcium oxalate stones, a mild oxalate restriction combined with maintaining normal calcium may help decrease the risk of future stone formation.
4. Fluid intake should be enough to result in 2.5 l of urine output, and possibly more if stone formation persists.
5. Patients with normal 24 h urinary calcium levels are recommended to take in 1,000–1,200 of calcium spread in the meals throughout the day.
6. For recurrent stone formers without identifiable risk factors, it is reasonable to recommend limiting the diet to 6–8 ounces of animal flesh protein daily to minimize stone risk.
7. For recurrent stone formers, a diet rich in fruits and vegetables increases excretion of potassium, magnesium, citrate, and urine output, all of which contribute to a decreased risk of future stones.

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# Part IV

# Integrating Nutritional Stone Prevention with Therapy for Other Comorbidities

# Overweight/Obesity: Metabolic Benefits to Reduce Stone Risk

12

Marcelino E. Rivera and Amy E. Krambeck

## Introduction

Obesity, defined by the World Health Organization (WHO) as a BMI >30 kg/m$^2$, is considered an epidemic in the United States and is estimated to afflict >20% of the population with nearly 11.5 million people affected nationwide [1]. The population of overweight individuals (BMI between 25 and 30 kg/m$^2$) is likewise increasing with as many as 40 million people affected. In fact, recent analysis would suggest that approximately two-thirds of the US population is overweight or obese [2]. Worldwide there has been an exponential increase in obesity with some countries reporting a near tripling of the rate of the obese population [3]. Prevalence of comorbidities including type 2 diabetes mellitus, hypertension, coronary artery disease, hypercholesterolemia, obesity-related restrictive lung disease, CKD, and nephrolithiasis has been demonstrated to increase as BMI increases [4]. The increasing westernization of the developing world with associated dietary changes has been associated with an increase in energy dense foods, a sedentary lifestyle, and is associated with the rapid increase in the rates of obesity. Even in many low-income countries, rates of obesity are now also increasing [5].

The association between obesity and urolithiasis is well studied, and obesity has been demonstrated to be an independent risk factor for stone disease [6]. Taylor et al. evaluated the incidence of symptomatic nephrolithiasis in a group of healthcare providers and found that both weight gain of >35 lb since age 21 and a BMI >30 kg/m$^2$ were associated with an increased risk of a stone event, relative risk (RR) of 1.39 (95% CI, 1.14–1.70). This increased risk was more pronounced for females, with younger females at higher risk than older females, RR 1.82 (95% CI, 1.50–2.21) and

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1.70 (95% CI, 1.40–2.05), respectively. Body mass index was also demonstrated to be related to symptomatic stone disease with an RR for men with a BMI of >30 kg/m$^2$ versus those with a normal weight BMI was 1.33 (95% CI, 1.08–1.63). Equivalent RRs for the same categories of BMI in older and younger women were 1.90 (95% CI, 1.61–2.25) and 2.09 (95% CI, 1.77–2.48), respectively [6].

In another analysis of stone-forming and non-stone-forming participants in the Health Professionals Follow-Up Study (599 stone-forming and 404 non-stone-forming men), Nurses' Health Study (888 stone-forming and 398 non-stone-forming older women), and Nurses' Health Study II (689 stone-forming and 295 non-stone-forming younger women), Taylor and colleagues evaluated correlations between 24-h urine studies and urinary stone risk profiles. They concluded that participants who had an elevated BMI had lower urinary pH values and they excreted more urinary oxalate, uric acid, sodium, and phosphate than participants with lower BMIs. A positive association between BMI and urinary calcium excretion was found only in men and younger women, and uric acid super saturation was also associated with greater BMI, likely due to the inverse relationship between pH and BMI [7].

This chapter will aim to describe the association between overweight/obesity and biochemical characteristics associated with stone disease in this particular group of individuals. We will also discuss nutritional therapies that decrease the risk of stone recurrence, improve 24-h urinary parameters, and are utilized to decrease weight and improve other comorbidities associated with the obese/overweight patient.

## Obesity and Low Urine Volume

Dehydration is a known risk factor for stone disease regardless of BMI. However, overweight/obese patients, in general, have been identified as having significantly low urine volumes as a cause for stone disease [8]. Thus, increasing fluid intake should be a baseline measure for all stone-forming patients. Borghi et al. prospectively followed patients with calcium stone disease for 5 years randomized to a high water intake protocol to achieve a urine volume of 2 l per day. During 5 years follow-up, patients in the high water intake group had fewer recurrences (12% vs. 27%, $p < 0.01$), and the time to recurrence was significantly longer (38.7 vs. 25.1 months, $p < 0.02$) compared with the group on regular amounts of fluid intake [9]. Likewise, chronic exposure to hot environments also increases the risk for stone disease [10].

To determine the efficacy and safety of diet, fluids, and supplement intervention for secondary prevention of nephrolithiasis, Fink et al. conducted a meta-analysis on reported randomized trials and found that increased water intake to >2 l = day or enough fluid intake to keep the urine output to more than 2.5 l per day decreased stone recurrence (relative risk: 0.39, 95% confidence interval: 0.19–0.80) [11]. Shuster et al. evaluated the consumption of soft drinks in stone-forming men with a baseline soft drink consumption >160 ml/day, randomized to abstain from soft drink intake versus no intervention [12]. At 3 years of follow-up, stone events were significantly lower in the intervention group (34% vs 41%, $p = 0.023$). Interestingly, decreased soft drink consumption did not decrease overall fluid volume as daily intake was similar between the two groups. Overweight and obese patients like all stone patients should be counseled to increase urine volume as a first-line therapy to prevent stone recurrences.

## Obesity and Increased Oxalate and Calcium Excretion and Lower Urinary pH

The pathophysiology of stone disease induced by obesity and metabolic syndrome is complex and multifactorial, but also varies. Individuals with obesity/metabolic syndrome preferentially form uric acid and/or calcium oxalate stones, likely related to significantly lower urinary pH. As previously discussed, urinary pH has been demonstrated to be inversely related to BMI, while insulin sensitivity has been found to be directly related to pH. Higher urinary pH levels have been observed during episodes of hyperinsulinemia, and decreased insulin sensitivity has been shown to result in low urinary ammonium and urinary pH [13]. The mechanism behind urinary pH and its relationship to obesity and metabolic syndrome have yet to be elucidated; however, several theories do exist. Most studies link obesity, low urinary pH, and uric acid nephrolithiasis, but there may also be a link between insulin resistance and calcium oxalate stone disease in the obese patient population.

Sakhaee and colleagues studied acid-base balance in pure uric acid, mixed calcium oxalate/uric acid stones, pure calcium stones, and healthy volunteers. The mean BMI for the uric acid, mixed calcium oxalate/uric acid, and pure calcium oxalate stone formers were 35, 33, and 34 kg/m$^2$ respectively. After standardized diets were given to subjects for a set of stabilization period, an oral ammonium chloride loading was performed. Interestingly, the rise in ammonium excretion in the healthy and pure calcium oxalate stone formers was five- to sevenfold greater than that of mixed or pure uric acid stone formers. These findings lead the authors to conclude that patients with mixed or pure uric acid stones have impaired ammonium excretion, but systemic acid-base balance is preserved due to titratable acidity in the urine. The lower urinary pH leads to precipitation of urate, thus increasing rates of stone disease in the form of both uric acid and mixed calcium oxalate stones in these patients [14].

As well as impaired ammonium excretion, obese individuals have been demonstrated to have increased circulating triglycerides as well as free fatty acids due to increased caloric intake and underutilization of ingested calories. The increase in circulating fats may serve as a substitute substrate for glutamine, thereby reducing the proximal renal tubular cell utilization of glutamine and renal ammoniagenesis. Another avenue that has not yet been thoroughly investigated is adipose accumulation in tissue which may also influence endogenous acid production [15].

BMI alone has been investigated as a potential independent risk factor in calcium oxalate stone formation. Siener et al. investigated the potential link between overweight and obese adults and oxalate stone disease in idiopathic calcium oxalate stone formers [16]. They identified 527 calcium oxalate stone formers, 363 men and 164 women with an average BMI of 25.1 and 25.9 kg/m$^2$, respectively. Approximately 10% of patients in either group were obese (BMI $\geq$30 kg/m$^2$). In this study, Siener and colleagues found significant comorbidities, hypertension, and coronary artery disease, associated with elevated BMI as well. They also observed a positive correlation between BMI and urinary uric acid, sodium, ammonium, and phosphate excretion and an inverse correlation between BMI and urinary pH in both male and female study participants. Uric acid excretion is known to increase the risk of calcium oxalate stone formation due to decreased

solubility of calcium oxalate in the setting of urate saturation [17]. There may also be a reduction in inhibitors of calculogenesis as well which would increase the likelihood of nucleation of calcium oxalate [18].

## Obesity, Urinary pH, and Citrate

Wrobel and colleagues investigated obesity and calcium oxalate stone disease and found that in a series of 100 consecutive stone formers, urinary pH and urinary citrate differed significantly between groups of normal weight, overweight, and obese groups [19]. Interestingly, 68% of the individuals in this study were either overweight or obese. All other urinary parameters and recurrence rates were not significantly different among the three groups, and there was a trend toward a decreased number of stone events in the higher BMI groups. In what appears to be the first investigation to evaluate recurrence risk and its association with BMI, the authors concluded that that body weight negatively influences single risk factors in calcium oxalate, but obesity is not a predictor for the risk of recurrence in calcium oxalate stone disease [19].

Lee et al. investigated the association between overweight/obesity and stone formation and recurrence and found that in a cohort of overweight/obese patients (mean BMI 27.1 kg/m$^2$), overweight/obesity was associated with increased excretion of uric acid, calcium, and sodium on 24 h urine analysis, but was also positively related to recurrent stone formation. In particular, they found that in first-time stone formers, overweight/obesity was highly associated with an increased incidence of stone recurrence. This relationship was not found in recurrent stone formers [20].

Shavit and colleagues also studied the effect of overweight/obesity on urinary parameters in groups on known stone formers [21]. In a cohort of >1,200 stone-forming patients, they found that overweight and obese stone formers demonstrate alterations on 24-h urinalysis that increase risk of stone formation. Principally increased urinary urate, sodium, and calcium and decreased urinary pH were the main findings in the overweight and obese stone-forming populations.

## Obesity and Urinary Sodium Excretion

Nouvenne et al. found that when idiopathic calcium stone patients were treated with sodium restriction (60 mmol = day) and high fluid intake, a reduction of 100 mmol of urinary sodium was accompanied by a reduction of 64 mg = day in urinary calcium, with 30% of patients achieving normal urine calcium [22].

Along with obesity, metabolic syndrome has been frequently cited as a risk factor for chronic kidney disease and nephrolithiasis and consists of three main conditions: central obesity, hypertension, and disorders of carbohydrate and lipid metabolism [23, 24]. Rendina et al. evaluated the effects of diet on biochemical

parameters in recurrent calcium oxalate stone formers with and without metabolic syndrome, as well as controls. They found that while on unrestricted diets, stone formers with metabolic syndrome exhibited higher 24-h urinary volumes, as well as higher calcium, sodium, oxalate, and urate, compared to both stone formers without metabolic syndrome and controls [18]. Urinary citrate was also lower in the metabolic syndrome stone-forming group when compared to controls. Patients were then counseled on a sodium restriction (2,300 mg/day), 2,000 calorie/day diet. Those that were compliant were observed to have significant decreases in 24-h calcium excretion and oxalate excretion leading the authors to conclude that urinary supersaturation of calcium oxalate is dependent on dietary sodium and reducing sodium intake significantly decreases calcium and oxalate excretion.

In a review of metabolic syndrome and urolithiasis, Wong et al. discuss the etiology of stone disease and the association with obesity and its complex association with modifiable risk factors, in particular, low fluid intake, excess dietary sodium, and animal protein intake [25]. The addition of hypertension, dyslipidemia, and insulin resistance increases the risk of stone disease with prior investigations, finding a nearly twofold increased risk of recurrent stone disease compared to those without metabolic syndrome traits [26]. West et al. also investigated this association in a large cohort of 18,470 patients in the National Health and Nutrition Examination Survey (NHANES III) and identified increased risk of stone disease as the number of metabolic syndrome traits increased [27].

Overweight and obese stone formers have similar metabolic derangements that increase the risk of stone disease, in particular, uric acid and calcium oxalate-based stones. Dietary changes aimed at decreasing urinary calcium, increasing urinary pH and volume, and decreasing urinary oxalate appear to be the principal modifications that can improve urinary parameters on 24-h urinalysis.

## Nutritional Therapy for Obesity and Stone Prevention Dietary Recommendations to Decrease Recurrence

The association between specific diet factors was recently identified that appear to translate to higher stone risk, such as increased animal protein intake, lower potassium intake, lower fluid intake, and lower calcium intake [28]. Dietary risk factors likely act by changing the urinary composition of both inhibitors and pro-calculogenic elements. In support of this idea, it has been reported that urinary supersaturation and the risk of stones are lower among individuals with food intakes closer to the Dietary Approaches to Stop Hypertension (DASH) diet, one that is high in fruits and vegetables, moderate in low-fat dairy products, and low in animal protein represents. There have been recent findings which support the utility of reducing sodium excretion in the urine as a means of decreasing risk of recurrent stone disease [22, 29]. Poor glycemic control has also been demonstrated to correlate with increased incidence of stone disease when compared to prediabetic and normal HbA1c levels [30]. See Table 12.1.

**Table 12.1** Dietary Recommendations for the obese stone former

| Dietary recommendations | Indication | Expected 24-h urine results |
|---|---|---|
| Urine volume to >2 l daily | Low urine volume | Increased urine volume, decrease in calculogenesis |
| Salt intake <2 g daily | Hypercalciuria | Decrease in calcium excretion |
| Protein intake to 0.8–1 g/kg daily | Hyperuricosuria, low urinary pH | Decrease in urate excretion, increase in urinary pH |
| Calcium intake 1,000–1,500 mg daily with meals | Hyperoxaluria | Decrease in oxalate excretion |
| Increase citrus fruit consumption | Hypocitraturia, low urinary pH | Increase citrate excretion |

While obese stone formers have been demonstrated to have an increased risk of stone disease, analysis of whether dietary modifications improve urinary parameters has been lacking until recently. In a retrospective analysis of normal weight, overweight, obese, and super-obese patients, Torcelli et al. [8] evaluated 214 patients, and of those, 86 were obese or super obese. All patients received dietary recommendations that were individually modified and included increasing their oral intake of fluids (at least 2 l per day); decreasing salt in diet to less than 1,500 mg per day; decreasing animal protein intake, with a target of 0.8–1 g per kilogram per day; and increasing fruits rich in citric acid and/or potassium citrate. Patients with hyperoxaluria underwent a detailed inventory of items they may be eating that were high in oxalate and were counseled on calcium intake (1,200 mg per day) with meals. All groups of patients had improvements in urinary parameters on dietary modifications. In patients who were obese, there were significant improvements in all urinary parameters; in particular, urinary citrate level had the greatest improvement, increasing more than four times. Normal levels of 24-h urinary parameters were reached by greater than 50% of patients. Among super-obese patients, there were likewise significant improvements similar to the obese group [8].

Yun and colleagues investigated the effects of sodium restriction on stone disease recurrence and found that urine sodium significantly correlated with BMI, urine volume, pH, calcium, uric acid, oxalate, and citrate excretion. When controlling for BMI, stone formers with increased urinary sodium excretion had significantly higher urine volume, pH, calcium, uric acid, oxalate, citrate, and magnesium [29]. Individuals with decreased urinary sodium excretion were found to have fewer stone events, leading the authors to conclude that urinary sodium is associated with altered metabolite excretion in urine and with an increased risk of recurrent stone formation. Dietary sodium restriction should be considered the first conservative measure against recurrent stone formation [29].

The efficacy of dietary recommendations was also evaluated in patients after their initial stone event by Kocvara and colleagues. Patients were prospectively randomized to two groups, an intervention group in which specific dietary recommendations were made and reevaluated after repeat metabolic evaluation at 6, 18, and 36 months. In the control group, only general dietary recommendations were made, which included moderate animal protein intake, restricted oxalate consumption, increased dietary fiber intake, and decreased sodium and adequate calcium intake.

Evaluation was carried out at 36 months. At 3 years of follow-up, there were significantly fewer recurrent stone events in the intervention group, where specific dietary recommendations were made as compared to the group that only received general dietary recommendations [31].

Specific dietary counseling has been shown to be beneficial in a separate investigation on dietary counseling and urinary stone parameters by Ortiz-Alvarado et al. [32]. The authors treated 137 patients with dietary modifications only to prevent stone recurrence. The patients were counseled to increase hydration to keeping urine volume above 2 l per day, sodium restriction to <2,400 mg per day, protein moderation to 3–4 oz twice per day, and adequate calcium intake (1,000–1,200 mg per day with meals), with an emphasis of timing with meals. Furthermore, citrate-containing juice, such as lemon juice, was advised. The investigators noted a significant improvement in urinary parameters, including decrease in urinary calcium, oxalate, and uric acid as well as increases in urinary citrate and volume with dietary modifications alone. These results further emphasize the importance of nutritional stone prevention as a first-line therapy.

In a recent Cochrane review of investigated dietary interventions aimed at preventing complications of idiopathic hypercalciuria, Escribano et al. found that diets that feature normal levels of calcium, low protein, and low sodium may reduce numbers of stone recurrences and decrease urinary oxalate excretion as well as reduce calcium oxalate supersaturation in idiopathic hypercalciuria with recurrent stone disease [33].

While many urologists support dietary recommendations as first-line therapy in the prevention of stone recurrence rates, due to time constraints, it is often difficult to obtain a full dietary history in all stone-forming patients. Interestingly, Wertheim and colleagues found that in a survey of endourologists regarding dietary counseling and stone disease, the majority urologists provide dietary recommendations for stone-forming patients, but most would like another provider to give recommendations likely due to time constraints [34]. This study points to an obvious issue with dietary counseling in stone-forming patients in that time plays a significant factor in how much education can be provided to patients in any one setting. Certainly utilizing nonphysician dietary specialists (e.g., registered dieticians) are essential in providing patient education and reinforcing dietary recommendations in the prevention of recurrent stone formation.

## Conclusions

Overweight and obese individuals have an increased risk of nephrolithiasis due to alterations in urinary parameters, in particular, decreased urinary pH and citrate and increased sodium, calcium, urate, and oxalate. Dietary modifications to normalize these parameters may reduce recurrence rates and potentially decrease the number of comorbidities frequently associated with obesity, namely, HTN, impaired fasting glucose, and dyslipidemia. Utilizing nonphysician specialists, specifically registered dieticians, to reinforce dietary modifications may assist with patient education and adherence to dietary recommendations.

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# Chronic Kidney Disease: Balancing Nutritional Needs with Nutrition Prevention of Kidney Stones

13

Terrie Holewinski and Kristina L. Penniston

## Introduction

More than 26 million Americans over the age of 20 years have chronic kidney disease (CKD). Kidney disease is the ninth leading cause of death in the United States [1, 2]. Risk factors for CKD include diabetes, high blood pressure, heart and cardiovascular disease, smoking, obesity, and abnormal kidney structure [2]. Family history is also implicated as a risk factor for CKD [3]. CKD is characterized by a gradual loss of kidney function over time. It is diagnosed when estimated glomerular filtration rate (eGFR or GFR), based on blood creatinine, is <60 mL/min/1.73 $m^2$ and/or with evidence of kidney damage longer than 3 months with or without decreased GFR [4]. Such evidence may include persistent albuminuria (defined as >30 mg albumin per gram of urine creatinine), proteinuria, or hematuria after the exclusion of other causes [4, 5]. While diabetes is the leading cause of kidney disease, high blood pressure is the second leading cause of end-stage renal disease (ESRD), the final stage of CKD and also referred to as kidney "failure." In 2011,

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**Table 13.1** Classification stages of chronic kidney disease (CKD)

| Stages of CKD[a] | Description | eGFR[b] (mL/min/1.73 $m^2$) |
|---|---|---|
| 1 | Kidney damage with normal or increased GFR | ≥90 |
| 2 | Kidney damage with mild decreased GFR | 60–89 |
| 3 | Moderate decreased GFR | 30–59 |
| 4 | Severe decreased GFR | 15–29 |
| 5 | Kidney failure | <15 or dialysis |

[a]Chronic kidney disease (CKD) stages 1 and 2; kidney damage estimated by spot albumin-to-creatinine ratio >17 for males or >35 for females in at least two measurements
[b]Estimated glomerular filtration rate (eGFR) from serum creatinine using the Modification of Diet in Renal Disease study equation based on age, sex, race, and calibration for serum creatinine

diabetes or hypertension was listed as the primary cause of seven of every ten new cases of ESRD [2]. African Americans are about 3.5 times more likely to develop ESRD than whites; Hispanic/Latinos are about 1.5 times more likely to develop ESRD than non-Hispanics [6].

In 2002, the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF KDOQI) published treatment guidelines [7] that stratified patients with CKD into five stages according to GFR (Table 13.1). Patients with CKD stages 3–5 are at increased risk of progressing to ESRD or of dying before the development of ESRD compared to patients with less severe CKD [8]. In 2009, the organization Kidney Disease: Improving Global Outcomes (KDIGO) convened a conference, after which an international work group was assembled to review and update the NKF KDOQI guidelines for CKD [4]. As the KDIGO guidelines ultimately differed little from the NKF KDOQI guidelines with respect to nutritional management, they will not be further addressed here.

Early nutrition intervention in patients with CKD is extremely important but complex. While certain dietary influences, including malnutrition, may hasten kidney function decline in susceptible individuals, the decline in kidney function itself reduces patients' nutritional status. The interrelationship between the renal pathology involved in CKD and dietary intake must thus be evaluated together. The primary goal of nutrition management in the early stages of CKD is to delay the progression of renal disease by (a) preventing protein-energy malnutrition, (b) balancing the diet by reducing/moderating protein intake if excessive and/or increasing intake of fruits and vegetables if deficient, (c) minimizing diet-induced uremic toxicity, (d) managing diabetes and promoting good glycemic control with diet, and (e) controlling blood pressure [9, 10]. General guidelines for healthy eating among patients with CKD are described (Fig. 13.1). But as individuals vary with respect to dietary contributors to CKD and to their baseline dietary habits, the above goals are accomplished with appropriately individualized and prioritized nutrition intervention. A registered dietitian nutritionist (RDN), particularly one with expertise in renal disease, evaluates and monitors patients' nutritional statuses throughout

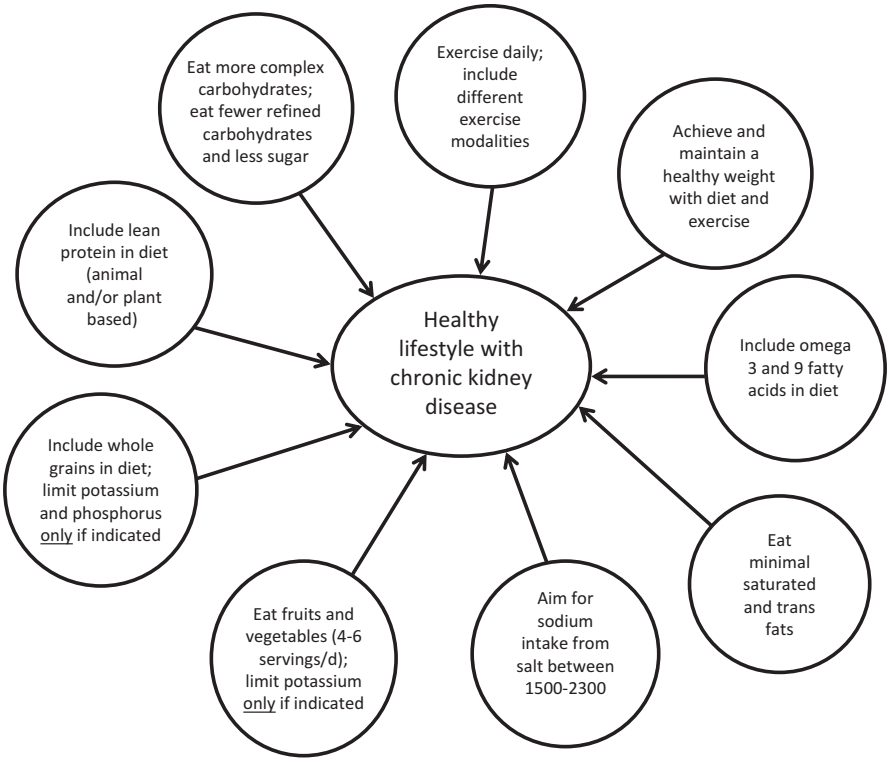


**Fig. 13.1** Healthy nutrition and lifestyle concepts for patients with chronic kidney disease, stages 1–5 (Adapted from the 2015 Dietary Guidelines for Americans)

the duration of care to determine when and which dietary interventions should be instituted [5, 9].

## Malnutrition and CKD

Malnutrition in CKD is common and is defined as inadequate intake of protein and/or energy over prolonged periods of time resulting in loss of fat and/or sarcopenia (loss of muscle stores) [11]. Malnutrition in patients with CKD is associated with increased morbidity and mortality; its etiology is multifactorial [5, 9, 12]. Malnutrition may ultimately lead to loss of vigor, poor rehabilitation and quality of life, and death [12]. Many non-dietary factors contribute to malnutrition in patients with CKD (Fig. 13.2).

While common lore is that patients with any form of CKD should reduce protein intake, studies consistently report inadequate oral intake, especially of protein, as a

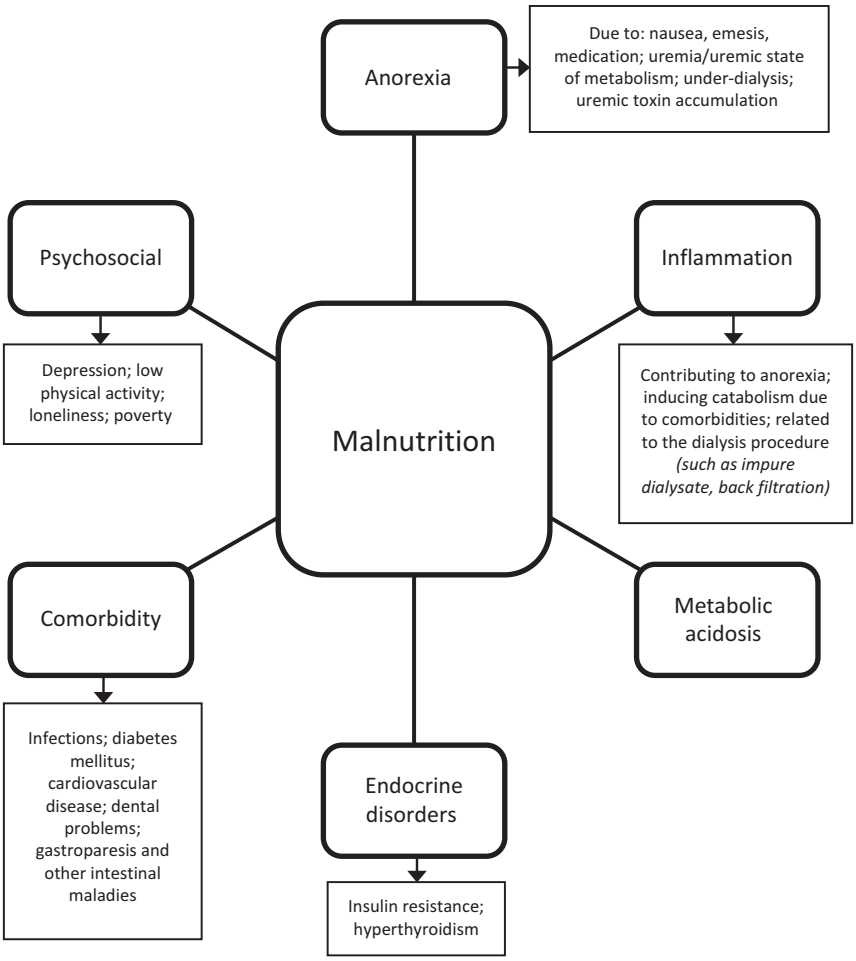


**Fig. 13.2** Factors contributing to malnutrition in patients with chronic kidney disease

major contributing factor to malnutrition, including in patients with only a mild decline in GFR (i.e., <50 mL/min). Studies have further documented that dietary protein intake declines progressively with declining GFR [12, 13]. The reason for malnutrition from inadequate protein intake by patients with declining kidney function is not fully understood, but overzealous dietary restrictions are thought to contribute [4, 9–12]. Although general dietary recommendations for a "renal diet" are to limit protein, sodium, potassium, phosphorus, and fluids, general dietary recommendations should not be applied to individuals. Not all patients with CKD should limit their intake of the above, especially those with preexisting malnutrition and poor oral intake. Dietary intervention should be instituted only after each patient's nutritional status and eating habits have been evaluated and there is a clear and

**Table 13.2** Specific nutrient recommendations for patients with chronic kidney disease

| Nutrition parameter | Stages 1–4 CKD | Stage 5: hemodialysis | Stage 5: peritoneal dialysis | Transplant |
|---|---|---|---|---|
| Protein (g/kg/day) | 0.6–0.75 with ≥50% kcals from HBV food sources[a] | 1.2 with ≥50 % kcals from HBV food sources[a] | 1.2–1.3 with ≥50 % kcals from HBV food sources[a] | Initially, 1.3–1.5 |
| | | | | Maintenance, 1.0 |
| Energy (kcal/kg/day) | If <60 years, 35 | If <60 years, 35 | If <60 years, 35 | 25–30 for maintenance; more if malnourished or underweight |
| | If ≥60 years, 30–35 | If ≥60 years, 30–35 | If ≥60 years, 30–35 (include calories from dialysate) | |
| Sodium (mg/day) | 2,000 | 2,000 | 2,000 | Unrestricted; monitor medication effect |
| Potassium (mg/day) | Unrestricted unless serum potassium is high | 2,000–3,000 | 3,000–4,000 | Unrestricted unless indicated by presence of hyperkalemia; monitor medication effects |
| Phosphorus (mg/day) | Need for restriction, if any, is determined by serum levels | 800–1,000 | 800–1,000 | Unrestricted unless indicated by presence of hyperphosphatemia |
| Calcium (mg/day) | 1,200 | ≤2,000 from diet and medications | ≤2,000 from diet and medications | 1,200 |
| Fluid | Unrestricted if urine output is normal | 1,000 mL/day + urine output | Monitored: 1,500–2,000 mL/day | Unrestricted unless indicated |

[a]*HBV* high biological value

demonstrated need for change [5]. This is the role of medical nutrition therapy as developed, prescribed, and implemented by a RDN. Specific dietary parameters for each stage of kidney disease are shown (Table 13.2).

## General Dietary Guidelines for Patients with CKD

Prior to the initiation of any diet restrictions or other modifications, patients with early CKD may not require specific nutrition therapy but, rather, may follow general healthy dietary guidelines, such as those promoted by the NKF KDOQI (Table 13.2) or the 2015 Dietary Guidelines for Americans (Appendix X). The 2010 version of these included, for the first time, recommendations targeting risk reduction for cardiovascular disease for the general population [14]. The guidelines included recommendations to decrease overweight and obesity and to include fruits, vegetables, whole grains, low-fat dairy, lean protein foods, and vegetable oils while limiting saturated fatty acids, trans-fatty acids, cholesterol, excess sugar, sodium, and refined grains. After the release of the 2015 guidelines [15], which were similar to those of 2010, many questioned whether they could or should be applied to patients with CKD [16]. The Dietary Approaches to Stop Hypertension (DASH) diet (Appendix X), a set of guidelines promoting a relatively rich intake of fruits, vegetables, calcium, and a lower sodium intake, has been proposed as a general diet capable of reducing progression of CKD [17, 18]. With the caveat that patients with CKD should be monitored for the presence of hyperkalemia and hyperphosphatemia, especially as the above dietary guidelines share a recommendation for a relatively high potassium intake (especially the DASH diet), there is general consensus that these guidelines are suitable for patients with CKD and that individual modifications should be made as needed, especially if/when patients progress to later stages.

## Individualized Diet Prescription for Patients with CKD

Individualized medical nutrition therapy is designed and implemented by a RD after evaluating a patient's medical history, renal function, and nutritional status. The following are key aspects of consideration in patients with CKD.

*Protein* The optimal dietary protein intake for patients with CKD stage 1 through 4 is controversial. Prior research suggested that strict control of dietary protein and phosphorus could delay the onset of chronic kidney disease. This clinical dogma has been questioned; however, the long-term effects of a low-protein diet on the progression of CKD are unknown [4, 5, 12]. In an extended follow-up of patients enrolled in the Modification of Diet in Renal Disease (MDRD) study, investigators evaluated the effects of protein restriction on kidney failure and mortality and found questionable efficacy of a 2–3 year dietary protein restriction with respect to the progression of nondiabetic kidney disease [19]. Because of this study and others with similar findings, and in light of higher rates of malnutrition and specifically

protein-calorie malnutrition in patients with CKD, many clinicians have called for a relaxation of dietary protein restriction in early stages of CKD. Ultimately, the results of individual patient assessment and evaluation should guide any nutritional intervention or restriction in patients with CKD. Patients' protein and total energy needs should be individualized per their GFR function (Table 13.2).

*Energy and fats* Calorie requirements for stable patients with CKD stages 1 through 4 who are consuming 0.8 g/kg/day of protein are comparable to those of normal healthy persons [4, 7]. Inadequate dietary intake of carbohydrates and fats leads to protein catabolism for energy and excessive accumulation of nitrogenous wastes in the bloodstream. When energy intake is optimal, nitrogen balance becomes more positive. This is beneficial because an adequate caloric intake allows dietary protein to be used for protein synthesis and maintenance of muscle tissue rather than for energy. Therefore, patients with CKD who are on lower-protein diets must consume more calories, up to 30–35 kcal/kg/day [20, 21]. Because many patients with advanced CKD may have inadequate protein intakes, which in some cases is compounded by an inadequate intake during earlier stages of CKD, they are prone to malnutrition by the time dialysis is started. When on dialysis, daily energy intakes of 35 kcal/kg, based on ideal body weight (Appendix X) for individuals younger than 60 years of age, are recommended. For those 60 years and older, 30–35 kcal/kg daily is recommended [22]. Exceptions include patients who are obese (>120 % of ideal body weight), who may be recommended fewer calories per kg of body weight in order to lose or maintain weight, and malnourished persons, who require more calories for repletion [11–13].

*Sodium* Sodium is an extracellular electrolyte essential for regulating fluid balance. Healthy kidneys maintain sodium balance by adjusting urinary sodium excretion in response to dietary sodium intake. Filtration of sodium decreases in CKD as does urine volume. Sodium needs should be estimated based on a patient's blood pressure and fluid balance. Dietary sodium intake is frequently restricted to 2,000–4,000 mg per day in early stages of CKD [5, 9]. While higher than the estimated adequate intake (Appendix X), this represents a "restriction" for most individuals because typical intakes in the United States are much higher. For advanced stages of CKD, it is ideal to restrict sodium to 2,000 mg per day or less in an effort to aid in the control of hypertension and to avoid excessive thirst and fluid consumption in patients with oliguria or anuria [4, 5, 22].

*Potassium* Potassium, an intracellular electrolyte, plays a key role in muscle contractions. The ability of the renal tubules to excrete potassium decreases as the GFR decreases. With a decrease in GFR, hyperkalemia may develop, which is related to irregular heartbeat and even death. In this event, potassium restriction of 2,000–3,000 mg/day is necessary to maintain serum levels in the normal range [4, 5]. In patients on hemodialysis, potassium accumulates in the body between treatments unless the patient has adequate gastrointestinal or urinary losses. Patients on hemodialysis are thus often placed on dietary potassium restrictions to avoid hyperkale-

mia. Hyperkalemia is exacerbated from eating potassium-dense foods, using potassium supplements, using hypertensive medications (e.g., angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, aldosterone receptor blockers), hypoinsulinism, or acidosis. Unlike sodium, potassium cannot be tasted in foods and is seldom listed on food nutrition labels, presenting a unique education challenge [23, 24].

*Phosphorus* CKD reduces the production and conversion of the prohormone version of vitamin D to active calcitriol $1,25(OH_2)D_3$ that in normal kidney function controls the absorption of phosphorus and calcium from the gastrointestinal tract. The kidneys filter approximately 7 g of phosphorus daily; 80–90 % is reabsorbed by the tubules, and the remainder is excreted in urine. In the early stages of CKD, hyperphosphatemia is prevented by an adaptive decrease in renal tubular phosphate resorption. Not until GFR falls to <20 mL/min does hyperphosphatemia usually become clinically evident. At this point, the diet should be limited to 800–1,000 mg/day [4, 5]. As with sodium, this amount actually exceeds the Recommended Dietary Allowance for phosphorus (Appendix X), which is 700 mg/day for adults, but represents a "restriction" as adults in the United States typically consume much more phosphorus. As CKD advances, diet alone often fails to control serum phosphorus; therefore, other measures, such as phosphate-binding medications or over-the-counter agents (e.g., calcium carbonate), are needed. Care should be taken to prevent phosphorus depletion because low serum phosphorus can aggravate other types of bone disease [24]. Phosphorus is present in highest concentration in foods of animal origin, including dairy. However, phosphorus additives also add significantly to dietary phosphate burden and are used to enhance the water-holding capacity of foods, increase pH to slow discoloration of meats, reduce cooking losses, retard oxidative rancidity, aid in microbial protection, and optimize the textural properties of foods. Manufacturers are not required to list the phosphorus content on food labels nor the phosphorus load of additives. Thus, the true phosphorus burden of the diet is not reflected in databases used to analyze the nutrient content of foods [25].

*Calcium* With a diet limited for protein and phosphorus, dietary calcium intake is also usually low. Yet a calcium intake of 1,200–1,500 mg/day is required for patients with a GFR of 10–40 mL/min/1.73m$^2$. Patients with advanced CKD with a GFR <10 mL/min/1.73$^2$ may need up to 2,000 mg/day [4, 5, 26]. The NKF KDOQI guidelines recommend that total elemental calcium from diet and binders not exceed 2,000 mg/day as patients advance to stages 4 and 5 [4]. Patients receiving active vitamin D analogues may require less calcium, in the range of 800–1,000 mg/day, in order to avoid vascular calcification, which is a growing concern in CKD [27].

*Fluids* Fluid is generally encouraged [28] and should not be restricted until or unless patients reach ESRD and then only in those whose urine output is insufficient (as in oliguria) or absent (as in anuria) [4, 5]. Fluid intake must match urine output (stages 1–4) or fluid volume removed during dialysis treatment (stage 5). Monitoring body weight will help determine when a fluid restriction is needed.

## Managing Patients with CKD and Kidney Stones

The concurrence of kidney stones and CKD is not uncommon. Nephrolithiasis, by many accounts, is a risk factor for CKD [29, 30]. Results from a recent study in Iceland, where the prevalence of kidney stones is relatively high, found that patients with recurrent kidney stones had a significantly lower level of kidney function and a higher prevalence of CKD age- and gender-matched controls. Approximately 9 % of all patients with kidney stones and 6 % of those who formed calcium stones had CKD, which is six- to sevenfold higher than in the control group [31]. Managing the nutritional needs of CKD while also aiming to prevent kidney stone formation and growth may be complex but need not be contradictory. As with nutrition therapy for other conditions, dietary recommendations for patients with both CKD and kidney stones should be tailored to each patient's unique risk factors for CKD progression and stone formation and growth as well as to his/her lifestyle, culture, eating habits, and food preferences. Dietary recommendations should also take into account barriers to adherence [32].

Depending on the stone risk factors to be addressed, potential areas of conflict with respect to stone prevention are most likely to arise in patients with CKD who require (1) dietary potassium restriction due to hyperkalemia, (2) fluid restriction due to oliguria or anuria, or (3) daily calcium intake to be within a narrow range, 800–1,000 mg/day, due to the use of active vitamin D analogues. These are addressed below. Other aspects of the nutritional management of patients with both CKD and a risk of kidney stones are fairly easily integrated.

*Potassium for stone prevention* In most stone formers, diets rich in potassium are recommended because potassium is frequently complexed in the diet with organic acids which serve as bicarbonate precursors and thereby reduce renal citrate resorption. This is especially true in calcium stone formers whose urinary citrate excretion may be suboptimal or low. More citrate in the urine is beneficial as citrate binds with calcium and forms a soluble complex. Patients who form uric acid cystine stones are also recommended to eat a diet rich in potassium as the bicarbonate potential of the organic acids complexed with potassium may help to raise urine pH, making both uric acid and cystine less likely to precipitate and form stones. Finally, the use of pharmacologic doses of potassium citrate, an alkalinizing agent, is common among people who form stones of all types – calcium, uric acid, and cystine – as it both enhances urinary citrate excretion and urine pH. In patients with CKD and hyperkalemia (which may not occur until later CKD stages), the use of pharmacologic potassium salts and the dietary contribution of potassium may require limitation. In the patient who is also practicing stone prevention, other modifiable risk factors would then need to be prioritized.

*Fluids for stone prevention* The importance of a high fluid intake and copious urine output in stone prevention cannot be understated. Unless the patient with CKD requires a fluid restriction, which is not common (especially in earlier CKD stages), there is no discrepancy between stone prevention and CKD. If, however, fluids are

to be restricted in the patient with both CKD and stones, greater attention to normalizing other risk factors would be required.

*Calcium for stone prevention* Calcium intake in the area of the Recommend Dietary Allowance for adults (1,000–1,200 mg/day) is appropriate for people who form stones. As with other minerals, the "window" for appropriate/adequate intake and the tolerable upper limit is fairly narrow. The tolerable upper intake level for calcium is 2,000–2,500 mg/day (Appendix X), depending on gender and age. Inadequate calcium intake by anyone compromises bone status. The idea that people who form calcium stones should limit calcium intake to below 1,000 mg/day not only places them at risk for premature bone loss but was proven ineffective nearly a quarter of a century ago for prevention of symptomatic kidney stone events [32]. In fact, an inadequate calcium intake is associated with a higher risk for calcium oxalate stones, presumably due to less calcium to control the absorption of oxalate from the gastrointestinal tract and thereby reduce its excretion in urine. On the other hand, too much calcium, as is not uncommon among those who take higher-dose calcium supplements, is a risk factor for hypercalciuria [33]. Patients with CKD who are taking active vitamin D analogues are at risk for vascular calcium deposits and, as such, may be required to maintain lower their calcium intakes. In this setting, the patient's ability to use calcium as an oxalate binder may be reduced. Other strategies to reduce the risk of calcium oxalate stone formation or growth should then be pursued.

## Conclusion

In the nutritional management of patients with CKD, implementing and adhering to individualized dietary recommendations can be a daily challenge given that food intake is not restricted to a once- or even twice-a-day event. Choices about foods within a single day abound – whether to eat? what to eat? when to eat? how much to eat? As kidney function may change over time, dietary modifications are necessary, and this further complicates nutritional management. Similarly, stone risk factors may change over time, requiring modification and/or re-prioritization of dietary goals. While there are few of any inherent contradictions between general dietary recommendations for maintaining kidney function and those for reducing risk for stone formation and growth, integration of all recommendations may be challenging on an individual level. This may be especially true as/if patients enter later stages of CKD or in patients whose stone disease is particularly aggressive or complex. In either case, patients with both kidney stones and CKD would benefit from attention by a RDN to ensure appropriate integration of nutrition therapy for both conditions.

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# Diabetes and Metabolic Syndrome: Improved Control May Reduce Stone Risk

14

Kathleen M. Zatavekas and Kristina L. Penniston

## Introduction

Diabetes mellitus and obesity are associated with kidney stones. Diet and lifestyle play a role in diabetes and obesity, both of which are sequelae of or associated with metabolic syndrome. Diet and lifestyle also play a role in the epidemiology of some kidney stones. Weight gain, increased body mass index (BMI, kg in body weight divided by height in meters squared), and diabetes were found to be associated with the incidence of stone disease in the Nurses' Health Studies I and II and in the Health Professionals Follow-up Study [1]. Since these studies, there has been data to confirm increased stone risk with the metabolic syndrome [2].

## What Is the Metabolic Syndrome?

Metabolic syndrome is a constellation of concurrent factors that raise the risk for cardiovascular disease and other health problems. It is "metabolic" in that it involves aberrations in biochemical processes involved in normal physiological homeostasis. It is a "syndrome" in that it is not singularly typified by any one feature. There are many definitions of the metabolic syndrome, including by groups such as the National Cholesterol

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Education Program Third Adult Treatment Panel, the World Health Association, the American Heart Association, and the European Group for the Study of Insulin Resistance (Table 14.1). Definitions by these groups agree that the presence of hypertension, dyslipidemia, and insulin resistance is critical for the diagnosis of metabolic syndrome. The International Diabetes Federation (IDF) has acknowledged a need for a universal diagnostic means to define the metabolic syndrome. The IDF definition differs from other definitions by including waist circumference with ethnicity threshold values as a means to identify central obesity plus two or more of the aforementioned core components. Of note, according to this definition, waist circumference need not be measured to identify the presence of central obesity if BMI is >30 [3, 4]. Some organizations are calling for the renaming of metabolic syndrome to insulin resistance syndrome [5].

## Urolithiasis and Diabetes Mellitus

Diabetes mellitus is one of the major manifestations of the metabolic syndrome. Diabetes mellitus type 2 (also known as type 2 diabetes) is a chronic metabolic disorder that develops over time and is characterized by hyperglycemia, insulin resistance, and relative insulin insufficiency [1]. The link between kidney stone disease and diabetes is complex and is associated with both uric acid stones and calcium oxalate stones [6]. Uric acid stones are more commonly seen in patients with diabetes. The rate of uric acid stones in patients with diabetes is around 30–40% compared to a rate of 5–10% in the general population [7]. Risk factors for uric stone formation are hyperuricosuria, acidic urine, and low urine volume. Risk factors for calcium oxalate stone formation are low urine volume, high urinary excretion of calcium and/or oxalate, and low urinary excretion of magnesium and/or citrate. These conditions may occur as a result of idiopathic, genetic, and/or lifestyle causes. In the presence of insulin resistance and obesity – common sequelae in patients with diabetes – there is increased uric acid excretion [8]. Also, when ammoniagenesis is impaired, which is common in diabetes, urinary pH is reduced, favoring the formation of uric acid stones. Notably, obesity – with or without diabetes – is linked to increased renal excretion of calcium and uric acid as well as urine acidity, all of which increase the risk of both uric acid and calcium oxalate stone formation [7, 9].

## Nutritional Management of Diabetes

Medical nutrition therapy (MNT) is recommended for people with type 1 and type 2 diabetes as part of their overall medical treatment plan [10]. Individualized MNT is provided by a registered dietitian nutritionist (RDN) who is knowledgeable in diabetes. For adults with diabetes, the aim of MNT is to emphasize eating a variety of nutrient-dense foods, in appropriate serving sizes, so that patients may realize and sustain favorable body weight goals, achieve good glycemic control, meet lipid and blood pressure goals, and postpone or avert diabetes and its complications. These goals require individualization as patients are quite heterogeneous with respect to their expression of the above.

**Table 14.1** Required and additional non-required criteria for diagnosing metabolic syndrome from national and international organizations

| | IDF[a] | AHA/NHLBI[b] | AACE[a] | NCEP[b] ATPIII | EGIR[a] | WHO[a] |
|---|---|---|---|---|---|---|
| Required criteria | | | | | | |
| Insulin resistance (or fasting insulin) in top 25% or type 2 diabetes mellitus | | | | | x | x |
| Glucose >100 mg/dL or 2 h glucose ≥140 mg/dL | | | | | | x |
| High risk for insulin resistance or BMI >25 or waist ≥102 cm (men) or ≥88 cm (women) | | | x | | | |
| Ethnic-based waist, European, ≥94 cm (men) or ≥80 cm (women); Asian, ≥90 cm (men) or ≥80 cm (women) | x | | | | | |
| Non-required criteria, at least 2 or 3: | | | | | | |
| Glucose, ≥100 mg/dL[c] | x | x | x | x | x | |
| 2 h glucose, ≥140 mg/dL | | | x | | | |
| HDL, <40 mg/dL | | | | | x | |
| HDL, ≤35 mg/dL (men) or ≤40 mg/dL (women) | | | | | | x |
| HDL, <40 mg/dL (men) or <50 mg/dL (women) | x | x | x | x | | |
| Triglycerides, ≥150 mg/dL | x | x | x | x | x | x |
| Obesity, waist ≥102 cm (men or ≥88 cm (women) | | x | | x | | |
| Obesity, waist/hip ratio >0.9 (men) or >0.85 (women) or BMI ≥30 | | | | | | x |
| Obesity, waist/hip ratio ≥94 cm (men) or ≥80 cm (women) or BMI ≥30 | | | | | x | |
| Hypertension, ≥130/85 mmHg | x | x | x | x | | |
| Hypertension, ≥140/90 mmHg | | | | | x | x |
| Microalbuminuria, ≤20 mcg/min or albumin/creatinine ratio ≥30 μg/mg | | | | | | x |

Criteria shown are from the recommendations of the International Diabetes Federation (2006); American Heart Association and National Heart, Lung, Blood Institute (2005); American Association of Clinical Endocrinology (2003); National Cholesterol Education Program Adult Treatment Panel III (2001); European Group for the study of Insulin Resistance (1999); and World Health Organization (1999)

[a]Requires 2 of the non-required criteria

[b]Requires 3 of the non-required criteria

[c]In 2003, the American Diabetes Association changed the criteria for impaired fasting glucose tolerance from 110 to 100 mg/dL. Some organizations set the criteria for elevated fasting glucose at 110 mg/dL. But because these were developed prior to the change, the table reflects only the more stringent definition

*Energy balance and distribution of macronutrients* For adults with type 2 diabetes who are overweight or obese, reducing energy intake while retaining a healthy and nutrient-adequate eating pattern is recommended. Even a moderate amount of weight loss may improve glycemia, blood pressure, and blood lipids, especially among those in the early stage of the diabetic disease process. To achieve a reasonable amount of weight loss, MNT, physical activity, and/or behavior change is encouraged [11]. As evidence suggests there is not a single dietary plan that is appropriate for all people with diabetes, the distribution of dietary macronutrients as well as micronutrients should be based on an individualized assessment of food preferences, eating patterns, and metabolic goals [12]. The Dietary Reference Intakes (DRIs) [13] – which include recommended dietary allowances (RDAs), adequate intakes (AIs), estimated safe and adequate daily dietary intakes (ESADDIs), and tolerable upper intake levels (ULs) (see Appendix 5 for a description and table of DRIs) – provide a general framework from which to individualize each patient's nutritional goals. According to the DRIs, the acceptable macronutrient distribution range for adults is 45–65% of total energy needs from carbohydrates, 10–35% from protein, and 20–35% from fat. Note that the wide ranges for each of these macronutrients include those that are recommended for patients with diabetes, underscoring the need for individualized dietary recommendations.

*Carbohydrate/dietary fiber* Both quantity and type of carbohydrate influence blood glucose levels. The total amount of carbohydrate eaten is the primary predictor of glycemic response. Monitoring carbohydrate amounts is thus a useful strategy for improving postprandial glucose control. Carbohydrates from fruits, whole grains, legumes, vegetables, and dairy are recommended. Other sources of carbohydrates, such as those with added sodium, sugar, and fats, are not recommended or, if consumed, recommended in lower amounts [10, 12]. Common lore suggests that patients with diabetes should limit their intake of carbohydrates. Indeed, many patients erroneously believe they should eliminate fruits and/or starchy vegetables from their diets. But without adequate carbohydrate intake, protein is used for energy as opposed to being used to synthesize new proteins critical for maintaining homeostasis and immune function. Thus, complete avoidance of these foods may compromise the nutritional quality of the diet and overall health. Instead of eliminating, strategies for good glucose control include the distribution of carbohydrates throughout the day, consuming carbohydrate-rich foods with meals, and avoiding concentrated carbohydrate doses. A variety of methods for diabetes meal planning are presented to patients by RDNs or diabetes educators and include the plate method, carbohydrate counting, and glycemic index [13]. Fiber, which can reduce the impact of food-derived glucose on blood glucose, is recommended in the same amounts as for the general population. Fiber is nondigestible and therefore provides little to no energy. Patients with diabetes should aim for about 25 (adult women) and 38 (adult men) grams of fiber daily. This amounts to approximately 14 g of fiber/1,000 kcals/day [14].

*Protein* The amount of protein intake required to optimize glycemic control among those with diabetes is controversial, but all experts agree that protein intake goals should be individualized within the DRI ranges [14]. People with diabetes, including those with diabetic kidney disease, should not reduce their dietary protein intake unless it is specifically advised; doing so could alter glycemic control and negatively impact kidney function, cardiovascular risk, and bone status [15]. Meats of all kinds, fish, poultry, cheeses, and lower-fat dairy foods, eggs, and some plant-based foods are all good sources of high biological value protein and should be encouraged in moderation.

*Fat* Fats are grouped into unsaturated (monounsaturated and polyunsaturated) and saturated fats. Trans fats, a special type of fat created during certain food processing techniques, have negative health effects similar to saturated fat. The amount of dietary saturated fat, cholesterol, and trans fats recommended for people with diabetes is the same as that for the general population [10]. The 2015 Dietary Guidelines for Americans recommendations include limiting saturated fats to <10% of calories and limiting trans fats as much as possible [16]. As evidence is lacking for an "ideal" amount of total fat intake for those with diabetes, the goal should be individualized, again within the range suggested in the DRIs. Because fat provides more than twice the energy per gram than either carbohydrates or protein, patients with diabetes who need to lose or maintain weight are encouraged to moderate and/or lower their fat intake [10]. Foods richer in unsaturated fats are overall more encouraged than foods richer in saturated or trans fats.

## Integrating Dietary Recommendations for Diabetes and Kidney Stone Prevention

Patients with diabetes are typically advised dietary recommendations that reduce the risk of hyperglycemia as well as those that reduce their risk for cardiovascular disease. RDNs can be instrumental in helping patients with both diabetes and kidney stones integrate dietary recommendations for both conditions. Below, the most common dietary aspects of kidney stone prevention are addressed with respect to whether or not they conflict with dietary recommendations to manage diabetes.

*Fluid intake No conflict with dietary recommendations for managing diabetes.* Patients with diabetes and a risk for urinary stones should drink as much as possible from a variety of beverages to induce the output of at least 2 L of urine. Concentrated fruit juices and sugary beverages should be limited, however, as these may result in a relatively quick spike in blood glucose.

*Calcium intake No conflict with dietary recommendations for managing diabetes.* Patients with diabetes and a risk for urinary stones should consume calcium at the levels recommended in the DRIs, which are specific for age and gender [14]. Food and beverage sources are preferred over calcium supplements as the risk for exces-

sive calcium intake is higher in those who supplement. Patients at particular risk for calcium oxalate stones, with or without evidence of hyperoxaluria, may be recommended to distribute their calcium intake at meals to maintain suitable control of dietary oxalate absorption as calcium binds oxalate in the gastrointestinal tract and reduces its absorption. An ideal scenario might be to include about 300 mg of calcium with each of three meals daily, providing 900 mg of calcium. Some yogurts provide around this amount of calcium per serving. Calcium-fortified nondairy milks typically provide this amount in six fluid ounces vs. dairy milk, which requires 8 oz to obtain 300 mg of calcium. Kefir and some other calcium-fortified products may also provide around 300 mg of calcium per serving. The additional 300–600 mg of calcium required per the DRIs, depending on age and gender, is easily obtained without supplementation from other food and beverage sources in a balanced diet.

*Low sodium No conflict with dietary recommendations for managing diabetes.* Patients at risk for calcium-containing stones are usually advised to limit sodium chloride (salt) intake because of its ability to raise urinary calcium excretion. Patients with diabetes are usually similarly advised due to their higher risk of cardiovascular disease. Patients with hypertension – a common additional feature of metabolic syndrome – are especially advised a lower salt intake. Thus, a lower salt intake is, with little difficulty, integrated in the dietary plan for diabetes and for reducing the risk of calcium-containing kidney stones whose primary etiology is hypercalciuria. Note that while reducing sodium intake may not be a top priority for the stone former without hypercalciuria or, for example, whose risk is not for calcium stones, it is still appropriate for the patient with diabetes to lower his/her sodium intake.

*Fruits and vegetables No conflict with dietary recommendations for managing diabetes.* However, two common challenges exist. A higher intake of fruits and vegetables is one way to enhance urinary citrate excretion, especially when including those with a higher concentration of bicarbonate precursors (organic acids) [17]. Patients with diabetes are sometimes frustrated with recommendations to increase their fruit and vegetable intake for stone prevention as fruits and starchy vegetables are ample sources of carbohydrates. Some patients perceive a conflict. Even though it is a misconception that fruit intake should be eliminated by people with diabetes, data show that some patients believe this [18]. In fact, fruits contain many compounds that are beneficial for health, including promoting a higher urinary citrate excretion. As discussed earlier, people with diabetes may safely eat fruits as long as they (a) eat them most frequently in their whole vs. juiced forms and (b) consume them with meals that also provide protein, fat, and fiber, all of which may blunt the effect of the carbohydrates from fruit on glycemic response.

The other challenge is when patients at risk for calcium oxalate stones, with or without hyperoxaluria, are commonly told – usually in the form of general recommendations – to reduce or eliminate high-oxalate foods, many of which are fruits and vegetables. All patients with diabetes should include vegetables and fruits in their meal planning strategies to meet fruit/vegetable intake recommendations. As

fruits and vegetables appear variably on lists of purportedly high-oxalate foods, confusion and frustration about which fruits and vegetables can be eaten by patients with both diabetes and a risk for calcium oxalate stones are common. In truth, most vegetables and other plant foods contain some oxalate; eliminating oxalate completely from the diet is not only impossible but inadvisable for health reasons. It is also unnecessary. When patients consume adequate calcium (as described earlier), they can usually safely consume most all fruits or vegetables regardless of whether they contain any oxalate. Individualized nutrition assessment and intervention in the form of MNT is usually necessary to identify those patients who may benefit from a more restricted list of acceptable fruits and vegetables, but even this usually requires only moderated or lower intakes of the highest-oxalate fruits and vegetables (Appendix 6).

*Protein intake No conflict with dietary recommendations for managing diabetes.* But challenges may exist. Patients with diabetes are frequently advised by diabetes educators to consume dietary protein sources along with carbohydrate-rich foods as a means to blunt the effect on blood glucose [15] and to use protein-rich foods vs. carbohydrate-rich foods as snacks between meals. Examples of such foods are largely animal derived (e.g., eggs, lean meats, cheeses, and other dairy). Conversely, patients at risk for uric acid stones (when higher uric acid production is a target of nutrition therapy) or calcium-containing stones (when hypercalciuria is a target of nutrition therapy) may be advised to moderate or reduce their intake of "flesh foods" (e.g., meats, poultry, fish, game, fowl) due to their potential as uric acid precursors or as contributors to higher dietary acid load and concomitant calciuria. While the consumption of these protein-rich foods by patients with uric acid or calcium stone risk might seem contraindicated, it need not be. It is not usually necessary to become totally vegetarian to reduce urinary uric acid excretion and the risk for uric acid stones. Uric acid synthesis and metabolism is complex and is not always significantly affected by diet. In fact, in one recent study, individuals who consumed a vegan diet had higher serum uric acid concentrations than meat eaters and non-vegan vegetarians [19] (see Appendix 7 for definition of diets). Another study confirmed that a balanced omnivorous diet could significantly reduce urinary uric acid excretion in those who changed from a Western-type diet [20]. Moreover, the intake of foods with a higher potential renal acid load can be offset by an ample intake of foods with an alkaline load [21]. Thus there is room for a moderate intake, individually assessed and implemented, of foods from animal tissue by patients with both diabetes and a risk for uric acid and/or calcium stones. This allows for their use as lower-carbohydrate foods in diabetes meal planning.

What about high-protein nuts and seeds? Many patients with diabetes are encouraged to use these low-carbohydrate foods as snacks for their ability to help in maintaining appropriate blood glucose control while also providing heart-healthy nutritional benefits [22]. On the other hand, nuts and seeds are commonly limited in calcium oxalate stone prevention due to their relatively high oxalate content. But depending on the severity of the patient's hyperoxaluria (if present) and/or on the etiology of his/her hyperoxaluria, a dietary oxalate restriction that allows the use of

nuts or seeds in diabetes meal planning could be devised. Especially when consumed with a simultaneous source of calcium, nuts and seeds may be enjoyed in moderation without perturbing urinary oxalate excretion [23]. Moreover, some patients who form calcium oxalate stones have other reasons for their stone formation (e.g., low urine citrate, high urine calcium, low urine volume) and do not benefit from attention to or restriction of their dietary oxalate intake. Attention in this instance to the primary risk factors is warranted. A referral to or consultation with a RDN could help in defining the protein needs of patients with both diabetes and a need for stone prevention (see referral form in Appendix 1).

*Fat intake No conflict with dietary recommendations for managing diabetes.* As noted earlier, patients with diabetes are typically advised to consume a low-fat diet. This has no conflict with general stone prevention recommendations and may actually complement dietary recommendations, especially for patients with malabsorption and/or a tendency for higher urinary oxalate excretion. When excessive dietary fat is consumed, it binds with calcium in the gastrointestinal tract, reducing the availability of calcium to bind dietary oxalate. Thus, a low-fat intake may be useful for stone prevention, especially in those prone to higher urinary oxalate excretion. A lower-fat intake is also useful for anyone working to reduce stone recurrence risk by losing weight. As fat provides more than twice the energy of carbohydrates and proteins (9 vs. 4 kcals per gram), its restriction can be a useful and efficient tool abetting weight loss.

## Summary

Dietary regimens to manage diabetes and prevent future kidney stone formation and/or growth are not contradictory, but their integration may be challenging. This presents an ideal opportunity to engage an RDN to individualize and integrate dietary recommendations that address both disorders and to suggest strategies for implementation. In some cases, a re-prioritization of dietary recommendations that reduce stone risk within existing diabetes meal planning recommendations may be all that is needed. In other cases, additional recommendations to those used in diabetes meal planning may be required. Patients should be advised that there is no inherent contradiction in managing diabetes while also preventing kidney stones and provided education and resources needed to implement appropriate dietary changes. Indeed, emerging evidence [24, 25] suggests that poor glycemic control may be an independent risk factor for kidney stones. As diabetes incidence increases and coalesces with urolithiasis, future nutritional studies that provide data to better understand how to reduce patients' risk factors for diabetes complications and stone recurrence are warranted.

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# 15 Malabsorptive Disorders and Inflammatory Bowel Disease: Assessing and Improving Nutritional Stone Risk

Joshua M. Garcia, Aaron Brafman, and Benjamin K. Canales

## Introduction

The relationship between calcium oxalate kidney stone formation and inflammatory bowel disease (IBD) was first noted in two large retrospective case series from the 1960s. In over 1,400 patients with inflammatory bowel disease, 92 of 1,468 patients (6%) were identified to have developed renal stones, an occurrence that appeared as frequent as other systemic complications of this disease process [1, 2]. The mechanisms behind this high stone incidence were confirmed in the 1970s to be a complication of fat malabsorption and chronic diarrhea, which resulted in enteric hyperoxaluria, decreased urine citrate concentration and pH, and decreased urine volumes [3, 4]. Since those early descriptions, other malabsorptive intestinal disease states have also been added to the IBD/stone- associated list, including jejunoileal bypass (historical) and Roux-en-Y gastric bypass for obesity, chronic mesenteric ischemia, and small bowel ostomies [5, 6]. In general, patients with ileocolonic disease (9–17%) tend to be more commonly affected than those with ileal (6–8%) or colonic disease (3–5%) alone, and stone composition varies between calcium oxalate (malabsorptive diseases, ileocolonic Crohn's disease) and uric acid (copious diarrhea, small bowel ostomies) depending on the disease state and amount of volume loss/diarrhea. This chapter will highlight the urinary abnormalities seen in modern bariatric surgical patients and in patients with the two most common forms of IBD (Crohn's, ulcerative colitis) with a focus on the nutritional aspects that can be improved in these stone-forming populations.

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## Roux-en-Y Gastric Bypass (RYGB) Surgery

### Background

Obesity has become an epidemic in the United States, with more than one third of Americans meeting the definition of body mass index [BMI] >30 kg/m$^2$ [7]. With that, bariatric surgery has become increasingly utilized to facilitate long-term weight loss. While bariatric surgery does have significant health benefits, including resolution of diabetes, hypertension, dyslipidemia, and obstructive sleep apnea, one negative sequela after bariatric intervention includes the development of nephrolithiasis. The pathophysiology of stone development is largely dependent of the type of bariatric procedure.

The most commonly performed bariatric operation is the Roux-en-Y gastric bypass (RYGB). This procedure involves stapling the lesser curvature of the stomach into a 20–30 mL pouch, transecting the jejunum 60–70 cm distal to the ligament of Treitz (duodenum), and sewing the distal portion to the stomach pouch. The proximally transected jejunum is then anastomosed anywhere from 80 to 120 cm down the jejunum, creating two limbs in the shape of a "Y" that effectively separate ingested food from the remnant stomach and duodenum until they meet at a distal jejunal common channel. The resulting weight loss is believed to be a result of not only decreased stomach capacity (restrictive weight loss) but also by redirecting pancreatic enzymes further down the alimentary tract. This "bypass" of the duodenum and jejunum reduces the small bowel's ability to absorb fat and calories from ingested food, thereby allowing more fat to enter the colon and eventually the stool (malabsorptive weight loss) [8]. The pathogenesis of stone formation in these patients and recommendations for stone prevention center on their decreased fluid intake, acidosis, and excessive fat within the colonic lumen.

### Pathogenesis: Hyperoxaluria

Based upon clinical data from more than 15 clinical studies, calcium oxalate kidney stone development in RYGB patients appears to be due to increased urinary oxalate, decreased urinary volume, and decreased urinary citrate [9]. Hyperoxaluria following RYGB surgery can be separated into three categories: changes in gut transporters, changes in gut environment, and nutritional changes (Fig. 15.1). Because little has been published on oxalate-based food preference changes in patients after RYGB, and because gut transporter changes are beyond the scope of this chapter, the RYGB focus here will be changes in gut environment. To date, the best clinical data suggests that intestinal oxalate permeability as a consequence of malabsorption of bile salts and/or fatty acids is the most likely pathway for hyperoxaluria, the so-called enteric hyperoxaluria (Table 15.1). As fat is malabsorbed, fat-soluble vitamins and calcium ions are saponified by free fatty acids in the gut, leading to steatorrhea and nutrient losses. With the diminished availability of intestinal calcium, there is an increased proportion of free colonic luminal oxalate. This free

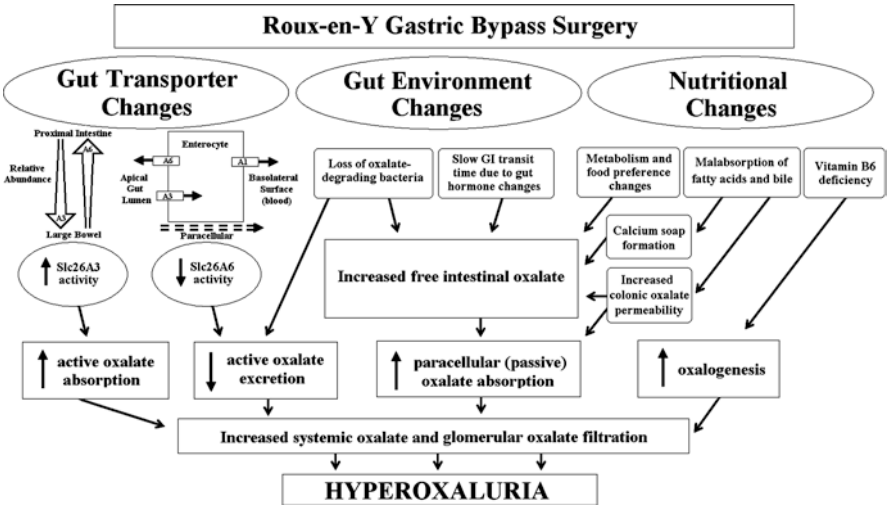


**Fig. 15.1** Schema of hyperoxaluria mechanisms following Roux-en-Y gastric bypass surgery. Proposed mechanisms fall into three categories: gut transporter changes, gut environment changes, and nutritional effects. All pathways ultimately lead to hyperoxaluria by increasing active or passive oxalate absorption, oxalogenesis, and/or decreasing active oxalate secretion in the GI tract. Gut transporter changes, specifically Slc26A3 and A6, are speculative due to lack of human studies and absence of highly sensitive and specific Slc26 antibodies in the gut and kidney. Although gut environment changes and vitamin B6 nutritional effects have been shown in a variety of different animal studies, they are also speculative since the data have not been specifically generated in relation to RYGB and oxalate. With strong historical and recent experimental human and animal data, increased intestinal oxalate permeability as a consequence of fat malabsorption remains the most likely pathway for increased free intestinal oxalate, oxalate absorption, and hyperoxaluria, modified from Canales et al. 2014 [9]

oxalate, therefore, is more likely to be passively absorbed along its gradient from an area of high concentration (gut lumen) to that of low concentration (bloodstream). Because oxalate is an end product of metabolism, absorbed oxalate must consequently be eliminated by the kidney into the urine (94% of all secreted oxalate) or excreted by the colon (6% of total body oxalate). Elevated urinary oxalate creates an environment in which urinary calcium and oxalate can precipitate into insoluble mineral complexes and eventually form kidney stones [10].

## Pathogenesis: Hypocitraturia and Low Urine Volumes

In addition to hyperoxaluria, RYGB patients develop hypocitraturia secondary to GI fluid losses, further increasing the risk of calcium oxalate supersaturation and stone formation. Based on both clinical and experimental data, a portion of RYGB patients have been shown to acquire metabolic acidosis after RYGB [11], believed to be due to gut bicarbonate and fluid losses secondary to chronic diarrhea. This acidosis leads to increased mitochondrial citrate utilization, renal citrate reabsorption, and

**Table 15.1** Anatomic, metabolic, and urinary differences in RYGB, Crohn's, and ulcerative colitis patients

| | RYGB | Crohn's disease | Ulcerative colitis |
|---|---|---|---|
| Underlying gut pathology | Restrictive and malabsorptive weight loss procedure | Etiology unknown; transmural inflammation involving entire GI tract (rectal sparing) | Etiology unknown; continuous ulcers on colonic mucosa, involves rectum |
| Systemic drugs for treatment | n/a | Sulfasalazine, methotrexate, biologics (e.g., infliximab, adalimumab), glucocorticoids | Sulfasalazine, glucocorticoids, cyclosporine, infliximab, antibiotics |
| Bowel deficits | Jejunum bypasses ileum | Resections occur anywhere along GI tract | Total colectomy for refractory disease |
| Systemic acidosis | Rare from diarrhea | Occasionally from chronic diarrhea | Common from chronic diarrhea |
| Stone types | CaOx | CaOx | CaOx |
| | | Uric acid | Uric acid |
| Underlying stone pathology | 1. Enteric hyperoxaluria | 1. Enteric hyperoxaluria | 1. Metabolic acidosis |
| | 2. Low urine volume | 2. Low urine volume/ dehydration | 2. Low urine volume/ dehydration |
| | 3. Metabolic acidosis | 3. Steroid-induced hypercalciuria | |
| | | 4. Metabolic acidosis | |
| 24-h urine profiles | | | |
| Low volume | Frequent | Frequent | Frequent |
| Hyperoxaluria | Frequent | Frequent | Rare |
| Hypercalciuria | Rare | Occasionally | Occasionally |
| Hyperuricosuria | Occasionally | Occasionally | Frequent |
| Hypocitraturia | Frequent | Frequent | Frequent |
| Hypomagnesuria | Occasionally | Occasionally | Occasionally |

decreased urinary citrate secretion. Citrate, a natural inhibitor of calcium crystallization, complexes with urinary calcium to lower calcium crystal saturation while raising urine pH. Therefore, RYGB patients with hypocitraturia are at further increased risk of calcium stone formation due to lowered urine pH and altered supersaturation. Finally, the restrictive component of RYGB may lower the amount of fluids these patients can ingest. This, combined with GI volume loss from chronic diarrhea, lowers the volume of urine production and increases urinary crystal supersaturation risk.

## Recommendations

Kidney stone formation, particularly calcium oxalate stones, in RYGB patients is a complex interplay of various environmental and nutritional components. With these mechanisms, there are several recommendations one can provide to patients to

**Table 15.2** Strategies, limitations, and solutions to reduce calcium oxalate stone risk in RYGB or IBD patients

| Prevention strategy | Limitations | Prevention solutions |
|---|---|---|
| Urine output >2 l/day | Compliance | Push fluids high in citrate (i.e., lemonade); downloadable phone application reminders |
| Low fat diet (<25% daily calories) | High prevalence of fatty foods | Patient education; downloadable nutritional phone applications to raise food awareness |
| Low oxalate diet (<80–100 mg/day) for hyperoxaluria | Found in vegetables and healthy foods (soy, peanuts, bran); variable bioavailability | Patient education[a]; oxalate "balance" instead of oxalate "avoidance" |
| Low salt (<2,300 mg/day) and animal protein (0.8–1.0 gm/kg/day) intake | Both are ubiquitous, particularly in American diet | Patient education; follow Dietary Approaches to Stop Hypertension (DASH)-style diet |
| Urinary electrolyte repletion (potassium citrate, magnesium oxide) | Tolerability, absorption efficacy, expense | Dispense in liquid or crystal/powder forms |
| Calcium citrate and dietary calcium to bind enteric oxalate | Tolerability, absorption efficacy, compliance, expense | Calcium-fortified foods; low-dose chewable citracal taken 5–6× daily with small meals |
| Probiotics for hyperoxaluria | No commercially available *Oxalobacter* sp.; unknown efficacy of *Lactobacillus* sp. | Yogurt contains protein, calcium, and forms of probiotics |
| Vitamin B6 (pyridoxine) for hyperoxaluria | Poorly studied in enteric hyperoxaluria; potential for neurotoxicity at high doses | Supplement low-dose B6 (50 mg/day) ×6 months and then discontinue |
| Replace long-chain fatty acids with medium-chain triglycerides (MCTs) | Variable amounts of MCT in packaged foods; may increase fecal volume | Palm, kernel, or coconut oil. If enteral feeds, 50/50 ratio long-chain fatty acids to MCTs |
| Stool frequency <5/day, particularly for IBD patients | Conventional therapies may not induce remission or decrease flare frequency | Immunomodulator/biologic therapies for nonresponders; refer to GI specialist |

Key: Modified from Table 3 [9] with permission
[a]High oxalate content foods can be found at: https://regepi.bwh.harvard.edu/health/Oxalate/files

minimize stone formation. Many of these strategies are similar to those recommended to all stone formers and are summarized in Table 15.2. These include increasing daily fluid intake to achieve urine volumes of >2 l/day and low oxalate intake of <100 mg/day. Additionally, low sodium and animal protein intake, as seen in the Dietary Approaches to Stop Hypertension (DASH) diet, may encourage favorable dietary patterns and impart a more balanced approach rather than one of "food avoidance." This is particularly important when counseling patients as sodium and animal-based protein are prevalent in the American diet. As discussed earlier, fatty acids result in increased elimination of intestinal calcium and therefore more

free oxalate. As such, RYGB patients can simply reduce their daily fat intake as well as increase calcium intake in the form of calcium citrate. Calcium citrate is preferred over calcium carbonate as it also aids in correcting metabolic acidosis and hypocitraturia, further decreasing the risk of stone formation [12, 13]. Other options for these patients include supplementation with probiotics and pyridoxine. Although the data in this area is limited, a brief review of these nutritional factors is important.

*Oxalobacter formigenes* is an anaerobic gut commensal bacterium that uses oxalate as its sole energy source. Because higher free gut luminal oxalate may lead to enhanced oxalate absorption and stone disease, lack of *Oxalobacter* colonization in calcium oxalate stone formers has been linked as a potential etiology of hyperoxaluria [14]. In 2005, patients with fat malabsorption, hyperoxaluria, and calcium oxalate stones caused by a variety of GI diseases, including six patients RYGB patients, were given the probiotic "Oxadrop®" (*Lactobacillus acidophilus* and *brevis*, *Streptococcus*, and *Bifidobacterium*) [15]. Over a period of 3 months, mean urinary oxalate levels decreased by 20% in these patients with fairly resistant hyperoxaluria [15]. This trial was followed by several encouraging case series in primary hyperoxaluria (PH) patients, a rare genetic disease characterized by abnormally high hepatic oxalate synthesis and high urinary oxalate excretion. These series showed reductions in urinary oxalate excretion in PH patients administered with viable *Oxalobacter* cells [16]. However, a recent multicenter randomized trial of orally administered *O. formigenes* in PH patients showed no difference in urinary oxalate levels between the treatment and control group [17]. Due to these discrepancies, Canales et al. evaluated the efficacy of orally administered *O. formigenes* in a rat model of RYGB surgery and found that urinary oxalate fell more than 70% over an 8-week bacterial gavage course [9]. Although more clinical trials are needed in this population, it seems reasonable to suggest that RYGB-stone formers try probiotics in the form of yogurt if they experience hyperoxaluria, as yogurt contains calcium (an oxalate binder) as well as forms of probiotics that may have beneficial effects on gut oxalate handling.

Pyridoxal L-phosphate (PLP), the metabolically active form of vitamin B6, is an important cofactor for the transamination reaction of glyoxylate to glycine. In the setting of vitamin B6 deficiency, the pathway is shunted from glycine production to that of oxalate, resulting in excessive urinary oxalate [18]. Vitamin B6 is water soluble and is not typically deficient in the American diet. However, a retrospective series of over 400 gastric bypass patients demonstrated that almost 20% of these patients were vitamin B6 deficient at 1 and 2 years postsurgery [19]. Although these patients did not have corresponding urine oxalate levels to determine causality, it seems reasonable to presume that B6 deficiency could lead to increased liver oxalogenesis, hyperoxaluria, and calcium oxalate stone disease (Fig. 15.1). More studies are needed in this area, especially because a retrospective study of empiric vitamin B6 supplementation in addition to dietary counseling in patients with idiopathic hyperoxaluria noted an approximately 30% decrease in urine oxalate on follow-up 24-h urine studies [20]. Lastly, due to light sensitivity, serum PLP can be difficult to measure accurately, and many clinical labs do not offer this as quantitative study.

Because of this, many practitioners offer low-dose supplementation in lieu of measuring PLP levels. Vitamin B6 can cause neurotoxicity at high levels, so a reasonable supplement regimen is around 50 mg daily for 6 months with discontinuation of the supplement after that time period (Table 15.2).

## Inflammatory Bowel Disease

### Background

Crohn's disease (CD) and ulcerative colitis (UC) are the predominant forms of inflammatory bowel disease (IBD) and involve chronic inflammation of the gastrointestinal tract.

The majority of patients with Crohn's disease present with fluctuating diarrhea (≥5 stools/day) due to a number of gut inflammatory causes. Because CD can affect the entire GI tract, some Crohn's patients with a diseased or resected distal ileum develop "bile salt malabsorption" due to unabsorbed bile acids that enter the colon (bile salts are produced by the liver and normally absorbed by specific receptors in the distal ileum). The resulting "bile salt" diarrhea is not only a watery diarrhea that affects colonic water and electrolyte absorption (dehydration, metabolic acidosis) but also an imbalance of bile acid leading to impaired micelle formation and high presence of fat in the stool (steatorrhea). While CD can involve the entire gastrointestinal tract, UC is characterized by recurring episodes of inflammation limited to the mucosal layer of the colon. UC commonly involves the rectum and may extend proximally in a continuous fashion to involve other parts of the colon [21]. Because of the distal colonic inflammation, UC patients tend to have small volume but frequent bowel movements, ranging from mild (≤ 4 stools/day) to severe disease (≥ 10 stools/day) with unrelenting cramps. Oftentimes, surgical bowel resection (small and large bowel in CD patients; large bowel only in UC patients) is necessary to control their disease process. Because both diseases involve diarrhea with or without malabsorption, both CD and UC confer risk of nephrolithiasis 10–100 times that of the general population [6] particularly the risk of uric acid [22] and oxalate-containing stones [23]. The pathogenesis of these types of stones and recommendations for their prevention is discussed below.

### Pathogenesis: Hyperoxaluria and Oxalate Stones

The leading theory for oxalate stone formation is enteric hyperoxaluria, a state in which increased oxalate concentration in the gut leads to increased absorption and supersaturation of the urine with oxalate, causing stones to precipitate. The mechanism behind this is thought to be that malabsorption causes chelation of calcium in the intestine by fats, reducing the amount of bound oxalate and thereby increasing oxalate absorption [22]. Although many patients with CD have hyperoxaluria [21, 24–26], patients with UC frequently do not because this is not a malabsorptive

disease [24, 25]. A recent small study showed that hyperoxaluria in patients with CD ($n = 46$) was correlated with increased intestinal absorption of oxalate and that bowel resection further increased the risk for stone formation [26]. Conversely, McConnell et al. (2002) showed that the urinary electrolytes citrate and magnesium, *not* urinary oxalate, correlated better to stone formation in IBD patients – even though they had hyperoxaluria. In particular, low urinary levels of magnesium negatively correlated to increasing length of terminal ileal resection and stone formation [25]. Another small series of IBD patients ($n = 22$) versus idiopathic stone formers showed that hyperoxaluria and hypocitraturia were correlated to stone risk in CD patients, but in UC patients, low urine volume drove production of predominantly uric acid stones [24]. Yet another study showed no difference in urinary electrolytes between CD versus UC patients [21] and instead showed that IBD patients actually had hypermagnesuria, which is protective against stone formation (Table 15.1).

In addition to the extent of disease and history of previous bowel resections, urinary electrolyte variability and stone risk may also be attributed to other drug regimens or to direct and indirect effects of bile acids. Corticosteroids, nonspecific immunosuppressants, are commonly used to treat moderate to severe Crohn's disease in either a pulsed fashion or chronically. Steroids are known to enhance bone resorption, inhibit gut calcium absorption, and increase urine calcium loss, potentially exacerbating the already increased risk of stone disease in these patients [22]. Malabsorbed fatty acids and bile acids in IBD patients have been speculated to increase the permeability of epithelial tight junctions in the colon, allowing more oxalate to pass from the intestine into the blood stream. In malabsorptive states, the percentage of oxalate absorbed from the gut and excreted in urine can be markedly increased, and hyperoxaluria often correlates with steatorrhea [27]. Unabsorbed bile acids may also exert damaging effects on intestinal oxalate-metabolizing bacteria, thereby increasing the luminal oxalate available for absorption. As previously discussed in the RYGB section, lack of *Oxalobacter formigenes* colonization has also been implicated as a cause of hyperoxaluria and stone risk in IBD patients [21, 28]. Kumar et al. (2004) showed that only 10% of IBD patients were colonized with *O. formigenes* compared with 56% of healthy controls, and patients without colonization had a significantly higher oxalate excretion. This may explain why UC patients are at increased oxalate stone risk despite having minimal malabsorption.

## Pathogenesis: Hyperuricosuria and Uric Acid Stones

Although not as well studied as calcium oxalate risk, uric acid stones require an environment of both supersaturation and acidic pH in order to precipitate. Chronic diarrhea and bicarbonate loss in IBD provide a urine environment ideal for uric acid stone formation. Diarrhea causes metabolic acidosis from loss of bicarbonate in the stool, resulting in dehydration and low urine volumes [22]. Trinchieri (2002) showed

that UC patients in particular were at an increased risk of uric acid stone formation because of metabolic acidosis and low urine pH. Cury et al. (2013) showed that UC patients with active disease are at increased risk for stone disease, regardless of the extent of disease. This finding was noteworthy as these particular 75 UC patients had not undergone colonic resection. Many UC patients with refractory disease will have their colon removed, providing high output of stool through ileostomies, placing them at high risk for dehydration and stone disease. Cury et al. (2013) also demonstrated that CD patients (without prior surgery) with ileocolonic disease had a greater risk of stones than those with ileal or colonic disease, likely due to more severe diarrhea [28].

## Recommendations

Although stone preventative recommendations in IBD patients are similar to those without bowel disease, perhaps the simplest recommendation is to refer patients to a gastroenterologist who specializes in IBD. Successful medical treatment allows the intestinal tissue to heal and relieves the associated diarrhea (termed "inducing remission"). Furthermore, medical therapy decreases the frequency of disease flares (termed "maintaining remission") and limits the number of times a patient may become hypovolemic or acidotic (Table 15.2). Adequate hydration with urine output between 2 and 3 L per day [29] should keep the urine dilute and prevent crystal supersaturation. For uric acid stone prevention specifically, both UC and CD patients could benefit from high levels of citrate and magnesium ingestion, either in the diet natively or with supplementation [22]. Protein restriction can also be useful in the setting of uric acid stones, as amino acid catabolism produces uric acid [22]. Although the pathogenesis of oxalate stones is not well delineated at this point, hyperoxaluria seems to be integral to their formation. Diets low in oxalate and high in calcium can help reduce oxalate absorption, as it will remain bound to calcium in the gut lumen and be excreted as a calcium oxalate complex in the stool [22]. Increasing calcium intake seems counterintuitive, but preventing excess absorption of oxalate is paramount to preventing stones.

In a similar vein, replacement of at least some fats in the diet with medium-chain triglycerides (MCTs) may be helpful. Long-chain fatty acids require bile to be absorbed in the distal ileum, but they are not absorbed by the colon, allowing them to chelate calcium and increase colonic oxalate absorption. However, MCTs can be absorbed in the colon, circumventing the malabsorption issue seen in CD [30, 31]. One study [32] showed that a high MCT diet in short-bowel patients increased fat absorption but also increased fecal volume, which may be an important consideration when counseling patients on adding MCTs to their diet (typically, MCTs are found in coconut and palm kernel oil and dairy products, the latter of which are actually constipating). Microbiome manipulation (e.g., with *O. formigenes*) may soon become possible and help prevent oxalate stones, although further research is necessary.

## Conclusion

In patients with RYGB and IBD, periods of dehydration and low urine flow undoubtedly play a large role in kidney stone pathogenesis. For RYGB patients with adequate urine volume, reduce free luminal oxalate by lowering dietary fat and oxalate content and by complexing ingested oxalate with bioavailable calcium with each meal. Because successful medical control of IBD may also control the underlying stone disease, CD and UC patients should be advised to have routine follow-ups with a gastroenterologist with a special interest in IBD. Should this fail to control their stone disease, manipulation of the urinary stone promoter/inhibitor balance (citrate, magnesium) and pH may lower both uric acid and calcium oxalate supersaturation and lead to lower stone formation rates. Prospective trials are needed to better quantify the extent to which these proposed prevention strategies reduce future stone risk in this recurrent stone population.

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# Part V

# Strategies for Providing Nutrition Therapy and Education to Patients

# Strategies for Counseling Patients in Clinic 16

R. Allan Jhagroo

## Introduction

Stone prevention therapy – both nutritional and medical – is effective only if it is followed. For some patients, kidney stone prevention is not taken as seriously as by others. Some have recurrent or especially aggressive disease, and the need for intervention is clear to them. Other patients may have only had a single event and see it as isolated or not disturbing enough to warrant life changes. Yet others may have recurrence, but it may be punctuated by variably long periods of quiescence, during which the pain and burden of kidney stones may be forgotten. While stone-related pain is usually temporary, and as surgical procedures offer resolution only of the acute stone event, there are potential long-term effects of stone disease. Some of these are without symptoms and may not manifest for many years. Data linking stone disease to bone, kidney, and even heart disease have now been published [1–3]. As providers, it is our responsibility to educate our patients and motivate them to adopt and maintain prevention regimens.

*So what are the steps involved in the implementation of stone prevention therapy?* The first step in therapy is appropriate identification of the problem(s) they could be inherited, anatomical, medical, and/or related to lifestyle factors. If the cause of a patient's stone formation is incorrectly identified, then inappropriate or ineffective therapy may be applied. This alone, especially if the specific therapy fails to achieve the desired or expected results, could reduce patients' interest in prevention and in maintaining preventive habits. But assuming accurate identification of the cause(s) of kidney stone formation and development of the appropriate therapeutic plan, communication of the plan to the patient is the next step. Ideally, the message should be conveyed to the patient in a way that he/she understands. This may require individualization of the way the message is conveyed or in the

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components of the message itself. Following this step, patient factors, such as willingness and ability to initiate therapy, take over.

*How do you know if patients are willing to implement stone prevention therapy?* For the most part, patients that are seen in stone prevention clinics have completed 24-h urine tests to help assess the risk for future stones. The effort of collecting this sample and submitting this test, in addition to attending the initial clinic appointment, has already resulted in the selection of patients more likely to be willing to make changes to prevent future stones. As these patients have made this effort, our job is then to facilitate the delivery of information and foster an overall environment that portends the greatest opportunity for success.

The objectives of this chapter are to (a) offer practical suggestions for effectively communicating stone prevention regimens to patients, including if and when adjunct providers such as registered dietitian nutritionists (RDNs) are optimally involved in patient care, and (b) evaluate different clinic appointment scenarios within which multiple providers are involved in patient care.

## Setting the Stage

*Metabolic evaluation* The metabolic evaluation and diagnosis of the patient's etiology for stone formation is multifactorial and may involve multiple specialists. In some clinical scenarios, this involves a multidisciplinary team which operates within the same clinic and sees patients together or on the same day. Providers may include, in various combinations, a urologist, nephrologist, dietitian, endocrinologist, and an advanced practice/nonphysician provider. In other scenarios, an interdisciplinary team of specialists may be involved who each see patients separately but communicate with each other to coordinate care. In yet other scenarios, a medical provider (e.g., nephrologist, urologist, internist, or primary care provider) with expertise in managing patients with stones evaluates patients independently, referring to others on an as needed basis.

*Therapeutic nutrition intervention* Many patients request dietary approaches before they agree to consider medication. In those who ultimately require medication, nutrition therapy may be supported as a way not only to empower the patient to be active in his/her therapy but also as a way to potentially reduce the quantity or dosages of medications needed. The American Urological Association supports targeted nutrition therapy for stone prevention [4]. RDNs can help to identify whether and which dietary habits may contribute to stone formation and are trained to prioritize and deliver nutrition therapy in an individualized manner. The prioritization of multiple dietary recommendations may be especially important as patient recall of recommendations may be limited in some cases [5] and require multiple encounters in order to deliver the entire regimen.

While physicians may be tempted to use results from the 24-h urine collection as surrogate markers for diet and as indicators for dietary therapy, 24-h urine

collections are merely "snapshots" in time and thus not always reflective of patients' routine or habitual diets. Moreover, some patients consciously alter their eating and drinking habits during urine collections to avoid the revelation of certain risk factors. While repeated 24-h urine tests can help to confirm habitual aspects of patients' diets [6], it is important to note that the same bias that was present in the first test may be present in subsequent tests as well. This may be due, in part, to the fact that many patients routinely collect their urine on the same type of day each time, i.e., during a weekend or off-work day. Collections on days that do not reflect the majority of days in a week may mask or lead to the undue expression of diet-related lithogenic risk factors. When considering dietary contributors to stone disease, the more habitual practices are the ones of greatest interest, not those that are practiced only occasionally. RDNs provide useful information to the physician when they collect, analyze, and interpret data from patient-reported usual/habitual intakes.

*Therapeutic pharmacologic intervention* While nutritional approaches might be tried in some patients, pharmacologic therapy is frequently concurrently prescribed, especially if nutrition therapy yields suboptimal results. The American Urological Association supports targeted pharmacologic therapy for stone prevention [4]. Medications should be prescribed for a clear purpose and linked to an identified risk factor from the patient's history or laboratory testing. The risks and benefits associated with the use of the medication being prescribed should be explained. When patients are reluctant to start a medication, it is helpful to clarify that the risk factor(s) at which the medication is aimed is beyond control of diet or other potentially modifiable factors. This may help to absolve the patient from self-blame in the event that dietary approaches were unsuccessful and may facilitate acceptance of the medication. Because the majority of medications prescribed come with an intention for lifelong therapy for stone prevention, even during periods of stone quiescence, patients may need motivation to continue with therapy. This may come in the form of education, including at follow-up appointments, or further explanation of how the medication works as well as a discussion of how patients' stone risk may be altered by the medication.

*Communication* The next step in providing stone prevention is communication of the therapeutic regimen. An important aspect of communication is the patient's acceptance of the expertise of the person delivering the message. Data show that patients are fairly accepting of information that comes from a physician [7]. But there are other therapeutic areas for which additional personnel may be utilized and which may enhance patient acceptance of and enthusiasm for prevention. For example, physicians managing patients with kidney stones may engage and/or integrate RDNs or other specialists into their practices. RDNs are specifically trained to design and implement nutrition interventions for a variety of chronic conditions, including urolithiasis [8, 9].

Because of the time and education involved in providing nutrition therapy – which involves assessment, diagnosis of the nutritional problem(s), and therapeutic intervention (see Chap. 1) – physicians may find it useful to either include a RDN

as part of their team or to refer patients to a RDN with experience in stone prevention. Data show that patients readily receive and trust dietary information provided by RDNs [10]. As such, physicians working with RDNs should set the stage for a favorable patient-provider interaction by validating the role of the RDN in patient care. In a multidisciplinary care setting, this can begin with the appointment scheduler, who may be asked to inform patients that a RDN will be involved in the clinic appointment. This message can be further reinforced when the patient appears for the appointment and is roomed. Finally, the physician can introduce the RDN to patients and explain how his/her involvement is necessary for designing the most optimal overall care regimen. Taking steps to ensure that patients understand the role of all the providers in their stone prevention care may promote patients' receptiveness to the information provided and their overall compliance with therapy.

## Sequence of Patient-Provider Interactions: Physician and RDN

The order in which patients are seen by and RDN and physician can vary. Most commonly, patients are seen by a physician and then subsequently by a RDN. Alternatively, patients are seen by the RDN first and then by the physician. At our clinic, the majority of our new patients are seen simultaneously in a group setting that includes both a RDN and physician. This has been described [11, 12]. We also see new patients in individual appointment settings. In these appointments, the physician typically interacts with the patient first and then consults with and engages the RDN. However, there are some scenarios in which the reverse order is advantageous, especially when the physician requires a careful assessment of a patient's diet and/or input as to any nutritional contributors to stone disease before making a definitive diagnosis or prescribing medication. The relative advantages and disadvantages of each sequence are reviewed below in Table 16.1.

*RDN before physician: within the same clinic appointment* This sequence can be helpful when unadulterated diet information is needed and especially when nutritional causes for stone formation need to be ruled in or out prior to considering other causes. Most physicians cannot afford the time nor do they have the training to perform this function. On the other hand, RDNs are trained in obtaining diet histories in nonjudgmental and objective ways. Furthermore, the information gathered needs to be quantified (e.g., average amount of calcium or oxalate consumed daily, estimated intake of sodium chloride, contribution of supplements to patients' nutritional intakes), a process with which many physicians may lack confidence [13]. In this scenario, the RDN reports to the physician prior to the physician's encounter with the patient. Armed with information about the patient's diet and potential contributors to stone formation, the physician then determines whether dietary intervention alone or diet plus pharmacologic therapy is indicated. If dietary intervention is involved, then the RDN might return to the patient's room after the physician concludes his/her encounter with the patient.

**Table 16.1** Advantages and disadvantages associated with variable order of provider interactions with a patient during a single clinic encounter

| Sequence of visit | Advantages | Disadvantages |
|---|---|---|
| RDN prior to physician | Unadulterated diet history (i.e., not influenced by physician assumptions or judgment) | May lengthen patient's appointment |
| | Can definitively rule in or out dietary contributor(s) to stone formation | Dietary prevention strategies provided by RDN may not be directed or vetted by physician |
| | May increase physician efficiency as role of diet, if any, is known before physician enters patient's room | |
| Physician prior to RDN | If diet is not a contributor to stone formation or growth, an unnecessary RDN encounter is avoided | May require multiple physician interactions (i.e., as physician may need to return to patient's room after receiving nutrition assessment from RDN) |
| | May avoid longer patient appointments | |
| | Physician able to direct and endorse dietary prevention strategies and communicate these to RDN before his/her involvement in patient care | May lengthen patient's appointment |
| Simultaneous physician and RDN (in an individual appointment setting) | All information available at the same time | Not efficient for providers; may result in fewer patients able to be seen in a given time frame |
| | Aids and informs shared decision-making as patients observe the actual development of therapeutic plan and underlying rationale of both providers | |
| Simultaneous physician and RDN (in a shared medical appointment setting) | All information available at the same time | Requires substantial preparation time by providers (e.g., to review patients' records, etc.) before entering appointment setting |
| | Aids and informs shared decision-making as patients observe the actual development of therapeutic plan and underlying rationale of both providers | Patients in group may influence other patients' feelings and/or responses |
| | Efficient use of time as more patients are seen within a given time period | |

A subset of patients is interested in dietary manipulations to prevent stones and has no interest in taking medications. Many of these patients may have only had one stone event and may reconsider medications in the future. This group of patients may especially benefit from seeing the RDN first, especially if the 24-h urine collection has not been completed or results are unavailable at the time of the

appointment. The physician could then follow the RDN with a brief patient interview and assessment to confirm a diet-only approach.

*RDN before physician: separate appointments* Some lower-risk patients, or patients reporting for an appointment without 24-h urine results, may be adequately served by dietary assessment and a trial of nutrition therapy prior to seeing the physician at the next appointment. This type of screening would take a trained RDN that is comfortable and experienced with stone prevention concepts. It could be coordinated with the physician with or without an actual encounter with the patient. While useful, this approach could, however, lead to a potential delay in care as a needed medication may be deferred until the patient is seen by the physician. This delay could result in loss of interest for prevention by the patient, especially if dietary therapy resulted in no change in stone condition.

*Physician before RDN: within the same clinic appointment* In the physician-before-RDN approach, the physician sees the patients as they arrive and moves through the clinic schedule as is typical for any medical specialty clinic. This is the most common sequence used in our clinic and allows for the physician to determine the utility of involving the RDN in the particular situation. This may ensure RDN efficiency by not bogging him/her down with patients who don't require nutrition therapy, but it can be problematic as well. While patients who declare no interest in meeting with a RDN should not be obligated to do so, some patients request for RDN involvement; this should be obliged if the RDN is available. Frequently, physicians will deem a patient uninterested or unmotivated in dietary prevention and therefore not offer RDN consultation. If the physician is correct, then this is a logical choice. But if there is any chance that the patient's enthusiasm or motivation for dietary prevention could be stimulated by the RDN, then this opportunity is lost.

Other times, the RDN might not be involved because diet is not suspected to be contributory to the patient's stone disease. This is easily gleaned in some cases. In others, however, it is more difficult to unequivocally rule out dietary causes, especially considering that (a) 24-h urine parameters are not surrogates for dietary intake, (b) patients may not provide full dietary disclosure to the physician, and/or (c) patient-reported dietary information may be misinterpreted by those without experience in assessing patients' diets. In cases where RDN involvement in the appointment is planned, patients should be informed of this early in the encounter so that the physician does not spend time gathering the same diet history that will eventually be elicited by the RDN. This not only enhances physician efficiency but also prevents the need for patients to repeat the same information to multiple providers, lends credibility to the role of the RDN in patient care, underscores the importance of diet in stone prevention, and sets the stage for a productive encounter with the RDN.

*Physician before RDN: separate appointments* In today's health care system, this is likely the approach most utilized by physicians who manage patients for stone disease. As most stone prevention clinics do not include a RDN member of the

team, dietary assessment and intervention require a separate appointment with a RDN. This scenario works well when diet is appropriately implicated in a patient's stone formation. How does the physician determine that dietary therapy is indicated? The two tools most commonly used are results from a patient's 24-h urine collection test and the physician's instinct about or knowledge of the patient's dietary habits. Unfortunately, neither method is a perfect means by which to screen for the need for nutritional therapy. As such, interventions implemented without dietary assessment may be misguided. For example, if it turns out that a patient's stone risk is primarily caused by diet, any medication prescribed by the physician would have been premature and could contribute to decreased enthusiasm by the patient for dietary therapy. Alternatively, a dietary approach implemented for an aberration not caused by diet would lead to a delay in medication, assuming one was available to control the observed risk factor. In both of these scenarios, the delayed input of the RDN could result in delay of optimal treatment.

*Simultaneous RDN and physician: shared medical appointment* This approach involves patients being seen simultaneously by the RDN and physician. We have used this approach with our new patients for the last 5 years [11, 12]. Medical information, including labs, medical histories, medications, and other relevant indices, are reviewed by the physician and RDN prior to the visit. After arrival, the patients are given a short general medical presentation that is followed by a focused nutrition assessment in a round-robin fashion. The information is gathered without immediate feedback provided. In a sequential fashion but in the presence of the group, each patient's 24-h urine results are reviewed and explained to them in the context of the medical history information obtained before the appointment. Decisions about each patient's therapeutic regimen are made with input from the patient, RDN, and physician in a three-way conversation. Because information about each patient's diet was obtained with the physician present, and because consultation between the physician and RDN occurs in real time during the appointment, decisions about initiating pharmacologic therapy can be made. At this time, questions by the patient as well as providers to each other are immediately answered. After all the patients have been reviewed and recommendations given, the physician leaves to enter documentation and prescriptions, if indicated, into patients' charts, and the RDN remains to provide a nutritional presentation that explains and provides therapeutic approaches for risk factors for which no medications were prescribed.

This method as the others has benefits as well as shortcomings. As noted, decisions about the use of medications are made quickly and with the benefit of multiple layers of information, including diet. If a patient's condition appears treatable without a medication, then this can be communicated to the physician and prescription medication delayed. I have found that patients in general like to see that a nutritional approach is attempted even if it may not end up being the final exclusive recommendation.

Our patients are largely satisfied with the shared medical appointment; surveys show a >93% satisfaction rate [11]. But there can be drawbacks. Although the RDN gathers dietary information in a nonjudgmental way in an effort to promote full and

honest disclosure, some patients have occasionally commented out loud about the dietary information of others. Although we have not studied this, it is possible that this could influence the answers some patients provide to questions about diet or about other aspects of their medical history. In addition, although concerted efforts to individualize nutrition therapy is made in the group setting, we are aware of the potential for patients to recall dietary recommendations which were made to another patient in the group and not to themselves. To avoid this, we provide each patient with their own stone prevention "prescription" sheet that identifies the specific nutritional and/or pharmacologic recommendations relevant to them.

A potential favorable aspect of the shared medical appointment is that the nutritional therapy given to some patients may address factors that are not yet visible in others. In this scenario, prior education about the corrective dietary recommendation could result in a higher level of understanding and acceptance of it, should it be added to a patient's regimen in the future as new risk factors emerge in subsequent 24-h urine collections. Typically, dietary stone prevention recommendations are not thought to confer a negative impact on a patient's health. For this reason, if a patient was to adopt a nutritional recommendation not specifically targeted to him/her, it would not likely impose a health risk. However, a priority is placed on individualizing patient's nutrition recommendations in the group setting as the number of dietary recommendations received may be related to recall and implementation. In our clinic, we have found that exceeding three dietary recommendations is associated with a drop in recall for some patients.

*Simultaneous RDN and physician: individual appointment* This last approach has been the least utilized by our clinic and likely not utilized in others. This approach is the least efficient with respect to provider time as both are present during each other's assessments. However, this may be the most ideal scenario as it confers all the benefits of the shared medical appointment with respect to definitive treatment decisions due to all information being available to both providers, with direct discussion and consultation between providers and with the patient.

## Conclusion

Stone prevention involving both a physician and a dietitian nutritionist can be provided in multiple ways. In general, effective communication with patients regarding the rationale for therapy and its potential implications remains, as always, a cornerstone of stone prevention counseling and can help to manage patients' expectations of and their role in therapy. The sequential approaches to evaluating and counseling patients, such as when multiple providers are involved at the same time in a common setting, have benefit. Information exchanged between providers may influence the order and/or type of therapy provided to the patient. In separate approaches to patient counseling, such as when patients are referred by the physician to another provider, such as a RDN, communication between providers may be delayed and could result in delay and/or changes to therapeutic approaches initiated.

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# Strategies for Providing Nutritional Therapy and Education to Stone-Forming Patients

17

Sutchin R. Patel

## Collaborating with a Registered Dietician Nutritionist

The AUA guidelines on the medical management of kidney stones specify that when obtaining a dietary history from a patient, one should elicit "their daily intake of fluids (amount and specific beverages), protein (types and amounts), calcium, sodium, high oxalate-containing foods, fruits and vegetables and over-the-counter supplements" [1]. Approximately three-quarters of urologists (72%) believe that they are able to provide effective dietary recommendations [2]. At the same time, urologists and other providers have identified lack of time, nutrition knowledge and dietary assessment, and interviewing skills as barriers to providing tailored nutritional counseling [3]. Patients' understanding of dietary recommendations may improve when they are given personalized or tailored recommendations [4]. Registered dietician nutritionists (RDNs) are trained to take detailed dietary histories utilizing food intake questionnaires and generally have more time to obtain this information from patients than a practicing urologist or nephrologist as well as provide a more customized nutritional counseling plan [5]. Thus having an RDN can further augment one's ability to identify dietary factors implicated in stone recurrence and provide customized nutritional counseling [5]. A multidisciplinary approach to nutritional counseling may also be more effective due to an observed phenomenon called the stone clinic effect [6]. Jhagroo et al. developed a shared medical appointment model to improve access as well as patient education and exposure to multidisciplinary care [7]. By incorporating presentation and multidisciplinary rounding in a group setting, patients' post-tests revealed that the patients in shared medical appointments had superior knowledge ($p < 0.02$) as well as higher patient satisfaction than the control patients. Another effect of the shared medical

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appointment was a decrease in appointment wait time and an increase in the number of patients seen per month (43% increase) [7].

A few academic institutions have an established stone clinic incorporating the expertise of a urologist, a nephrologist, and a registered dietician nutritionist. A commonly asked question is "How does one recruit or find an RDN in a private practice setting for their patients to see?" Hospitals are required to have registered dieticians for inpatients and frequently also have outpatient registered dieticians [5]. Potential pathways to collaborate with an RDN include speaking to the clinical nutrition director of your hospital to request an outpatient RDN to staff your clinic with you, asking HMO and health insurers in your area for the names of their outpatient RDNs that you can refer your patients to, or hiring an RDN to work exclusively with you in your practice [5]. As RDNs perform all steps of the nutrition care process (nutrition assessment, diagnosis, intervention, monitoring and evaluation), RDNs can be used for whichever part of the process that the physician may feel the patient needs, from obtaining a detailed dietary assessment to developing and implementing a nutrition plan to address it. Correspondence and communication between the physician and RDN are important in order to confirm appropriate therapeutic management and identify the need for modification over time as stone risk factors disappear and/or emerge [5].

## Strategies for the Private Practice Urologist/Nephrologist

The effective practical delivery of medical nutritional therapy requires the urologist/nephrologist to spend time listening to a patient's specific needs/current diet and correcting misconceptions as well as educating the patient in regard to nutritional recommendations to help prevent urolithiasis. One of the largest obstacles to good dietary counseling is time. A survey of endourologists found that time spent with stone formers for nutritional counseling varied from <4 min (31%) to ≥10 min (23%) with 64% feeling this to be insufficient time [3]. It is paramount to have the time to listen to a patient's specific needs and their diet as well as to correct "false myths." Many of our current patients come to us with preconceived ideas on why they make stones (whether it be from the Internet or from what they have heard from family and friends), and it is important to validate correct information, but unfortunately much time can also be spent debunking nutritional and scientific myths. A study by Traver et al. searched 458 consecutive sites related to kidney stones and dietary information on the Internet [8]. They reviewed Internet-based information regarding four dietary modifications and found that the information found was frequently incomplete and the most common misconception found was that calcium restriction was beneficial [8].

Repeating dietary recommendations in the beginning visits with patients can further help patients retain the information. As urologists spend time with a patient during multiple time points during the treatment of urolithiasis (initial hospital visit—if patient is seen in ER/hospital) and follow-up after procedure (s/p shock wave lithotripsy, ureteroscopy, or percutaneous nephrolithotomy), each "point of

contact" is an important opportunity to help educate the patient and their family. It is also important to discuss dietary recommendations, when possible, with the patient's husband/wife since a patient's dietary changes may affect the entire family or may be best supported by their husband/wife. It can be difficult for a patient to make effective dietary changes if their significant other is responsible for food preparation or if they are unaware of the dietary changes recommended. When discussing dietary recommendations, it is important not to give the patient a long list of recommendations or dietary changes. Stone-forming patients surveyed regarding dietary recommendations following clinic appointments were found to have high recall and low "false" recall when given ≤3 dietary recommendations [9]. Thus it is important to prioritize the recommendations to allow for better retention of the information and likely better compliance.

When discussing dietary recommendations with a patient, it is important to consider the patient's occupation and work environment. This will allow you to tailor your recommendations so that they are more practical and to allow you to identify any barriers to compliance. We have to look beyond the classic occupations that require stone-free status such as pilots. Different occupations and work environments can lead to difficulty in consuming a large fluid intake if there is not access to fluid (or time to drink fluids), if there is not easy access to a bathroom, or if the occupation does not allow for frequent work interruptions (Table 17.1).

**Table 17.1** Examples of some occupations with barriers to nutritional counseling

| |
|---|
| *Patients that self-restrict fluid intake due to limited bathroom access/work interruption* |
| Truck drivers |
| Cabdrivers |
| Grocery clerks |
| Tollbooth workers |
| Construction workers |
| Teachers |
| Healthcare professionals working in operating room (surgeons/anesthesiologists, nurses, techs) |
| *Patients with environments leading to high insensible losses* |
| Roofers |
| Dry cleaners |
| Cooks |
| Construction workers |
| *Patients who may have limited access to fresh fruits and vegetables* |
| (Due to limited food options) |
| Truck drivers |
| Cabdrivers |
| Any profession that requires significant travel (reliance on eating out or limited dietary options) |

Please keep in mind that the occupations above represent generalizations. There may be significant heterogeneity within a particular occupation allowing for more or less barriers to compliance with nutritional counseling recommendations. There is no substitute for discussing possible barriers to dietary recommendations with each patient

Patients that work outdoors in a hot and/or humid environment may have significant insensible losses due to sweating, and thus it is important to explain to these patients that they will need to drink considerably more fluid than 2–3 L/day. Occupations that fit this scenario may include roofers, landscapers, construction workers, and lifeguards. An extreme example of this was reported in a study of 50 US Marines that were on a 1-month training exercise in the Mojave Desert during the month of July. Despite drinking an average of 17 L of water per day, the daily urine output decreased 68% to 0.52 L per day [10]. Teachers many times may self-restrict their fluid intake during school hours as they cannot leave their classrooms unattended for a bathroom break. Linder et al. sent electronic surveys focusing on urolithiasis in a hospital and showed that healthcare professionals who work in the operating room (including surgeons, anesthesiologists, nurses, operating room techs) reportedly have significantly less fluid intake compared to employees not working in the operating room ($p = 0.04$) and that working in the operating room was associated with a significantly increased risk of stone formation (HR 1.43; $p = 0.04$) [11]. Evaluating patients' access to fluid as well as access to a bathroom and interruptions at work to use the bathroom is important, as patients may self-restrict fluid intake at work due to these factors [12]. Being able to tailor your dietary counseling with this population of patients, by recommending that they significantly increase their fluid intake as soon as they get home, is important. Sleep disturbances are another barrier to good fluid intake, and thus it is not unreasonable to have patients stop drinking fluid prior to bedtime as well as making sure that the patient is void prior to sleeping to minimize nocturia [12]. Truck drivers may have difficulty following certain dietary recommendations due to their long hours driving (they may self-restrict fluid intake to minimize bathroom stops) and because their diet intake may be restricted to processed foods (limited access to fresh fruits and vegetables) during their drives. Attention must also be placed on a patient's bowel habits as diarrhea (loss of fluid in feces) in cases of gastric bypass or ileostomy can also be a factor in low urine volume. In order to help our patients decrease their stone recurrent risk, we must be willing to tailor our recommendations to each patient's lifestyle and occupation (Table 17.2).

When discussing fluid consumptions, it is also important to determine what fluids the patient drinks on a regular basis [1]. A number of different beverages, such as alcoholic beverages, coffee, tea, and citrate-rich beverages, have been shown in observational studies to be associated with a lower risk of stone formation, while sugar-sweetened beverages have demonstrated an increased risk [13–18]. It is however important to understand that these beverages have not been evaluated in randomized controlled trials [1]. Though it is preferable for patients to consume citrate-rich beverages, recommending that patients try to avoid sugar-sweetened beverages and that they add additional citrate-rich fluid to what they already drink to increase their fluid consumption is important. The danger of having a patient replace what they were previously drinking with a citrate-rich beverage (as opposed to having them add citrate-rich beverages to their current fluid intake) is that they may drink less fluid overall when trying to substitute what they were previously drinking.

**Table 17.2** Barriers to increasing stone former fluid intake (solutions are listed under each barrier)

| |
|---|
| Not clearly informed of benefits of increased fluid intake |
| – Good nutritional counseling |
| Did not remember being told to increase fluid intake |
| – Repeat dietary recommendations during patient visits |
| – Make sure to prioritize dietary recommendations and give patients ≤3 recommendations to maximize recall |
| Don't like the taste of water |
| – Flavored water or beverages (try to avoid sugar-sweetened beverages) |
| Does not feel thirsty |
| – Timed fluid intake throughout the day |
| – Carry a water bottle |
| Does not have water available at work |
| – Carry a water bottle |
| Self-limits fluid intake because he/she does not have access to a bathroom at work |
| – Increase fluid intake upon finishing work |
| Self-limits fluid intake because he/she cannot tolerate workplace interruptions |
| – Increase fluid intake upon finishing work |
| Self-limits fluid intake due to sleep disturbances/nocturia |
| – Stop fluid intake 1 h prior to bedtime, void prior to bedtime |

Reference # [12]

Other barriers to increasing fluid intake include "not liking the taste of water" and the lack of thirst awareness [12]. Solutions to these problems include considering a plethora of water flavors that are commercially available as well as considering timed drinking of fluid. Carrying a fluid container with visible fluid markings has been shown to help patients increase their fluid intake. Though we encourage our patients to have a high fluid intake, the real focus is on their urine output, and thus the AUA guidelines recommend stone formers to consume a fluid intake that will achieve a urine volume of at least 2.5 L daily [1]. In order to help patients determine if they are reaching that goal, we can determine their urine volume when they do their 24-h urine metabolic study, but it can also be convenient to give patients a urine hat to place on their toilet so that they can monitor their urine output when they are at home. Penniston et al. showed that specific gravity measured at specific time points during a 24-h interval can predict total urine volume (with a specific gravity <1.010 predicting a 24-h urine volume of greater than 2 L). Providing hydrometers or dipsticks to patients, along with instructions for accurate reading of results, may be used as biofeedback to help them gauge how well they are doing in order to reach their target daily urine volume. Furthermore, specific gravity measurements between regularly scheduled clinic visits may also provide information regarding variations in patients' stone risk [19]. Urine color can be used as a rough gauge to help patients determine if they need to drink more fluid. Urine color charts are available and have been used in other clinical situations to help determine hydration status [20]. Setting a goal that the patient's urine should be clear can help patients gauge how hydrated they are on a daily basis. It is however important to

note that urine color by itself is not as accurate and should not be a replacement for a 24-h urine output measurement.

When giving dietary recommendations to our patients, we are also serving as a teacher. As such we have to be aware that patients learn via different methods and that not all patients are effective verbal students. Illustrating fluid intake is important, and it is common for a patient to ask how much fluid is 2.5 L or simply how much is 1 L of fluid. Thus we must not only be able to convert a liter to ounces (1 L = 33.814 US oz) or quarts (1 L = 1.05669 US quart) or gallons (1 L = 0.264172 US gal) or cups (1 L = 4.22675 cups) but to relate it to common household containers. For instance, a 2 L soda bottle, a 16 oz plastic soda/water bottle (approximately two 16 oz soda bottles are 1 L), most aluminum soda cans are 12 oz (approximately three cans would be just over 1 L), or a milk gallon (approximately half a gallon is 2 L) are all common household containers that can be used to show a patient how much fluid they need to drink. Patients will generally also quantify their fluid intake in "glasses" of water, milk, juice, etc. A small glass holds approximately eight fluid ounces (which is one cup); thus, approximately four glasses (32 oz) are 1 L of fluid. Having fluid containers available to help patients visualize how much fluid they should be drinking can be a great teaching tool, but these may not be available in most practice offices. Besides fluid intake, it is also important to discuss portion size and what constitutes a serving. For instance, when discussing decreasing the intake of flesh proteins (red meat, poultry, fish) in a patient with uric acid stones, the patient can be told that a serving of red meat or poultry is 3 oz which is quantified as approximately the size of a deck of cards. Three oz of fish has been described as the size of a thin checkbook. Eating the correct serving size of meat or working on decreasing portion size can thus be helpful in decreasing purine intake in these patients. The serving size for fruits and vegetables is a cup which is approximately what you can fit into the palm of your cupped hand. The rise in obesity over the past 30 years has been paralleled by increases in the portion size of many foods and the prevalence of eating food away from home (more processed or "fast foods") [21]. Handouts discussing dietary recommendations or that list foods that have high sodium or oxalate can be helpful adjuncts and reference tools for patients as they implement their dietary changes.

Finally, when providing dietary recommendations, it is important to manage patient expectations in regard to the benefits of nutritional counseling. Many patients may feel hopeful that changing their diet will eliminate their stone risk and thus become frustrated if they form a future stone despite being compliant with nutritional guidelines. It is important for patients to understand that the risk of stone recurrence is high, with a recurrence rate as high as 40% within 5 years of the initial episode [22]. Patients should be told that the overall risk for stone formation is a combination of genetic factors (which one cannot change) and environmental factors (which is the target of our dietary and/or medical therapy). Thus nutritional therapy (with or without medical therapy) may not guarantee that they are stone-free in the future, but it may increase the time interval to their next stone episode and may decrease the rate of future stone growth.

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# Appendices: Table of Contents



Penniston 1 refers to the chapter "Principles of Human Nutrition"
Penniston 2 refers to the yet-to-be-submitted chapter "Dietary Assessment of Patients Who Form Kidney Stones." Some of the appendices will also be cited in that chapter


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# Appendix 1 Form for Referring Patients to a Registered Dietitian Nutritionist (RDN) for Medical Nutrition Therapy for Stone Prevention

**COPY THIS FORM FOR MAKING REFERRALS TO A REGISTERED DIETITIAN**. Complete as much of the form as you are able to. Also, to comply with the Health Insurance Portability and Accountability Act of 2002, please protect the personal health information contained in the completed form.

## KIDNEY STONE COUNSELING REFERRAL FORM – FOR MEDICAL NUTRITION THERAPY BY RDN

**NAME OF PATIENT** _____ **DATE OF BIRTH** _____ **MEDICAL RECORD NUMBER** *(IF APPLICABLE)* _____

**LAST APPOINTMENT DATE** _____ **WEIGHT** _____ **HEIGHT** _____ **DOES THE PATIENT CURRENTLY HAVE STONES? IF YES, DESCRIBE LOCATION** _____

**DID YOU PRESCRIBE MEDICATIONS TO PREVENT STONES? – LIST MEDS**

**DID YOU RECOMMEND DIETARY CHANGES TO PREVENT STONES? – LIST CHANGES**

**REASON FOR YOUR REFERRAL:** Medical nutrition therapy for prevention of kidney stone recurrence Please detail any specific concerns or questions:

**NUMBER OF PRIOR STONE EVENTS** _____ **YEAR OF (OR AGE AT) FIRST STONE EVENT** _____ **FAMILY HISTORY FOR STONES** *(LIST RELATIONS)* _____

**PRIOR SURGERIES FOR STONES, IF ANY, AND YEAR(S)** _____ **PRIOR PASSAGES OF STONES, IF ANY, AND YEAR(S)** _____

**PRIOR STONE COMPOSITION RESULTS** *(LIST PERCENTAGE(S) OF EACH COMPONENT FOLLOWED BY THE YEAR OF ANALYSIS, IF AVAILABLE)*

_____CaOx monohydrate (whewellite):_____
_____CaOx dihydrate (weddellite):_____
_____CaPhos carbonate (carbonate apatite):_____
_____Calcium hydroxyl phosphate (hydroxyapatite):_____
_____CaPhos dihydrate (brushite): _____
_____Cystine: _____
_____Tricalcium phosphate (whitlockite):_____
_____Uric acid (urate):_____
_____Sodium urate monohydrate):_____
_____Ammonium urate:_____
_____Silica:_____
_____Xanthine:_____

**24-H URINE RESULTS** *(FOR MOST RECENT ANALYSES; GIVE DATES AND AMOUNTS OF EACH COMPONENT AS AVAILABLE)*

**Date 1:** _____ Ca (mg) _____ Ox (mg) _____ Cit (mg) _____ Uric acid (mg) _____ Phos (mg) _____ Vol (L) _____ pH _____
Mg (mg) _____ $Na^+$ (mEq) _____ $K^+$ (mEq) _____ $SO_4$ (mmol) _____ $NH_4$ (mmol) _____ UUN (g) _____ Creatinine (mg) _____

**Date 2:** _____ Ca (mg) _____ Ox (mg) _____ Cit (mg) _____ Uric acid (mg) _____ Phos (mg) _____ Vol (L) _____ pH _____
Mg (mg) _____ $Na^+$ (mEq) _____ $K^+$ (mEq) _____ $SO_4$ (mmol) _____ $NH_4$ (mmol) _____ UUN (g) _____ Creatinine (mg) _____

**Date 3:** _____ Ca (mg) _____ Ox (mg) _____ Cit (mg) _____ Uric acid (mg) _____ Phos (mg) _____ Vol (L) _____ pH _____
Mg (mg) _____ $Na^+$ (mEq) _____ $K^+$ (mEq) _____ $SO_4$ (mmol) _____ $NH_4$ (mmol) _____ UUN (g) _____ Creatinine (mg) _____

**LIST PATIENT'S CURRENT MEDICATIONS**: _____

**LIST COMORBIDITIES, MEDICAL CONCERNS**: _____

**REFERRING PROVIDER** _____ **YOUR NPI #** _____

**SIGNATURE** _____ **DATE** _____

**PHONE** _____ **FAX** _____ **EMAIL** _____



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## RATIONALE FOR DATA INCLUSION IN RDN REFERRAL FORM

The following information explains why it is important to include data for the referral to a Registered Dietitian Nutritionist for medical nutrition therapy. While you may not be able to provide all the information requested, any data you are able to provide will be useful.

| | |
|---|---|
| REASON FOR REFERRAL TO DIETITIAN FOR MEDICAL NUTRITION THERAPY | Can list specific concerns, underlying diseases or conditions that are thought to contribute to stone formation, information about length and/or aggressiveness of patient's stone history, etc. |
| NEW Rx PRESCRIPTIONS | Important for interpreting results of 24-h urine collections and other parameters from before any new medications were being used by the patient |
| NEW DIETARY CHANGES | Important for distinguishing between prior dietary habits (and over-the-counter supplement use) and those only recently implemented. Also important when evaluating patients' knowledge and understanding of impact of diet on stones. |
| STONE EVENTS & FAMILY HISTORY | The number of prior stone events, surgeries, and existence of family medical history related to stones can help to assess severity and aggressiveness of stone disease and may inform nutritional prioritization. |
| STONE COMPOSITION | If available, stone composition is important in guiding the prioritization of medical nutrition therapy for stone prevention. |
| 24-HOUR URINE RESULTS | Provides important data to assess risk and points the way for specific lines of investigation during diet assessment. The date of the collection reveals its proximity to prior stone event(s) and to initiation of any new therapies. The 24-h urine creatinine measure is important in assessing accurateness of the time period during which the urine was collected. |
| CURRENT MEDICATIONS | Certain medications - such as antibiotics and carbonic anhydrase inhibitors - can promote stone formation. Dietary strategies to compensate for these effects and for others can be implemented. Other medications have interactions with dietary components and are thus crucial in assessing nutritional status as well as effects on stone promoters and inhibitors. |
| COMORBIDITIES | Important to assess contributing or co-mingling factors that affect stone formation and growth. Also important for integrating dietary recommendations with those received and in place for other conditions. |
| ADDITIONAL INFORMATION & COMPLICATING FACTORS | Certain laboratory measures may be useful, such as vitamin D status, parathyroid hormone, and serum calcium, potassium, and phosphorus. Other complicating factors, such as prior bowel or bariatric surgery, short bowel, or neurogenic bladder, are also important to note as they may have implications for the nutrition therapy regimen. |

For more information about DIET AND STONES, visit the AMERICAN UROLOGICAL ASSOCIATION (AUA) website at: **https://www.auanet.org/education/guidelines/management-kidney-stones.cfm**. There you may read an abstract of the guidelines, view the individual guideline statements, and download the unabridged version of the guideline.

Also refer to the AUA PATIENT GUIDE TO KIDNEY STONES. This may be downloaded and provided to patients. Visit **http://www.urologyhealth.org/educational-materials/kidney-stones-a-patient-guide**. Additional stone materials are available for download at **http://www.urologyhealth.org/educational-materials?filters=769**. These additional materials include the following factsheets: "Diagnosing and Treating Kidney Stones," "Kidney Stones-What You Should Know," and "Preventing Kidney Stones."

Registered dietitian nutritionists may also wish to review the chapter on diet and kidney stones in the Nutrition Care Manual of the ACADEMY OF NUTRITION AND DIETETICS. Patient educational materials are also available there.

# Appendix 2 Dietary Guidelines for Americans: 2015–2020

| The guidelines | |
|---|---|
| 1 | Follow a healthy eating pattern across the lifespan. All food and beverage choices matter. Choose a healthy eating pattern at an appropriate calorie level to help achieve and maintain a healthy body weight, support nutrient adequacy, and reduce the risk of chronic disease |
| 2 | Focus on variety, nutrient density, and amount. To meet nutrient needs within calorie limits, choose a variety of nutrient-dense foods across and within all food groups in recommended amounts |
| 3 | Limit calories from added sugars and saturated fats and reduce sodium intake. Consume an eating pattern low in added sugars, saturated fats, and sodium. Cut back on foods and beverages higher in these components to amounts that fit within healthy eating patterns |
| 4 | Shift to healthier food and beverage choices. Choose nutrient-dense foods and beverages across and within all food groups in place of less healthy choices. Consider cultural and personal preferences to make these shifts easier to accomplish and maintain |
| 5 | Support healthy eating patterns for all. Everyone has a role in helping to create and support healthy eating patterns in multiple settings nationwide, from home to school to work to communities |

## Key Dietary Guidelines Recommendations

*Consume a healthy eating pattern that accounts for all foods and beverages within an appropriate calorie level.*

**A healthy eating pattern includes:**

- A variety of vegetables from all of the subgroups—dark green, red and orange, legumes (beans and peas), starchy, and other
- Fruits, especially whole fruits
- Grains, at least half of which are whole grains
- Fat-free or low-fat dairy, including milk, yogurt, cheese, and/or fortified soy beverages
- A variety of protein foods, including seafood, lean meats and poultry, eggs, legumes (beans and peas), and nuts, seeds, and soy products
- Oils



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**A healthy eating pattern limits:**

- Saturated fats and *trans* fats, added sugars, and sodium

Key Recommendations that are quantitative are provided for several components of the diet that should be limited. These components are of particular public health concern in the United States, and the specified limits can help individuals achieve healthy eating patterns within calorie limits:

- Consume less than 10% of calories per day from added sugars[1].
- Consume less than 10% of calories per day from saturated fats[2].
- Consume less than 2,300 milligrams (mg) per day of sodium[3].
- If alcohol is consumed, it should be consumed in moderation—up to one drink per day for women and up to two drinks per day for men—and only by adults of legal drinking age.[4]

In tandem with the recommendations above, Americans of all ages—children, adolescents, adults, and older adults—should meet the *Physical Activity Guidelines for Americans* to help promote health and reduce the risk of chronic disease. Americans should aim to achieve and maintain a healthy body weight. The relationship between diet and physical activity contributes to calorie balance and managing body weight. As such, the *Dietary Guidelines* includes a Key Recommendation to meet the *Physical Activity Guidelines for Americans*.[5]

---

[1] The recommendation to limit intake of calories from added sugars to less than 10 % per day is a target based on food pattern modeling and national data on intakes of calories from added sugars that demonstrate the public health need to limit calories from added sugars to meet food group and nutrient needs within calorie limits. The limit on calories from added sugars is not a tolerable upper intake level (UL) set by the Institute of Medicine (IOM). For most calorie levels, there are not enough calories available after meeting food group needs to consume 10 % of calories from added sugars and 10 % of calories from saturated fats and still stay within calorie limits.

[2] The recommendation to limit intake of calories from saturated fats to less than 10 % per day is a target based on evidence that replacing saturated fats with unsaturated fats is associated with reduced risk of cardiovascular disease. The limit on calories from saturated fats is not a UL set by the IOM. For most calorie levels, there are not enough calories available after meeting food group needs to consume 10 % of calories from added sugars and 10 % of calories from saturated fats and still stay within calorie limits.

[3] The recommendation to limit intake of sodium to less than 2,300 mg per day is the UL for individuals ages 14 years and older set by the IOM. The recommendations for children younger than 14 years of age are the IOM age- and sex-appropriate ULs.

[4] It is not recommended that individuals begin drinking or drink more for any reason. The amount of alcohol and calories in beverages varies and should be accounted for within the limits of healthy eating patterns. Alcohol should be consumed only by adults of legal drinking age. There are many circumstances in which individuals should not drink, such as during pregnancy.

[5] US Department of Health and Human Services. *2008 Physical Activity Guidelines for Americans*. Washington (DC): US Department of Health and Human Services; 2008. ODPHP Publication No. U0036. Available at http://www.health.gov/paguidelines. Accessed December 29, 2016

# Appendix 3 Healthy Eating Patterns

A. *Dietary Guidelines for Americans*. Guidelines are published every 5 years for public health professionals and are designed to help Americans make healthy food choices and serve as the foundation for nutrition policies and programs in the United States. Each version reflects the current body of nutrition science.

| Food group | Amount[a] in the 2,000-calorie-level pattern |
|---|---|
| Vegetables | 2 ½ cups or equivalents per day |
| • Dark green | • 1 ½ cups or equivalents per week |
| • Red and orange | • 5 ½ cups or equivalents per week |
| • Legumes (beans and peas) | • 1 ½ cups or equivalents per week |
| • Starchy | • 5 cups or equivalents per week |
| • Other | • 4 cups or equivalents per week |
| Fruits | 2 cups or equivalents per day |
| Grains | 6 oz or equivalents per day |
| • Whole grains | • ≥3 oz or equivalents per day |
| • Refined grains | • ≤3 oz or equivalents per day |
| Dairy | 3 cups or equivalents per day |
| Protein foods | 5½ oz or equivalents per day |
| Seafood | 8 oz or equivalents per week |
| Meats, poultry, and eggs | 26 oz or equivalents per week |
| Nuts, seeds, and soy products | 5 oz or equivalents per week |
| Oils | 27 g per day |
| Limit on calories for other uses (% of calories)[b] | 270 kcal per day (14%) |

[a]Quantity equivalents for each food group are defined in Appendix 3 of the 2015–2020 Dietary Guidelines for Americans, available at https://health.gov/, accessed December 29, 2016. Specific amounts and recommended portion sizes will vary for those who need less than 2,000 or more than 2,000 calories per day

[b]Assuming food choices to meet food group recommendations are from nutrient-dense sources, this category accounts for calories from added sugars, refined starches, solid fats, alcohol, and/or eating more than the recommended amount of nutrient-dense foods

B. *Guidelines for the DASH (Dietary Approaches to Stop Hypertension) Diet*. The DASH diet is promoted by the National Heart, Lung, and Blood Institute of the National Institutes of Health to prevent and manage hypertension and to



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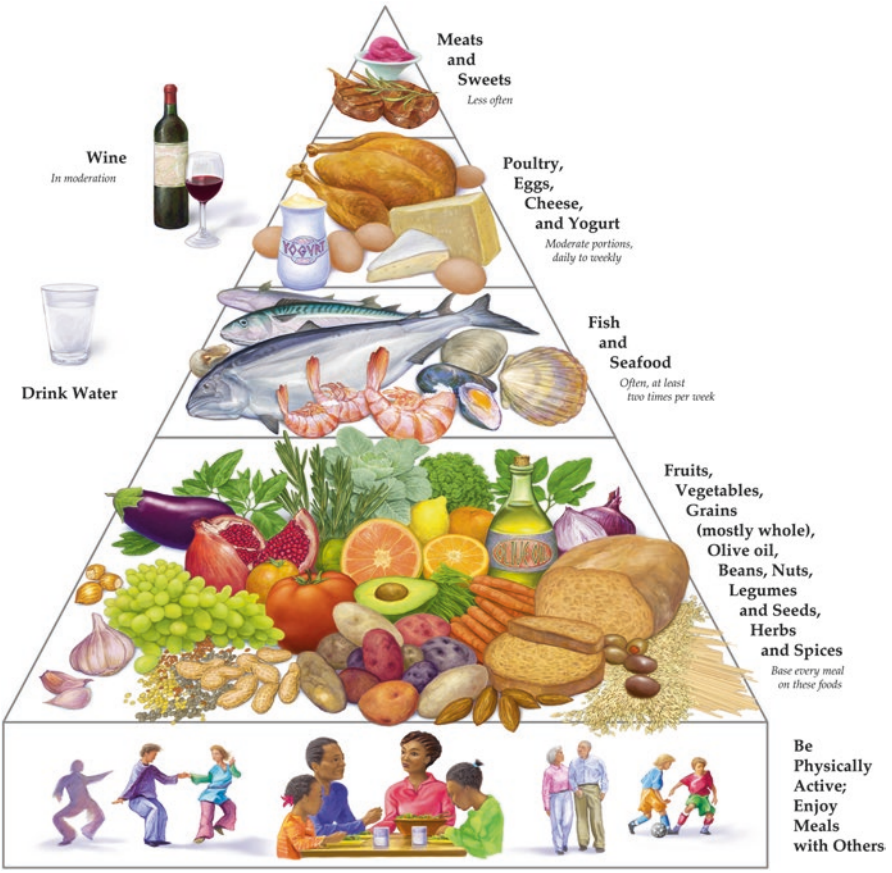
maintain heart health (Satterfield G, Anderson J, Moore C: Evidence supporting the incorporation of the dietary approaches to stop hypertension (DASH) eating pattern into stroke self-management programs: a review. J Neurosci Nurs 2012;44:244–50). It emanated from multinational studies that tested the effects of dietary patterns on blood pressure. Favorable results from these and other studies showing even more health benefits have resulted in widespread promotion of the DASH diet.

| Food group | Daily servings (except as noted) | Serving sizes |
|---|---|---|
| Grains and grain products | 7–8 | 1 slice bread |
| | | 1 cup ready-to-eat cereal[a] |
| | | 1/2 cup cooked rice, pasta, or cereal |
| Vegetables | 4–5 | 1 cup raw leafy vegetable |
| | | 1/2 cup cooked vegetable |
| | | 6 oz vegetable juice |
| Fruits | 4–5 | 1 medium fruit |
| | | 1/4 cup dried fruit |
| | | 1/2 cup fresh, frozen, or canned fruit |
| | | 6 oz fruit juice |
| Low-fat or fat-free dairy foods | 2–3 | 8 oz milk |
| | | 1 cup yogurt |
| | | 1½ oz cheese |
| Lean meats, poultry, and fish | 2 or fewer | 3 oz cooked lean meat, skinless poultry, or fish |
| Nuts, seeds, and dry beans | 4–5 per week | 1/3 cup or 1½ oz nuts |
| | | 1 tablespoon or 1/2 oz seeds |
| | | 1/2 cup cooked dry beans |
| Fats and oils[b] | 2–3 | 1 teaspoon soft margarine |
| | | 1 tablespoon low-fat mayonnaise |
| | | 2 tablespoons light salad dressing |
| | | 1 teaspoon vegetable oil |
| Sweets | 5 per week | 1 tablespoon sugar |
| | | 1 tablespoon jelly or jam |
| | | 1/2 oz jelly beans |
| | | 8 oz lemonade |

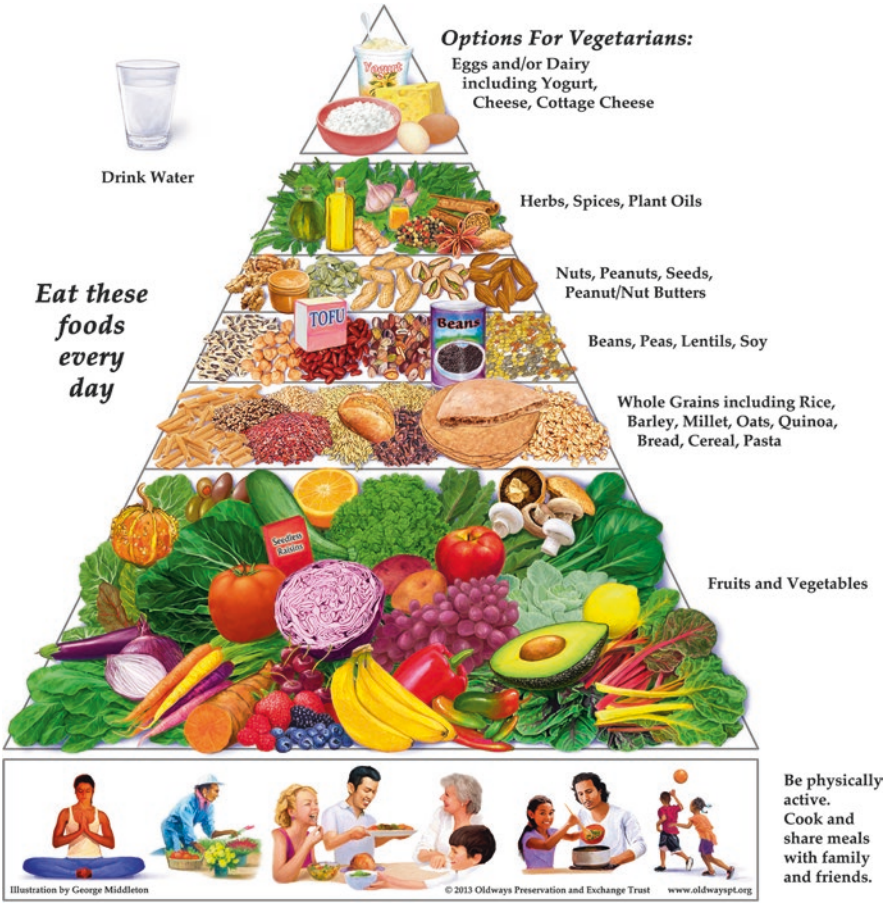
[a]Serving sizes vary between ½ cup and 1 ¼ cups; check the product's nutrition label
[b]Fat content changes serving counts for fats and oils: For example, 1 tablespoon of regular salad dressing equals 1 serving; 1 tablespoon of low-fat salad dressing equals ½ serving; and 1 tablespoon of fat-free salad dressing equals 0 servings

C. *Guidelines for the Mediterranean Diet*. The origin of this dietary pattern is the historic eating patterns of the people of Greece, Southern France, Spain, and parts of Italy. Widespread evidence supporting the Mediterranean diet has amassed, particularly for lowering the risk of cardiovascular disease (Bloomfield HE, Kane R, Koeller E. Greer N, MacDonald R, Wilt T: Benefits and harms of the Mediterranean diet compared to other diets [internet]. Washington (DC):

Department of Veterans Affairs (US); 2015 Nov.). Pyramid available at http://www.oldwayspt.org/.

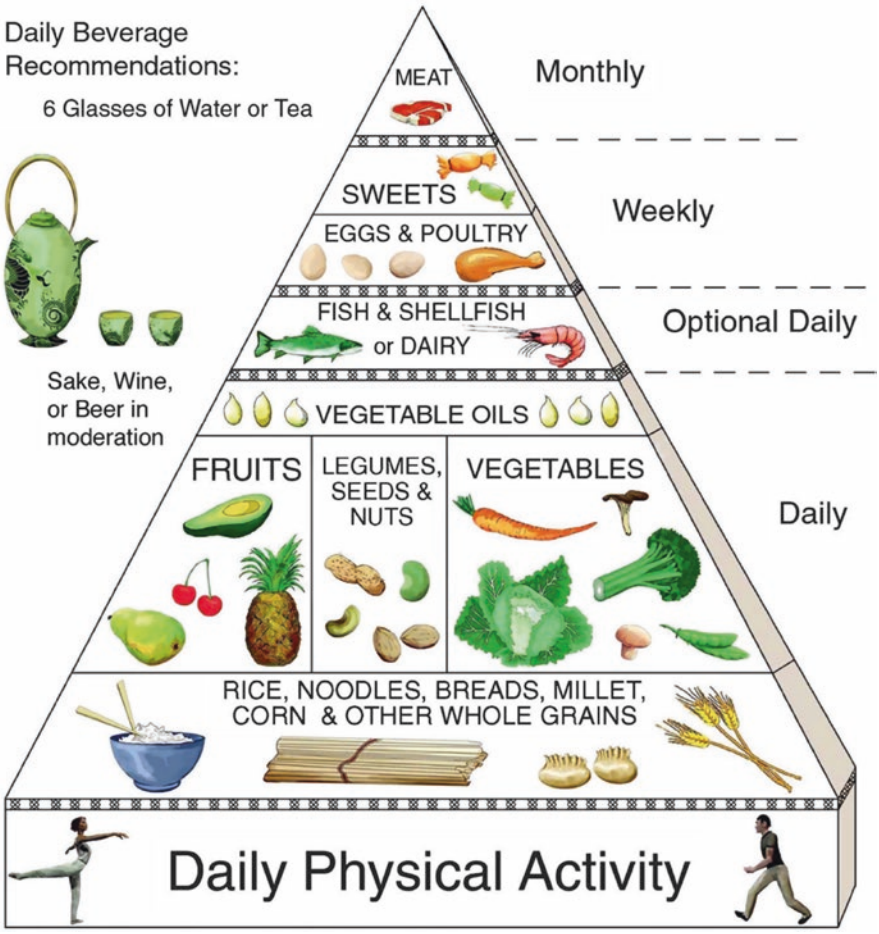



D. *Guidelines for Vegetarian and Vegan Diets*. Vegetarian diets of all types, whether dairy and/or eggs are consumed, are plant based. As such, they are typically rich in fiber and phytochemicals with antioxidant and prebiotic properties. Pyramid available at http://www.oldwayspt.org/.



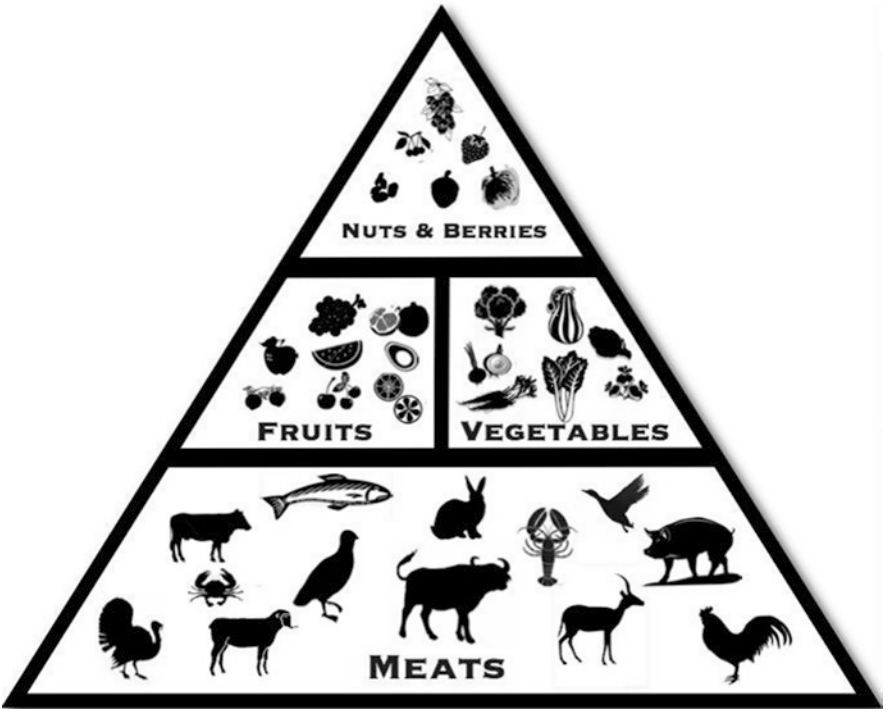

E. *Guidelines for the African Heritage Diet*. Research has demonstrated that the prevalence of metabolic syndrome in young African men increases as they consume more nontraditional foods, such as in the typical Western-style diet (Garrido et al. S Afr Med J 2009;99:331–4). The diet is similar to the Mediterranean and DASH diets in emphasizing plant foods but includes foods traditional to many African and African-American cultures. Pyramid available at http://www.oldwayspt.org/.


F. *Guidelines for the Asian Diet*. Lower rates of cardiovascular disease, obesity, and cancer have long been observed in Asian countries and among people following Asian-style dietary patterns. The diet is plant dense, including consumption of grains such as rice and noodles. A relatively high consumption of fish and seafood is recommended. A number of studies have shown poorer health outcomes after immigration from an Asian-style dietary pattern to a Western-style pattern (Dharod JM: What changes upon resettlement: understanding difference in pre- and post-resettlement dietary habits among South-Asian refugees. Ecol Food Nutr 2015;43:209–23). Pyramid available at http://www.oldwayspt.org/.




G. *Guidelines for the Latin-American Diet*. Emphasizing foods traditionally consumed in Latin-American cultures, this dietary pattern includes ample plant foods, especially beans and legumes. The Latin-American diet is associated with better nutritional status and reduced risk of common chronic diseases (Bermudez OI, Tucker KL: Trends in dietary patterns of Latin-American populations. Cad Saude Publica 2003;19 Suppl 1:S87–99). Pyramid available at http://www.oldwayspt.org/.


H. *Guidelines for the Paleolithic Diet*. This is a highly controversial dietary pattern that upends most other healthy eating guidelines. It features little to no cereal grains or refined flours; instead, carbohydrate needs are to be met from fruits and vegetables (Eaton et al. Eur J Clin Nutr 1997;51:207–16). Dairy is variably allowed according to some proponents. Studies in patients with type 2 diabetes have shown promise with respect to improvements in fat mass and insulin sensitivity as well as glycemic control (Otten et al. Diabetes Metab Res Rev. 2016; May 27 [Epub ahead of print]). Other studies have shown an inverse association of the diet with biomarkers of inflammation and oxidative stress (Whalen et al. J Nutr 2016;146:1217–26). Pyramid available at http://paleodietnews.com/.


NUTS & BERRIES
FRUITS
VEGETABLES
MEATS

# Appendix 4

## Calculations for Body Weight and Body Mass

*Ideal body weight* (*IBW*) is an estimate of the weight thought or estimated to be optimal for an individual and is based on gender, height, and weight. Other factors that may be included are a person's build and muscle status.

Males: 50 + 2.3 kg for every inch over 5 ft

Females: 45.5 + 2.3 kg for every inch over 5 ft

*Adjusted body weight* (*ABW*) is used to calculate energy needs when actual body weight is >30% of the calculated IBW and most often used in overweight and obese individuals.

0.4 × (actual weight − IBW in kg)

*Usual body weight* (*UBW*) is the weight an individual recalls or the weight at which he/she spent during most of adult life and most often used in assessing the magnitude and rate of weight change.

## Estimating Energy Requirements

*Common equations that use weight, height, and age to predict the basal energy expenditure of normal adults.* The equations below do not reflect physical activity or other factors that may alter energy expenditure such as critical illness. Also not included are equations that require the assessment of fat mass or other variables such as respiratory quotient.

| Equation name | Equation factors for body weight, height, and age in years |
|---|---|
| Harris-Benedict (1918)[a] | |
| – Males | $66.47 + (13.75 \times kg) + (5.003 \times cm) - (6.755 \times y)$ |
| – Females | $655.1 + (9.563 \times kg) + (1.850 \times cm) - (4.676 \times y)$ |
| Revised Harris-Benedict (1984)[a] | |
| – Males | $88.362 + (13.397 \times kg) + (4.799 \times cm) - (5.677 \times y)$ |
| – Females | $447.593 + (9.247 \times kg) + (3.098 \times cm) - (4.330 \times y)$ |

(continued)



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| Equation name | Equation factors for body weight, height, and age in years |
|---|---|
| Mifflin-St Jeor (2005)[a] | |
| – Males | $(10\times \text{kg})+(6.25\times \text{cm})-(5\times y)+5$ |
| – Females | $(10\times \text{kg})+(6.25\ \text{cm})-(5\times y)-161$ |
| Institute of Medicine (2005)[b] | |
| – Males | $662-(15.91\times \text{kg})+(539.6\times m)+(9.53\times y)$ |
| – Females | $354-(9.36\times \text{kg})+(726\times m)+(6.91\times y)$ |

[a]Body weight is kilograms (kg), height is centimeters (cm), and age is years ($y$)
[b]Height is expressed in meters (m), and age is years ($y$)

# Appendix 5 Dietary Reference Intakes

**Table A5.1** Daily macronutrient goals for age-sex groups based on dietary reference intakes and Dietary Guidelines recommendations

| Macronutrients | Source of goal | F 14–18[a] | M 14–18[b] | F 19–30[c] | M 19–30[d] | F 31–50[a] | M 31–50[e] | F 51+[f] | M 51+[c] |
|---|---|---|---|---|---|---|---|---|---|
| Protein, g | RDA | 46 | 52 | 46 | 56 | 46 | 56 | 46 | 56 |
| Protein, % kcal | AMDR | 10–30 | 10–30 | 10–35 | 10–35 | 10–35 | 10–35 | 10–35 | 10–35 |
| Carbohydrate, g | RDA | 130 | 130 | 130 | 130 | 130 | 130 | 130 | 130 |
| Carbohydrate, % kcal | AMDR | 45–65 | 45–65 | 45–65 | 45–65 | 45–65 | 45–65 | 45–65 | 45–65 |
| Dietary fiber, g | 14 g/1,000 kcal | 25.2 | 30.8 | 28 | 33.6 | 25.2 | 30.8 | 22.4 | 28 |
| Added sugars, % kcal | DGA | <10% | <10% | <10% | <10% | <10% | <10% | <10% | <10% |
| Total fat, % kcal | AMDR | 25–35 | 25–35 | 20–35 | 20–35 | 20–35 | 20–35 | 20–35 | 20–35 |
| Saturated fat, % kcal | DGA | <10% | <10% | <10% | <10% | <10% | <10% | <10% | <10% |
| Linoleic acid, g | AI | 11 | 16 | 12 | 17 | 12 | 17 | 11 | 14 |
| Linolenic acid, g | AI | 1.1 | 1.6 | 1.1 | 1.6 | 1.1 | 1.6 | 1.1 | 1.6 |

*RDA* Recommended Dietary Allowance, *AMDR* Acceptable Macronutrient Distribution Range, *DGA*, 2015–2020 Dietary Guidelines recommended limit, 14 g fiber per 1,000 kcal, basis for AI for fiber

[a]Goals based on 1,800 kcals total energy intake

[b]Goals based on 2,200–3,200 kcals total energy intake

[c]Goals based on 2,000 kcals total energy intake

[d]Goals based on 2,400–3,000 kcals total energy intake

[e]Goals based on 2,200 kcals total energy intake

[f]Goals based on 1,600 kcals total energy intake



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**Table A5.2** Daily micronutrient goals for age-sex groups based on dietary reference intakes and Dietary Guidelines recommendations

| | Source of goal | F 14–18 | M 14–18 | F 19–30 | M 19–30 | F 31–50 | M 31–50 | F 51+ | M 51+ |
|---|---|---|---|---|---|---|---|---|---|
| *Minerals* | | | | | | | | | |
| Calcium, mg | RDA | 1,300 | 1,300 | 1,000 | 1,000 | 1,000 | 1,000 | 1,200 | 1,000[a] |
| Iron, mg | RDA | 15 | 11 | 18 | 8 | 18 | 8 | 8 | 8 |
| Magnesium, mg | RDA | 360 | 410 | 310 | 400 | 320 | 420 | 320 | 420 |
| Phosphorus, mg | RDA | 1,250 | 1,250 | 700 | 700 | 700 | 700 | 700 | 700 |
| Potassium, mg | AI | 4,700 | 4,700 | 4,700 | 4,700 | 4,700 | 4,700 | 4,700 | 4,700 |
| Sodium, mg | UL[b] | 2,300 | 2,300 | 2,300 | 2,300 | 2,300 | 2,300 | 2,300 | 2,300 |
| Zinc, mg | RDA | 9 | 11 | 8 | 11 | 8 | 11 | 8 | 11 |
| Copper, mcg | RDA | 890 | 890 | 900 | 900 | 900 | 900 | 900 | 900 |
| Manganese, mg | AI | 1.6 | 2.2 | 1.8 | 2.3 | 1.8 | 2.3 | 1.8 | 2.3 |
| Selenium, mcg | RDA | 55 | 55 | 55 | 55 | 55 | 55 | 55 | 55 |
| *Vitamins* | | | | | | | | | |
| Vitamin A, mg RAE | RDA | 700 | 900 | 700 | 900 | 700 | 900 | 700 | 900 |
| Vitamin E mg AT | RDA | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 |
| Vitamin D, IU | RDA | 600 | 600 | 600 | 600 | 600 | 600 | 600[c] | 600[c] |
| Vitamin C, mg | RDA | 65 | 75 | 75 | 90 | 75 | 90 | 75 | 90 |
| Thiamin, mg | RDA | 1 | 1.2 | 1.1 | 1.2 | 1.1 | 1.2 | 1.1 | 1.2 |
| Riboflavin, mg | RDA | 1 | 1.3 | 1.1 | 1.3 | 1.1 | 1.3 | 1.1 | 1.3 |
| Niacin, mg | RDA | 14 | 16 | 14 | 16 | 14 | 16 | 14 | 16 |
| Vitamin B6, mg | RDA | 1.2 | 1.3 | 1.3 | 1.3 | 1.3 | 1.3 | 1.5 | 1.7 |
| Vitamin B12, mcg | RDA | 2.4 | 2.4 | 2.4 | 2.4 | 2.4 | 2.4 | 2.4 | 2.4 |
| Choline, mg | AI | 400 | 550 | 425 | 550 | 425 | 550 | 425 | 550 |
| Vitamin K, mcg | AI | 75 | 75 | 90 | 120 | 90 | 120 | 90 | 120 |
| Folate, mcg DFE | RDA | 400 | 400 | 400 | 400 | 400 | 400 | 400 | 400 |

*RDA* Recommended Dietary Allowance, *AI* Adequate Intake, *UL* tolerable upper intake level

[a]Calcium RDA for males >71 years is 1,200 mg

[b]The AI for sodium is 1,500 mg for individuals 19–50 years, 1,300 mg for individuals 51–70 years, and 1,200 mg for individuals >70 years

[c]Vitamin D RDA for individuals >70 years of age is 800 IU

**Table A5.3** Tolerable upper intake levels for micronutrients for age groups based on dietary reference intakes

| | 14–18 years | 19–30 years | 31–50 years | 51+ years | >70 years |
|---|---|---|---|---|---|
| *Minerals* | | | | | |
| Calcium, mg | 3,000 | 2,500 | 2,500 | 2,000 | 2,000 |
| Iron, mg | 40 | 45 | 45 | 45 | 45 |
| Magnesium, mg[a] | 350 | 350 | 350 | 350 | 350 |
| Phosphorus, mg | 4,000 | 4,000 | 4,000 | 4,000 | 3,000 |
| Potassium, mg[b] | – | – | – | – | – |
| Sodium, mg | 2,300 | 2,300 | 2,300 | 2,300 | 2,300 |
| Zinc, mg | 23 | 34 | 40 | 40 | 40 |
| Copper, mcg | 890 | 900 | 900 | 900 | 900 |
| Manganese, mg | 9 | 11 | 11 | 11 | 11 |
| Selenium, mcg | 400 | 400 | 400 | 400 | 400 |
| *Vitamins* | | | | | |
| Vitamin A, mcg[c] | 2,800 | 3,000 | 3,000 | 3,000 | 3,000 |
| Vitamin E mg[a] | 800 | 1,000 | 1,000 | 1,000 | 1,000 |
| Vitamin D, IU | 4,000 | 4,000 | 4,000 | 4,000 | 4,000 |
| Vitamin C, mg | 1,800 | 2,000 | 2,000 | 2,000 | 2,000 |
| Thiamin, mg[b] | – | – | – | – | – |
| Riboflavin, mg[b] | – | – | – | – | – |
| Niacin, mg | 30 | 35 | 35 | 35 | 35 |
| Vitamin B6, mg | 80 | 100 | 100 | 100 | 100 |
| Vitamin B12, mcg[b] | – | – | – | – | – |
| Choline, mg | 3,000 | 3,500 | 3,500 | 3,500 | 3,500 |
| Vitamin K, mcg[b] | – | – | – | – | – |
| Folate, mcg DFE | 800 | 1,000 | 1,000 | 1,000 | 1,000 |

Values do not include those for pregnant or lactating individuals

[a]No dietary UL is established; the UL refers to supplemental sources only

[b]No UL has been established

[c]The UL for vitamin A applies only to the preformed vitamin (i.e., not provitamin forms, such as carotenoids with vitamin A potential)

# Appendix 6

**Table A6.1** Food sources of oxalate

| Food item | Measure | Oxalate per measure (mg) |
|---|---|---|
| Spinach | 1 cup if raw; ½ cup if cooked | 340–755 |
| Rhubarb, fresh | ½ cup | 200–540 |
| Swiss chard | About 3.5 oz raw | 187 |
| Almonds | 1 oz or about 22 kernels | 120–130 |
| Potato with skin, baked | 1 medium size | 50–100 |
| Navy beans, canned | ½ cup | 50–75 |
| Cashews | 1 oz or about 18 kernels | 50–75 |
| Bran flakes with raisins cereal | 1 cup | 46–57 |
| Fruit and fiber with dates, raisins, and walnuts cereal | 1 cup | 41–45 |
| Miso soup | 1 cup | 40–111 |
| Yams | ½ cup cubed | 40–78 |
| French fries | 4 oz | 40–51 |
| Mixed nuts (with peanuts) | 1 oz | 39–56 |
| Candies with nuts (e.g., snickers) | 2 oz | 38 |
| Chocolate syrup | 2 tablespoons | 38 |
| Multi-bran chex cereal | 1 cup | 36–58 |
| 40% bran cereal | ¾ cup | 36 |
| Bamboo shoots | 1 cup | 35–78 |
| Cranberry almond crunch cereal | 1 cup | 35 |
| Okra | ½ cup | 31–57 |
| Brownies | 1 oz or ½ brownie | 31 |
| Rutabaga | ½ cup mashed | 31 |
| Hot chocolate, made from powder | 1 cup | 30–65 |
| Okra, cooked | ½ cup | 30–60 |
| Shredded wheat and bran cereal | 1 cup | 30–53 |
| Pineapples, dried | ½ cup | 30 |
| Turnips | ½ cup mashed | 30 |

(continued)


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| Food item | Measure | Oxalate per measure (mg) |
|---|---|---|
| Oranges | 1 | 29 |
| Frosted mini-wheats cereal | 1 cup | 28–38 |
| Sweet potatoes | 1 cup | 28 |
| Fudge sauce | 2 tablespoons | 28 |
| Lentil soup | 1 cup | 37–39 |
| Peanuts | 1 oz | 27–32 |
| Soy protein isolate | 1 oz | 27 |
| Carrot juice | 1 cup | 27 |
| Bulgur, cooked | 1 cup | 25–86 |
| Beets, raw | ½ cup | 25–85 |
| Raisin squares mini-wheats cereal | ¾ cup | 25–41 |
| Banana nut crunch cereal | 1 cup | 25 |
| Oatmeal crisp with almonds cereal | 1 cup | 24–51 |
| Veggie burger | 1 patty | 24 |
| Brown rice, cooked | 1 cup | 24 |
| Pineapple, canned | ½ cup | 24 |
| Figs, dried | 5 pieces | 24 |
| Dates | 1 | 24 |
| Honey nut clusters cereal | 1 cup | 23–35 |
| Cocoa powder | 4 teaspoons | 20–67 |
| Raspberries | 1 cup | 20–50 |
| All bran buds cereal | ½ cup | 20–49 |
| Mueslix apple and almond crunch cereal | 2/3 cup | 20–24 |

If available, data for oxalate were compiled from four sources, all of which were accessed online on January 5, 2017: (1) the USDA nutrient database available at https://www.ars.usda.gov/northeast-area/beltsville-md/beltsville-human-nutrition-research-center/nutrient-data-laboratory/docs/oxalic-acid-content-of-selected-vegetables/; (2) the Nutrition Data System for Research dietary analysis software application (University of Minnesota); (3) the Harvard School of Public Health Nutrition Department file download site, available at https://regepi.bwh.harvard.edu/health/nutrition.html; and (4) the Wake Forest Baptist Health website, available at http://www.wakehealth.edu/Urology/Kidney-Stones/Oxalate-Content-of-Foods.htm

Data for the oxalate content of foods is highly variable depending on the source of the data. In a comparison of the oxalate content of 522 foods (Penniston et al. data unpublished) between the Nutrition Data System for Research software and the list maintained on the Harvard School of Public Health website (sources cited above), food oxalate values differed significantly ($P = 0.048$). The difference was much higher for ready-to-consume breakfast cereals ($P < 0.001$). The mean difference in oxalate content for a standard serving size of all foods was 8.6 mg. However, the highest difference between the two sources was 352 mg. When examining only foods with ≥25 mg oxalate per standard serving, the mean difference between the two sources was 39 mg. When examining only foods with ≥40 mg oxalate per standard serving, the mean difference was 63 mg

**Table A6.2** Foods with little to no oxalate per serving. Some foods are commonly cited as having a "high" oxalate content but actually have little to no oxalate per standard serving size according to reputable sources. The foods in the table below have ≤4 mg oxalate per standard serving size; many have <1 mg/serving

| |
|---|
| *Beverages* |
| • Beer |
| • Coffee |
| • Soda (cola) |
| • Soy milk |
| *Condiments* |
| • Catsup/ketchup |
| • Mustard, yellow |
| • Salsa |
| • Soy sauce |
| *Fruits* |
| • Blackberries |
| • Blueberries |
| • Cranberries |
| • Fruit cocktail |
| • Strawberries |
| *Vegetables* |
| • Broccoli |
| • Green peppers |
| • Kale |
| • Lettuce, iceberg |
| • Lettuce, romaine |
| • Mustard greens |
| • Red peppers |
| • Zucchini |

Data from https://regepi.bwh.harvard.edu/health/nutrition.html and http://www.wakehealth.edu/Urology/Kidney-Stones/Oxalate-Content-of-Foods.htm, accessed January 5, 2017

# Appendix 7 Description of Vegetarian Diets

| Name of diet | Does consume | Does not consume |
|---|---|---|
| Vegetarian ("umbrella" term for someone who consumes plant foods of all kinds) | – Plant foods and plant by-products of all kinds (i.e., vegetables, fruit, nuts, seeds, legumes, and grains) | Tissue (flesh) from any mammal, fowl, fish, or marine invertebrate |
| | – May or may not consume animal by-products[a] | |
| Flexitarian (or part-time vegetarian) | – Plant foods and plant by-products of all kinds | |
| | – Occasional meat, eggs, and/or dairy | |
| Lacto-ovo vegetarian | – Plant foods and plant by-products of all kinds | – Tissue from any mammal, fowl, fish, or marine invertebrate |
| | – Dairy and dairy products[b] | – Meat by-products[c] |
| | – Eggs and egg products[d] | |
| Lacto-vegetarian | – Plant foods and plant by-products of all kinds | – Tissue from any mammal, fowl, fish, or marine invertebrate |
| | – Dairy and dairy by-products[b] | – Meat by-products[c] |
| | | – Eggs (may or may not eat egg products[d]) |
| Ovo-vegetarian | – Plant foods and plant by-products of all kinds | – Tissue from any mammal, fowl, fish, or marine invertebrate |
| | – Eggs and egg by-products[d] | – Meat by-products[c] |
| | | – Dairy (may or may not eat dairy by-products[b]) |
| Pescetarian (or pesca-vegetarian) | – Plant foods and plant by-products of all kinds | – Tissue from any mammal, fowl, fish, or marine invertebrate |
| | – Fish and/or seafood | – Meat by-products[c] |
| | | – Dairy (may or may not eat dairy by-products[b]) |
| | | – Eggs (may or may not eat egg products[d]) |

(continued)



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| Name of diet | Does consume | Does not consume |
|---|---|---|
| Pollotarian (or pollo-vegetarian) | – Plant foods and plant by-products of all kinds | – Tissue from any mammal, fowl, fish, or marine invertebrate |
| | – Poultry, fowl, and eggs | – Meat by-products[c] |
| | | – Dairy (may or may not eat dairy by-products[b]) |
| Vegan | – Plant foods and plant by-products of all kinds | – Tissue from any mammal, fowl, fish, or marine invertebrate |
| | | – Animal by-products of any kind[a] |
| Beegan | – Plant foods and plant by-products of all kinds | – Tissue from any mammal, fowl, fish, or marine invertebrate |
| | – Honey | – Meat by-products[c] |
| | | – Dairy and dairy by-products[b] |
| | | – Eggs and egg by-products[d] |
| Raw vegan | – Plant foods and plant by-products but largely uncooked (sprouted grains allowed) | – Cooked foods of any kind (though the degree of uncooked foods allowed varies from 75% to 100%) |
| | | – Tissue from any mammal, fowl, fish, or marine invertebrate |
| | | – Animal by-products of any kind[a] |

[a]Animal by-products include eggs, dairy, honey, and meat by-products
[c]Dairy by-products include butter, cream, sour cream, and cheeses
[b]Meat by-products include gelatin and meat/fish broths
[d]Egg by-products include liquid, frozen, and dried egg products and also foods with eggs as ingredients (e.g., mayonnaise, baked goods)

# Appendix 8 Food Sources of Calcium

The table lists foods providing at least 100 mg of calcium per standard serving

| Food | Serving size and preparation | Calcium (mg) |
|---|---|---|
| Sardines (canned with bones) | 3 oz | 320 |
| Mustard spinach, chopped | 1 cup, raw | 315 |
| Calcium-fortified nondairy milks (brands vary) | 8 oz | 300–450 |
| Calcium-fortified orange or other fruit or vegetable juices (brands vary) | 6 oz | 300–375 |
| Dairy milk (includes buttermilk, eggnog) | 8 oz | 300 |
| Skim milk powder | ¼ cup | 290 |
| Sesame seeds, whole, roasted | 1 oz | 280 |
| Ricotta cheese[a] | ½ cup | 260 |
| Calcium-fortified ready-to-consume breakfast cereals (variable) | ½ to 1 cup | 250–1,000 |
| Tofu processed with calcium (variable) | 4 oz | 250–800 |
| Hard cheeses[a] (cheddar, swiss, gouda) | 1-½ oz | 250–310 |
| Salmon (canned with bones) | ½ can | 230 |
| Soft and semisoft cheeses[a] (mozzarella, camembert, feta) | 1-½ oz | 200–330 |
| Turnip greens, cooked from raw | ½ cup, cooked | 190 |
| Black-eyed peas, canned | ½ cup | 185 |
| Pudding made with milk | ½ cup | 150–200 |
| Pizza made with cheese,[a] regular crust | 1 slice | 200 |
| Salmon (canned with bones) | 3 oz | 180 |
| Soup[a] made with milk | 1 cup | 175–200 |
| Molasses, blackstrap | 1 tablespoon | 170 |
| Macaroni and cheese[a] | 1 cup | 160 |
| Figs, dried and uncooked | ½ cup, uncooked | 150 |
| Sesame tahini | 2 tablespoons | 130 |
| Seaweed | 1 cup, raw | 125 |

(continued)



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| Food | Serving size and preparation | Calcium (mg) |
|---|---|---|
| Shrimp (canned) | 3 oz | 125 |
| Turnip greens | ½ cup, cooked | 120 |
| Cowpeas | ½ cup, cooked | 105 |
| Kale, chopped | 1 cup, raw | 100 |

Data are from the USDA Food Composition Databases available at https://ndb.nal.usda.gov/ndb/ (accessed January 5, 2017) and from the Agricultural Research Service (ARS) Nutrient Database for Standard Reference, release 17, available at https://health.gov/dietaryguidelines/dga2005/document/html/appendixb.htm, Accessed December 31, 2016

[a]High in salt (sodium chloride)

# Appendix 9 Food Sources of Magnesium

The table lists foods providing at least 100 mg of magnesium per standard serving

| Food | Serving size and preparation | Magnesium (mg) |
|---|---|---|
| Seeds (pumpkin, squash), whole kernels | 1 oz, roasted | 151 |
| Brazil nuts, whole | 1 oz | 107 |
| 100% bran cereal, ready-to-eat | 1 oz | 103 |
| Halibut | 3 oz, cooked | 91 |
| Quinoa | ¼ cup, dry | 89 |
| Spinach, canned | 1/2 cup | 81 |
| Almonds, whole | 1 oz | 78 |
| Spinach, fresh | ½ cup, cooked | 78 |
| Cashews, whole | 1 oz, dry roasted | 74 |
| Soybeans, mature | ½ cup, cooked | 74 |
| Pine nuts, dried | 1 oz | 71 |
| Mixed nuts, with peanuts | 1 oz, oil roasted | 67 |
| White beans, canned | ½ cup | 67 |
| Pollock, walleye | 3 oz, cooked | 62 |
| Black beans | ½ cup cooked | 60 |
| Bulgur | ¼ cup, dry | 57 |
| Oat bran, raw | ¼ cup, dry | 55 |
| Soybeans, green | ½ cup, cooked | 54 |
| Tuna, yellowfin | 3 oz, cooked | 54 |
| Artichoke hearts | ½ cup, cooked | 50 |
| Peanuts | 1 oz, dry roasted | 50 |
| Lima beans, baby, from frozen | ½ cup, cooked | 50 |

[a]Data are from the Agricultural Research Service (ARS) Nutrient Database for Standard Reference, release 17. Available at https://health.gov/dietaryguidelines/dga2005/document/html/appendixb.htm, accessed December 31, 2016



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# Appendix 10 Food Sources of Sodium

The table lists foods particularly rich in sodium per standard serving

| Food | Serving size and preparation | Sodium (mg) |
|---|---|---|
| Salt, table | 1 teaspoon | 2,325 |
| Submarine sandwich with processed meats | 1 sandwich, 6″ roll | 1,651 |
| Sauerkraut, canned | 1 cup, solids and liquids | 1,560 |
| Potato salad, homemade | 1 cup | 1,323 |
| Bacon cheeseburger on a bun | 1 sandwich, with condiments | 1,314 |
| Tomato sauce, canned | 1 cup | 1,284 |
| Baking soda | 1 teaspoon | 1,259 |
| Cured ham | 3 oz, roasted | 1,128 |
| Baked beans, canned, with meat | 1 cup | 1,106–1,114 |
| Macaroni and cheese, canned | 1 cup | 1,061 |
| Salted fish (cod, mackerel), canned anchovy | 1 oz | 1,030–1,970 |
| Cottage cheese, 1 and 2% | 1 cup | 918 |
| Soy sauce | 1 tablespoon | 900–1,100 |
| Salami, beef and pork | 2 slices (about 55 oz), cooked | 820 |
| Pretzels, hard, salted | 10 (about 60 oz) | 814 |
| Soups, canned | 1 cup | 600–1,000 |
| Bacon, cooked | 2 slices | 600 |
| Frozen entrée, variety of major brands | 1 meal | 500–2,500 |
| Bread, pita, white | 6½″ pita | 322 |
| Vegetables, canned with salt | 1 cup | 300–800 |
| Buttermilk | 8 fluid ounces | 257 |
| Bagel, English muffin | 4″ bagel or 1 muffin | 215–400 |
| Pizza, with cheese and toppings, variable crust thickness | 1 slice | 200–1,300 |

(continued)


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| Food | Serving size and preparation | Sodium (mg) |
|---|---|---|
| Breads, rolls, biscuits, muffins | 1 slice or serving | 200–500 |
| Luncheon meats, packaged | 1 oz | 200–400 |
| Snacks (potato chips, corn chips, salted nuts) | 1 oz | 200–300 |
| Catsup/ketchup, barbecue sauce | 1 tablespoon | 165–400 |
| Cheeses, various types | 1 oz | 150–450 |
| Salad dressings, creamy types | 1 tablespoon | 100–250 |
| Cereals, ready-to-consume | ¾ to 1 cup | 0–350 |

Data are from the Agricultural Research Service (ARS) Nutrient Database for Standard Reference, release 17, available at https://health.gov/dietaryguidelines/dga2005/document/html/appendixb.htm, Accessed December 31, 2016

# Appendix 11 Food Sources of Phytate

The table lists foods rich in phytate per standard serving (>650 mg/serving)

| Food | Serving size and preparation | Phytate (mg) |
|---|---|---|
| Soybeans, mature seeds, raw | ½ cup | 2,438 |
| Wild rice | ½ cup | 1,936 |
| Cashew nuts | ½ cup | 1,306 |
| Hickory nuts | ½ cup | 1,260 |
| Brazil nuts | ½ cup | 1,259 |
| Walnuts, black, shelled | ½ cup | 1,226 |
| Corn germ flour | ½ cup | 1,024 |
| Soy flour | ½ cup | 958 |
| Filberts (hazelnuts), shelled, chopped | ½ cup | 956 |
| Almonds | ½ cup | 909 |
| 100% bran cereal, ready-to-eat | 1 oz (about ½ cup) | 887 |
| Peas, dried, raw | ½ cup | 851 |
| Soy isolate | ½ cup | 844 |
| Wheat bran, crude | 1 oz | 843 |
| Black-eyed peas, dried, raw | ½ cup | 815 |
| Pecans, shelled | ½ cup | 793 |
| Corn meal | ½ cup | 754 |
| Chickpeas (garbanzo beans), raw | ½ cup | 730 |
| Split peas, dry | ½ cup | 664 |

Data are from Barbara F. Harland. Table A.7: phytate content of foods. In: Spiller GA editor. CRC Handbook of Dietary Fiber in Human Nutrition. 3rd ed. Boca Raton, FL: CRC Press; 2001. p 673–680



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# Appendix 12 Food Sources of Potassium

The table lists foods providing at least 375 mg potassium per standard serving

| Food | Serving size and preparation | Potassium (mg) |
|---|---|---|
| Potato, baked, flesh, and skin | 1 medium | 1,081 |
| Plantain | 1 medium, raw | 893 |
| Sweet potato, with skin | 1 medium, baked | 694 |
| Beans (white, soy, lima, pinto, kidney, navy, split pea, great northern, refried) | 1 cup, cooked | 700–1,180 |
| Beet greens | 1 cup, cooked | 655 |
| Cabbage, Chinese | 1 cup, cooked | 631 |
| Papaya | 1 medium, raw | 553 |
| Fish (halibut, salmon, Pacific rockfish, haddock, cod, swordfish, tuna) | 4 oz, cooked | 530–610 |
| Tomato puree, sauce, juice, or paste (canned) | ¾ cup | 530–1,330 |
| Beets | 1 cup, cooked | 519 |
| Prune juice, carrot juice, canned | 6 oz | 515–530 |
| Molasses, blackstrap | 1 tablespoon | 498 |
| Orange juice, raw or chilled ready-to-consume | 8 oz | 450–495 |
| Vegetables (Brussels sprouts, squash, artichokes, broccoli) | 1 cup, cooked | 450–495 |
| Winter squash | ½ cup, cooked | 448 |
| Banana | 1 medium, raw | 422 |
| Spinach | ½ cup, cooked | 419 |
| Yogurt, various brands | 8 oz | 400–575 |
| Peaches, dried | ¼ cup, uncooked | 398 |
| Prunes | ½ cup, stewed | 398 |
| Milk, non- and low-fat | 8 fluid ounces | 382–400 |
| Pork chop, center loin | 3 oz, cooked | 382 |
| Apricots, dried | ¼ cup, uncooked | 378 |
| Rainbow trout, farmed | 3 oz, cooked | 375 |

Information compiled from the USDA nutrient database, available at http://ndb.nal.usda.gov/ndb/nutrients/index (Accessed January 4, 2017)


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# Appendix 13 Potential Renal Acid Load of Foods

The table lists food groups and their average potential renal acid load (PRAL)

| Food group | Serving size used for PRAL calculation | Average calculated PRAL/ serving (mEq) |
|---|---|---|
| Meat, poultry | About 4 oz | 9.5 |
| Fish | About 4 oz | 7.9 |
| Flour, from various grains | 1 cup, dry | 7.0 |
| Spaghetti, noodles | About ¾ cup, cooked | 6.7 |
| Cheeses with high-protein content[a] | 1 oz | 5.9 |
| Breads, bagels, muffins, rolls | About 3½ oz | 3.5 |
| Cheeses with lower protein content[b] | 1 oz | 2.0 |
| Yogurt, milk | 1 cup | 1.0–2.4 |
| Vegetables | About ½ cup | −2.8 |
| Fruits | 1 piece or about ¾ cup | −3.1 |

Data adapted to table from Remer T, Manz F: Potential renal acid load of foods and its influence on urine pH. J Am Diet Assoc 1995;95:791–7. Note that the PRAL values for individual foods within groups vary greatly; values in the table are averages per group

The higher (more positive) the number for PRAL, the higher its acid load; negative values represent alkaline potential

[a]Examples of high-protein cheeses, providing 7–10 g protein per 1 oz serving, include parmesan, edam, Romano, cheddar, mozzarella (part skim milk), Swiss, and Colby

[b]Lower-protein cheeses include blue, camembert, feta, cottage cheese, and cream cheese



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# Appendix 14 Foods Rich in Organic Acids

The table lists foods with relatively high concentrations of polycarboxylic organic acids[1] that are bicarbonate precursors when ingested in their non-protonated form, though is some evidence to suggest alkalinization and citraturic effects from ingestion of polycarboxylic acids in the protonated state.[2] Acids with 2 Xs indicate a higher relative prevalence than those with a single X. The table does not show all of the organic acids in the foods listed.

| Food | Malic acid | Citric acid | Tartaric acid | Succinic acid |
|---|---|---|---|---|
| Bananas | XX | XX | X | |
| Limes | XX | XX | X | |
| Tomatoes | XX | XX | X | X |
| Apricots | XX | XX | | |
| Beans | XX | XX | | X |
| Broccoli | XX | XX | | X |
| Carrots | XX | XX | | X |
| Cranberries | XX | XX | | |
| Pineapple | XX | XX | | |
| Potatoes | XX | XX | | |
| Rhubarb | XX | XX | | |
| Grapes | XX | X | XX | |
| Cherries | XX | X | X | X |
| Pears | XX | X | X | |
| Apples | XX | X | | X |
| Blackberries | XX | X | | |
| Currants | X | XX | XX | X |
| Grapefruit | X | XX | X | |
| Lemons | X | XX | X | |
| Blueberries | X | XX | | |
| Boysenberries | X | XX | | |
| Elderberries | X | XX | | |
| Figs | X | XX | | |
| Gooseberries | X | XX | | |
| Oranges | X | XX | | |

(continued)



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| Food | Malic acid | Citric acid | Tartaric acid | Succinic acid |
|---|---|---|---|---|
| Strawberries | X | XX | | X |
| Plums | X | | X | |
| Nectarines | X | | | |
| Peaches | | X | XX | |
| Bilberries | | X | | |
| Kiwi | | X | | |
| Kumquats | | X | | |
| Raspberries | | X | | |
| Tangerines | | X | | |
| Avocadoes | | | XX | |
| Passionfruit | | | XX | |
| Peas | | | XX | |

[1]Data for relative concentration of organic acids are from https://www.indigo.com/documents/File/Natural%20Acids%20of%20Fruits%20and%20Vegetables.pdf, accessed January 5, 2017

[2]Rodgers AL, Webber D, de Charmoy R, Jackson GE, Ravenscroft N: Malic acid supplementation increases urinary citrate excretion and urinary pH: implications for the potential treatment of calcium oxalate stone disease. J Endourol 2014;28:229–36

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