Dietary Botanicals and Supplements

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15.1 Introduction

Dietary supplements are recognized by the federal government as products intended for ingestion that add value to a person's diet. Examples of dietary supplements include vitamins, minerals, and herbs [1]. Such supplements are regulated under the law differently than pharmaceuticals. Like pharmaceuticals, dietary supplements are required to accurately list their ingredients, provide an expiration date, and be made under good manufacturing conditions. Dietary supplements, however, do not have to prove their efficacy before being sold on the market, nor do they need a prescription [1]. Many Americans take supplements, including the geriatric population [2], so it is important that healthcare providers be prepared to give accurate advice on dietary supplements. Given that supplements are less regulated, but patients are using them, it behooves the physician who cares for elderly patients to know the clinical research on dietary supplements.

Acting as a guide for the patient in using dietary supplements safely requires similar knowledge as in prescribing pharmaceuticals, namely, understanding mechanism of action, indications, contraindications, interactions, and adverse effects. However, due to both the different process of governmental regulation and differences in supplements themselves, there are other things to consider when helping patients choose dietary supplements wisely. This chapter will illustrate both the commonalities with prescribing pharmaceuticals and unique challenges and benefits that dietary supplements can provide.

As stated above, the FDA requirement of proof of efficacy that is needed for pharmaceuticals does not exist for dietary supplements. However, there is significant research that has been done on numerous dietary supplements, which are highlighted below. This also illustrates the first principle of dietary supplement evaluation: the onus is on the medical provider to identify the research that is available on a given dietary supplement. In addition to sources such as Ovid or PubMed, two other sources provide data on dietary supplements: the Natural Medicines Comprehensive Database and American Botanical Council, both online resources that identify clinical studies and basic science research.

Once efficacy is identified for a specific dietary supplement, then quality issues need to be assessed. This includes standardization of a dietary supplement over time and from lot to lot. That is, does the specific dietary supplement contain *what it says it does* on the label, and are the ingredients clearly stated? An example of a transparent label is presented in Fig. 15.1 for fish oil.

One way to assess the quality of a dietary supplement is to look at third-party testing. For example, an independent organization that tests supplements' quality is ConsumerLab.com [3]. ConsumerLab.com summarizes scientific research on supplement efficacy and identifies specific supplements that have similar ingredients to those used in clinical trials. In addition, they perform testing on specific brands and then publish if the amounts found in the dietary supplement match what is posted on the label. They will often also evaluate other quality markers for a supplement, such as the level of PCBs (an industrial pollutant) that is found in a given lot of fish oil. Another third-party certification is by NSF and USP labeling program – finding either of these labels on a supplement bottle indicates that the supplement manufacturer has been evaluated and found to have good manufacturing practices, i.e., practices that are designed to produce standardized and quality supplements [4, 5]. Medical providers need to know not only the clinical research for a given dietary supplement but also the available specific products on the market that match the researched supplements.

This process of vetting a specific dietary supplement and then being transparent with the patient can be outlined in a few steps:

1. Identifying and summarizing clinical outcome studies on the beneficial effects of a dietary supplement for a specific indication
2. Identifying in those same studies how the supplement was processed
3. Identifying that the supplement is safe for the patient to take, specifically making sure to:
   (a) Avoid a supplement that would have significant supplement/pharmaceutical interaction.
   (b) Avoid a supplement that would be unsafe for the patient's specific clinical condition.

Supplement Facts

Serving Size: **2 Soft Gels**

Amount Per Serving		% Daily Value*
Calories	10	
Calories from fat	10	
Total Fat	1.0 g	2%
Saturated Fat	0 g	0%
Trans Fat	0 g	†
Total Omega-3s	715 mg	†
EPA (Eicosapentaenoic Acid)	195 mg	†
DHA (Docosahexaenoic Acid)	390 mg	†
Other Omega-3s	130 mg	†

* Percent Daily Values are based on a 2,000 calorie diet.
† Daily Value not established.
Less than 5 mg of Cholesterol per serving.
Contains less than 2% of the Daily Value of vitamin A.

Ingredients: algal oil (marine algae oil [Schizochytrium sp.], high-oleic sunflower oil, rosemary extract, natural mixed tocopherols, ascorbyl palmitate), soft gel capsule (modified cornstarch, glycerin, carrageenan, sorbitol, water, carob color). No gluten, milk derivatives, or artificial colors or flavors.

Fig. 15.1 Nordic natural fish oil label. *Example of transparent fish oil label. Note that dietary supplements dosages are described in "serving size." The relevant ingredients for fish oils are listed as a total of 585 milligrams of EPA and DHA combined, in two tablets*

4. Finding that same supplement on the market in one or more brands that are available for purchase
5. Communicating that product information, along with indication to the patient, with the following information:
   (a) Dosing information.
   (b) Duration of time to take the supplement.
   (c) Any significant adverse interactions of which the patient should be aware.
   (d) Any monitoring labs that may need to be done while taking the supplement.
   (e) Given that insurance coverage for dietary supplements is variable, and generally doesn't exist, a comment on cost of the supplement is helpful for the patient.
   (f) Being aware of reputable places a patient can purchase the supplement.
6. Documenting the dietary supplement in the medical record and documenting the information given to the patient

Dietary supplement information can be provided in handouts to the patient at the end of the visit. The authors utilize a common electronic medical record (EMR) and have it printed out in the patient instruction section of the after-visit summary (AVS). In addition, dietary supplement recommendations, once vetted, can then be archived as "smartphrases" for quick reference and quick insertion into a patient's chart. See Fig. 15.2 for an example showing the directions for fish oil in the treatment of elevated triglycerides, given to the patient in an AVS.

This general process of dietary supplement guidance applies regardless of the patient's clinical condition or age. In the geriatric population, however, special attention needs to be paid to supplement/pharmaceutical interactions, given the polypharmacy that an elder patient may be using. In this chapter, various dietary supplements with evidence for use in the geriatric population will be discussed, using the principles of efficacy and quality described above. These are brief highlights only – always refer to references for more detail, especially relating to contraindications and interactions.

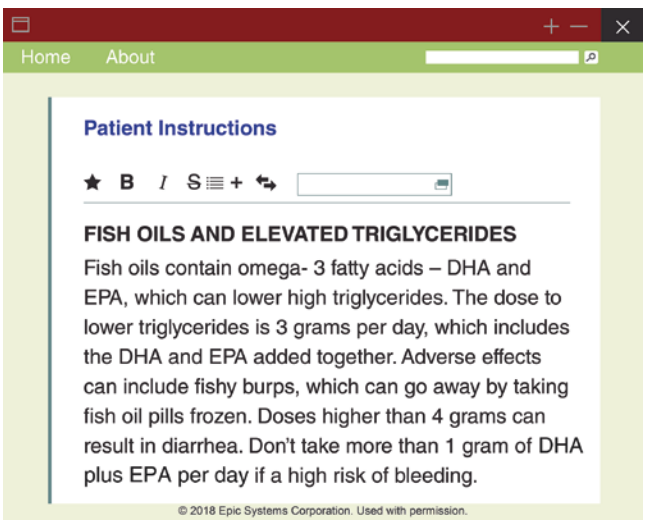

Fig. 15.2 Screenshot of EPIC after-visit summary with fish oil instructions for treating hypertriglyceridemia

15.2 St. John's Wort

Background *Hypericum perforatum* is an herb that has been extensively studied for depression in the adult population, including in the elderly. Aerial parts of the plant (leaves, stems, flowers) have been processed to create an herbal extract that then has been consumed in pill form. The mechanism of action for St. John's wort (SJW) has not been fully elucidated, but is believed to involve reduction of monoamine uptake in the synapses, thus allowing for increased availability of serotonin, dopamine, and norepinephrine [6]. There is also evidence indicating a role in modulating cortical plasticity [7]. Given that SJW contains various compounds with possible effects, multiple mechanisms of action are likely.

Indication SJW has been demonstrated to benefit patients with mild to moderate major depression in adults [8]. It appears not to be efficacious for severe major depression and appears to have potency similar to the conventional selective serotonin reuptake inhibitor (SSRI) antidepressants. One of the extracts found to be beneficial is an extract called WS 5570, described further below.

Studies focusing specifically on the elderly have not been as extensive as the overall adult population looking at St. John's wort, but those smaller studies have shown consistent efficacy and no special risk in the elderly [9, 10]. *SJW neither has mechanisms of action suggesting risk in elders, for example, it doesn't provide anticholinergic effect, nor has there been clinical adverse effects to suggest that it would be contraindicated or unsafe in the elderly.*

Dosing/practical considerations In an effort to provide standardization and quality for herbs, herbal extracts can be standardized to specific markers. For instance, a typical St. John's wort (SJW) extract found to be beneficial for depression has been standardized to 3–6% hyperforin and 0.12–0.28% hypericin content [11]. One such extract has been named WS 5570 in the literature. It is important to note that the hyperforin and hypericin content are not the active ingredients per se in SJW – standardization is simply used as a marker of quality. Total daily doses for efficacy range from 500 mg to 1200 mg. It has been studied at a dose of 300 mg three times a day, but a reasonable approach to recommending it would be to suggest starting at 300 mg daily and then titrating up to the maximum dose as needed for effect as a once-a-day dose, avoiding a thrice-daily administration, if possible. Like the SSRIs, SJW will take some time to have effect, and so patients should be followed closely in the first few weeks after starting the supplement and then evaluated for full clinical effect in 4–6 weeks.

Herein lies an illustration of how an herbal supplement must be understood differently from a pharmaceutical. St. John's wort is processed to be standardized to the hyperforin or hypericin content, but as such is not processed to be *one simple compound.* This lies in contrast to pharmaceuticals like metoprolol, a common beta-blocker, for example. Metoprolol is a single compound that accounts for its clinical

efficacy. SJW (and other herbal supplements) has multiple compounds that can have a role in its activity.

Adverse Effects The Cochrane review demonstrated less dropouts during the studies than conventional pharmaceuticals, and its overall side effect profile was better than placebo. Gastrointestinal complaints, restlessness, and sedation have rarely been observed, but not at rates above placebo. Rare allergic reactions and photosensitivity also need to be monitored [10]. Given the concerns for adverse effects in the elderly population, i.e., avoiding medicines on the Beers list, it is reassuring that St. John's wort is well tolerated.

Interactions St. John's wort does have significant drug-herb interactions. SJW is a known inducer of the cytochrome enzymes, specifically P450 3A4, 2C19, and possibly 2E1 [10, 12]. In addition, it can have an effect on p-glycoprotein. All of these effects mean that SJW carries a strong risk of affecting serum levels of some common pharmaceuticals. A table listing those medicines with common indications is below (Table 15.1).

Clinical adverse effects from these interactions have been documented [12], illustrating the importance of open dialog with elderly taking supplements as well as documenting their use in the medical record, especially if there is polypharmacy.

Summary St. John's wort appears efficacious and safe in the geriatric population for the treatment of mild to moderate major depression. The adverse effect profile appears safe and without special concern in the geriatric population. However, its use in any patient with polypharmacy should be very carefully studied or avoided altogether.

Table 15.1 SJW interactions

Pharmaceutical	Category
Oral contraceptives	Anti-conception agents
Fexofenadine	Antihistamine
Indinavir	Anti-HIV agent
Nevirapine	Anti-HIV agent
Ritonavir	Anti-HIV agent
Dextromethorphan	Antitussive
Erythromycin	Antibiotic
Digoxin	Cardiovascular agent
Nifedipine	Cardiovascular agent
Alprazolam	Central nervous system agent
Amitriptyline	Central nervous system agent
Bupropion	Central nervous system agent
Buspirone	Central nervous system agent
Carbamazepine	Central nervous system agent (anti-seizure)
Midazolam	Central nervous system agent (benzodiazepine)
Methadone	Central nervous system agent (opiate)
Cimetidine	Digestive agent (H2 blocker)
Omeprazole	Digestive agent (proton-pump inhibitor)
Finasteride	Genitourinary agent
Cyclosporin	Immunosuppressive agent
Tacrolimus	Immunosuppressive agent
Theophylline	Pulmonary agent
Fluoxetine	SSRI
Atorvastatin	Statin
Simvastatin	Statin

Source: Knuppel [13], Shi [12]

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15.3 *Ginkgo biloba*

Background *Ginkgo biloba* is a tree native to Southeast Asia and has been cultivated in Europe and North America. Traditionally, the nuts were used for food, while the leaves were cultivated for medicinal purposes. The leaves contain the following classes of ingredients: (1) ginkgo flavonoids; (2) diterpenes called ginkgolides; and (3) bilobalide, a sesquiterpene [14]. Like St. John's wort described above, ginkgo has multiple compounds that may account for its beneficial actions. Specifically, extracts of the leaves have evidence for treatment of dementia when standardized to 22–27% ginkgo flavonoids and contain less than 5 ppm of ginkgolic acids [15]. This extract has been identified as EGb 761. The mechanism of action for its effect in dementia treatment includes:

- Improving and preserving mitochondrial function and energy metabolism
- Promoting hippocampal neurogenesis and neuroplasticity
- Enhancing cerebral blood flow by decreasing blood viscosity [16, 17]

Indication *Ginkgo biloba* EGB 761 has benefits in the treatment of both vascular dementia and Alzheimer's dementia. A Cochrane review in 2008 expressed concern about poorly designed studies and thus lack of proven effect for ginkgo [18]. However, more recent reviews demonstrate clear benefit of *Ginkgo biloba* EGB 761 in mild to moderate dementia [10, 17, 19]. In dementia patients, *Ginkgo biloba* EGB 761 improves nighttime behavior and sleep issues such as irritability, anxiety, depressive symptoms, and apathy as well as activities of daily living (ADLs) [19]. This may result in less caregiver's distress, a common problem in caring for patients with dementia. It did not appear to have an effect on psychotic symptoms, however [20].

Dosing/practical considerations For dementia, total daily dose of 240 mg of the EGB 761 extract, requiring 20 weeks for efficacy to be apparent. Though helpful for treatment of dementia, it does not have evidence for prevention of dementia [18, 21].

Adverse effects *Ginkgo biloba* is generally well tolerated in studies, with adverse effects being generally mild, such as headache or dizziness. Most studies did not see any difference in adverse effect from placebo [15]. As mentioned above, there is a postulated mechanism of decreasing blood viscosity for ginkgo, but *Ginkgo biloba* EGB 761 does not appear to affect platelet function [22]. There have been case reports associating ginkgo with GI bleeds, intracranial bleeds, and postoperative bleeding [22]. In some of these case reports, patients were also taking antiplatelet agents or anticoagulants. Increased bleeding risk as an adverse effect was not generally seen in the studies of ginkgo, and a meta-analysis did not show increased risk of bleeding nor change in bleeding parameters in patients taking *Ginkgo biloba* EGB 761 [22].

Interactions There are some concerns about drug-supplement interactions with ginkgo. Some concerns about interactions can be summed up:

- The bleeding risk – while bleeding risk has not been clearly proven in ginkgo, it is prudent to avoid ginkgo patients who are on anticoagulant medications, such as Coumadin or direct-acting oral anticoagulants (DOACs).
- An interaction with alprazolam has been documented, where levels were decreased of the medication while taking ginkgo [23].
- Some decreased plasma concentrations were seen of atorvastatin and simvastatin while taking *Ginkgo biloba*, but did not translate into changes in their cholesterol-lowering ability [24, 25].

Summary *Ginkgo biloba* has shown efficacy in treating mild to moderate dementia, when taken as the extract EGB 761. This beneficial effect has been seen in both vascular and Alzheimer's dementias. Adverse effects are minimal, though it is prudent to avoid its use in patients with bleeding risk, as well as those taking anticoagulants.

15.4 Probiotics

Background Probiotics are microorganisms that add a health benefit to the host when ingested, as defined by the World Health Organization [26]. The human gut microbiome consists of approximately 10^{14} microbes, which actually outnumber the number of human cells in the body, and can comprise 1000 different species [27]. It is now known that the gut microbiome plays various roles in human health and that the biome can be influenced by various factors, such as diet, physiologic GI factors, and antibiotics [27]. The addition of probiotics, or "good" bacteria and yeast, is a means to contribute beneficially to this microbiome. The genera most commonly found to be of benefit include *Saccharomyces*, Bifidobacterium, and *Lactobacillus* [26]. Bifidobacterium and *Lactobacillus* are genera of bacteria, while *Saccharomyces* comprise beneficial fungus or yeast. In addition, they rarely cause any clinical disease [28]. These microorganisms provide various clinical improvements, and not just in GI disease. In a general sense, the microbiome has been identified as being responsible for an intact mucosal immune response [28], as the first line of protection for much of infectious etiologies. Probiotics have been identified to have various mechanisms of action, affecting the immunologic cells of the gut, improving the epithelial barrier, and affecting pathogenic bacteria. More specifically, those actions include:

- Change in interleukin IL-10 and IL-12 production
- Decrease in pro-inflammatory cytokines
- Increase in mucin production by epithelial cells
- Decrease in apoptosis and increase in regeneration of epithelial cells
- Reduction of intestinal lumen pH
- Inhibition of adhesion of pathogenic bacteria
- Secretion of bacteriocins to antagonize pathogenic bacteria [26, 28]

Figure 15.3 sums up the benefits of probiotics [26].

Indication In the geriatric population, antibiotic-associated diarrhea (AAD) and, more specifically, *Clostridium difficile* infection (CDI) are important health burdens. Elders are at risk for CDI due to decreased gastric acid secretion, increased exposure to antibiotics, waning natural defenses, and possible alterations in the microbiome [29]. In addition to responsible prescribing practices, such as good antibiotic stewardship and avoidance of unnecessary proton-pump inhibitor (PPI) prescribing, probiotics can play an important role in prevention of AAD and CDI [30, 31].

Probiotics lower risk in patients at high risk for CDI (>5%), though not clearly in patients at lower risk [31]. Given the increased risk borne by the elderly, they are likely to be of benefit. Indeed, a recent evaluation showed that probiotics given to hospitalized patients on antibiotics, over the age of 65 years and with mild increased risk of CDI (>1.6%), was a cost-effective strategy [30].

Dosing/practical considerations One of the difficulties with probiotics in clinical practice is deciding on the optimal species to use and at what dose. As mentioned above, the hallmark of the gut microbiome is diversity, and the literature reflects this diversity. Multiple species of bacteria have been studied in clinical outcomes and specifically CDI prevention. One systematic review of probiotics in AAD identified nine different bacteria studied, with several studies using a mix of probiotic bacteria genera [32]. However, some trends have begun to emerge. As mentioned above, the species of beneficial yeast *Saccharomyces boulardii* has evidence in CDI prevention. In addition, the genera *Lactobacillus* has also shown benefit, with good effect associated with species *Lactobacillus rhamnosus GG*

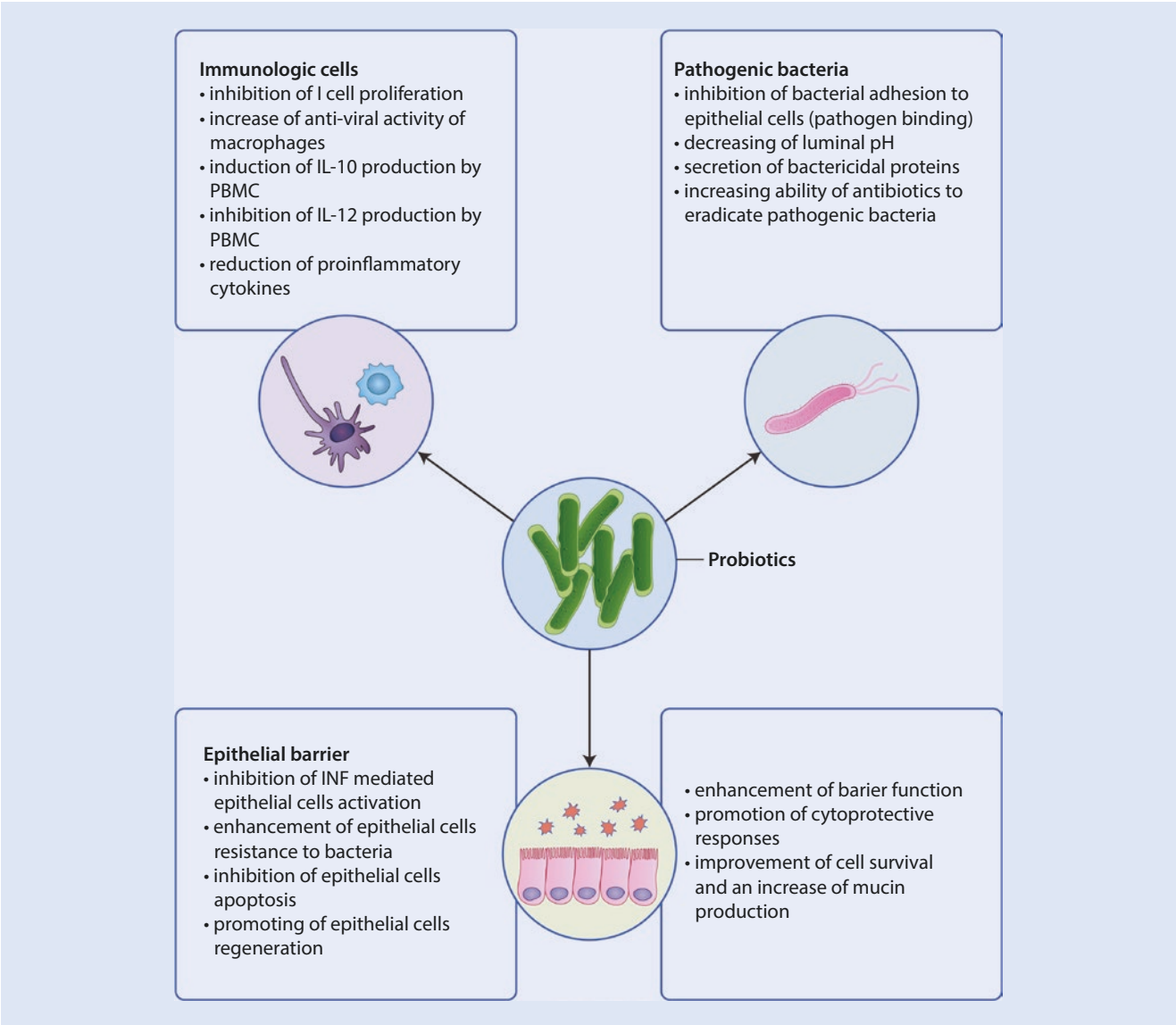

Fig. 15.3 Probiotic mechanism of action graphic. (Modified from Dylag et al. [26])

and *Lactobacillus acidophilus*. The probiotics need to be started within 2 days of initiation of antibiotics and continued for 21 days [30]. Administer the probiotics separately (>2 hours) from the antibiotics, to diminish any untoward effects of the antibiotic on the probiotic [33]. Lastly, the daily dose should be at or above a threshold of 10–20 billion colony forming units, which can be taken together or divided up twice a day.

Adverse effects The side effect profile for probiotics is generally benign – an Agency for Healthcare Research and Quality (AHRQ) study evaluated the available literature for adverse effects and found none requiring hospitalization [34]. The recent Cochrane review identified common mild side effects being equivalent to the controls and included abdominal cramping, nausea, soft stools, flatulence, and taste disturbance [31]. Contraindications for probiotics are minimal: avoid use in patients with central lines especially if immunosuppressed and also in patients who have severe pancreatitis – outcomes for patients with severe pancreatitis may worsen when given probiotics [35].

Summary *Clostridium difficile* infection is an illness that elders are at particular risk, especially when hospitalized and receiving antibiotics. Probiotics, specifically *Saccharomyces boulardii* and two *Lactobacillus* genera provide beneficial prevention for CDI. The risk profile appears low, with minimal adverse effects and very few known drug-supplement interactions.

15.5 Glucosamine and Chondroitin Sulfate

Background Glucosamine sulfate is a normal constituent of glycosaminoglycans in cartilage matrix and synovial fluid. It is believed to support the cartilage by stimulating chondrocytes

and synovial cells while inhibiting cytokines that increase inflammation via creation of COX-2. There is speculation that the sulfate moiety provides clinical benefit in the synovial fluid by strengthening cartilage and aiding glycosaminoglycan synthesis, implying that non-sulfated glucosamine forms may not be as effective; however, this is unproven. Chondroitin is a glycosaminoglycan that appears to inhibit cartilage degradation by blocking leukocyte elastase and increasing creation of hyaluronic acid. Chondroitin is usually made from bovine trachea. Glucosamine and chondroitin (GC and CS) are often used together and have often been evaluated together in studies, however their bioavailability and therefore efficacy may be improved when taken separately. Other supplements combined with GC/ and/or CS in practice and studies include methylsulfonylmethane (MSM), curcumin [36, 37], boswellia, quercetin [37], and others.

Indications Efficacy of GC/CS for the treatment of osteoarthritis (OA) is controversial, with some studies showing benefit and others no benefit, however this may be a reflection of poor bioavailability of some forms [38–41]. (Natural Medicines database, accessed 9/5/2019, lists Glucosamine sulfate as '*Likely effective*', and Chondroitin sulfate as '*Possibly effective*'). Pharmaceutical grade crystalline Glucosamine sufate, e.g. Dona brand or combination products like InvigoFlex distributed by WynnPharm (with or without Chondroitin sulfate) has the best clinical evidence, and therefore may be the preferred formulation. See: Differentiation of patented crystalline glucosamine sulfate from other glucosamine preparations will optimize osteoarthritis treatment [42]. Some major trials do suggest improvement in joint narrowing in patients with OA [43], while its ability to reduce pain in studies has been mixed [44, 45].

Doses/practical considerations Use pharmaceutical grade Glucosamine sulfate such as Dona brand. New evidence suggests that taking Glucosamine sufate and Chondroitin sulfate separately, e.g. 10–12 hours apart, may enhance their bioavailability, as opposed to the common GS/CS combinations often promoted. A "fair trial" to assess benefits in a patient with OA might be 3 months.

Adverse effects GC/CS is generally tolerated well but may occasionally cause GI upset or more rare side effects. Various theoretical concerns, such as that glucosamine might raise blood pressure or blood sugar, have not been an issue in clinical studies or experience (Natural Medicines database, accessed 9/5/19).

Contraindications/cautions Theoretical concerns that chondroitin may interfere with cell adhesion and increase prostate cancer progression, as well as a theoretical and remote concern of prion disease from diseased cow trachea, have not been demonstrated in clinical trials; nevertheless, it may be prudent to avoid chondroitin in men with prostate cancer. In addition, due to possible slight increase in eye pressure on glucosamine, patients with severe glaucoma should avoid it or have their eye pressure closely monitored (Natural Medicines database, accessed 9/5/19).

Interactions Monitor PT/INR levels in patients on warfarin and GC/GS. Other interactions are minor or theoretical (Natural Medicines database, accessed 9/5/2019).

Summary Glucosamine sulfate and chondroitin sulfate can be used safely in geriatric patients with osteoarthritis and may provide some benefit. At dosages of 1500 mg and 1200 mg daily, respectively, taken apart, the geriatric patient may be able to achieve some pain control and reduce progression of OA. This improved pain control may allow for less use of medications such as nonsteroidal anti-inflammatory drugs (NSAIDs), which carry some risk for elderly patients.

15.6 Vitamin D

Background Vitamin D (calciferol) is the name for a family of hormones/vitamins that have central roles in calcium/bone metabolism as well as modulating immune, cellular differentiation and myriad other functions. Vitamin D metabolic systems are found in virtually all organs and tissues, implying its central role in health. Typically, about 80% comes from photosynthesis, induced by direct sunlight on bare skin (however, this effect does not significantly occur through windows, sunscreen, or clothes), with the remaining 20% coming from diet [46]. Because it is a fat-soluble hormone, we can deposit it in our body's "fat depot bank" during the warmer months to be released as needed during the "vitamin D winter." This ability to store vitamin D allows us to survive at more polar latitudes and likely was a main evolutionary driver of paler skin during our species' migration out of our ancestral African home, where our normal skin color is darker to protect against damage from intense solar radiation [47]. As with most hormones, the cholecalciferol formed in the skin or absorbed from food is a pre-hormone; the body will activate this as needed in the liver and kidneys and locally in different tissues as needed to serve its functions. See Fig. 15.4 for a description of metabolism and effects of vitamin D [48, 49]. Vitamin D assessment and supplementation is often mis-interpreted and mis-applied. Generally speaking, there is little evidence that supplementing in patients who are not deficient has any clinical benefit, therefore limit supplementation to those who are clearly deficient as measured by a validated 25 (OH) Vit. D lab value. Like most nutrients, there is likely a range of of adequate levels in different individuals, e.g. a level of 15 ng/ml may be adequate for one person and mildly deficient for another. The RDA is set to cover 97.5% of the population based on present understanding of the role of Vit. D in the body, which is likely in its infancy, especially as relates to non-musculoskeletal functions of Vit. D. When to test for Vit. D deficiency is highly controversial. Routine screening is clearly not indicated, but whether to test for (and then treat if deficient) patients with various chronic diseases associated with Vit. D deficiency (causality usually unproven) is unclear. Since most chronic diseases, such as cardiovascular, metabolic, depressive, autoimmune disorders, etc. often are highly multi-factorial, it is unlikely that correcting Vit. D deficiciency per se will have a marked effect in most

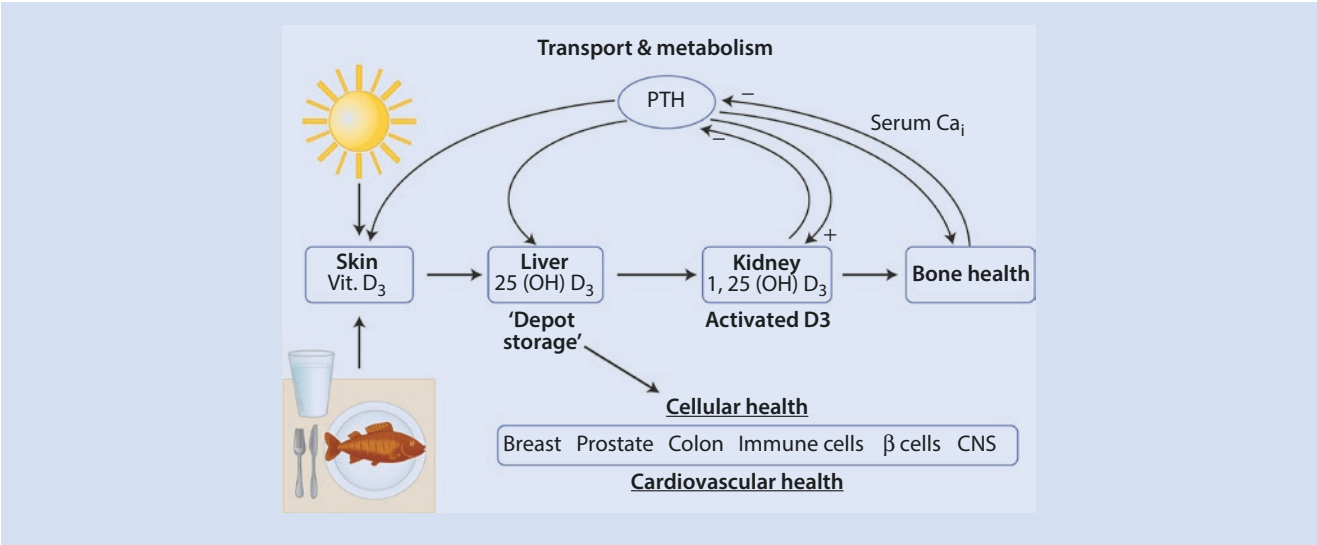

Fig. 15.4 Vitamin D graphic

cases. This is reflected in numerous randomized controlled trials with often mixed or conflicting results. But this does not imply that one should not treat clear Vitamin D deficiency, just that one should not view it as a magic bullet.

Indications Vitamin D should be given as supplementation to prevent and correct vitamin D deficiency when natural sources are difficult or impractical to obtain because of lifestyle or medical issues. Correcting deficiency is especially important if geriatric patients are suffering from disorders likely related to vitamin D deficiency such as osteoporosis and frequent unexplained falls, though it is unclear if Vitamin D supplementation by itself is effective at reducing these disorders. Vitamin D deficiency is considered the most common nutritional deficiency worldwide, probably due to indoor living styles with avoidance of sun exposure (note that *excess* sun exposure definitely is bad for the skin, including increasing risk of skin cancer). Technically, skin photosynthesis of vitamin D is optimized at 1/4 the minimal erythema (slight pinking of skin) sun exposure dose for one's skin phototype. For example, 15 minutes per day would be needed for light skin, while 45 minutes per day would be needed for very dark skin/day. This sensible dose does not appear to significantly increase skin cancer. Main dietary sources are fortified foods such as milk and fish liver oils.

Monitoring Avoid routine screening or supplementation for Vitamin D deficiency in community dwelling patients, as there is no convincing evidence of benefit in this setting. Screen for vitamin D deficiency in those at high risk, such as insufficient sun exposure, and in diseases associated with vitamin D deficiency. Such individuals include patients with the following conditions:

- Osteoporosis or osteopenia
- Frequent unexplained falls
- Severe chronic kidney disease
- Hyperparathyroidism
- Malabsorption syndromes such as after bariatric surgery
- Ingestion of medications that interfere with vitamin D

Most vitamin D deficiency is asymptomatic, though if severe can present with myalgias and osteomalacia-/osteoporosis-related symptoms in adults. Lab definitions of deficiency are somewhat variable depending on method used but are generally as follows:

- Vitamin D insufficiency (low-normal levels): 20–29 ng/ml (50–73 nmol/L). This category is controversial and considered normal by some authorities. There is little evidence that treatment or maintenance supplementation in response to a level is this range has any clinically meaningful benefit it most clinical situations. Levels in this range in the fall season (when the patient should be Vt. D replete from a warm season's worth of sunlight and is about to enter the 'Vitamin D winter' in which they cannot photosynthesize Vit. D from the sun at temperate latitudes) could be supplemented to allow a buffer zone of Vit. D stores. If the patient likely will get some sun, levels in the spring (when the patient has used up their 'Vitamin D stores') at this level may not need treatment.
- Mild deficiency: 12–19 ng/mL (30–49 nmol/L). This range may be sufficient in some individuals, but since it is not practically posible to be clear if this is sufficient or not for a given individual, treating and then putting on a maintenance dose if still at risk for Vit. D deficiency is considered reasonable by many authorities to ensure has adequate stores.
- Moderate deficiency: 5–11 ng/mL (12.5–29 nmol/L). Treat all patients, then likely put on a maintenance dose.
- Severe deficiency: <5 ng/mL (12.5 nmol/L). Treat all patients, then put on a maintenance dose.

Routine lab vitamin D screening or monitoring is not needed but can be done if concern that patient is not correcting a

deficiency or is having health issues suspected to be worsened by vitamin D deficiency, such as osteoporosis, frequent falls, and others. There is extensive literature showing associations between vitamin D deficiency and many chronic diseases (causality yet unproven), including cardiovascular disease, cancer, autoimmune diseases, worsening of various infectious diseases such as HIV and TB, asthma, hypertension, cognitive decline, depression, and many others [49].

Dose/practical considerations For prevention of vitamin D deficiency in adults at risk of deficiency, a practical dose of 1000 units/day of vitamin D3 (cholecalciferol), taken with healthy fat in a meal, is usually sufficient. This dose, while moderately above the RDA, takes into account human inconsistency in pill taking and variations in absorption, and is in the safe range. 2–3 times or occasionally even higher doses may be needed in malabsorption syndromes, morbid obesity and drug-induced Vt. D deficiencies. To treat vitamin D deficiency generally requires 50,000 units orally per week of vitamin D for 8 weeks or more, depending on the level of deficiency. As an alternative, cholecalciferol (vitamin D3) at 5000 units orally per day can be given, again for 8 weeks. If the original cause of the deficiency is likely to continue, once repletion is completed, supplement with a maintenance dose (e.g., 1000 units/daily) indefinitely is important to prevent relapse of the deficiency.

Vitamin D deficiency treatment in severe liver or kidney disease requires special considerations such as using the hydroxylated forms to compensate for the loss of natural hydroxylation in the liver and kidney.

Adverse effects Vitamin D when properly prescribed is very safe. Avoid excess doses in patients with a risk of hypercalcemia. Except in special situations, avoid excess maintenance doses above the upper tolerable limit of 4000 units/day or artificially raising the serum level above 40–60 ng/mL with supplementation.

Interactions Various medications can interfere with vitamin D absorption or metabolism and thus may require monitoring of levels and supplementation. Such medications include some anticonvulsant, anti-tuberculosis, and HIV drugs.

Summary Vitamin D is clinically relevant in the geriatric population given risks of osteoporosis, frequent falls, and related fractures as well as possible deficiencies when homebound or institutionalized. Patients at risk should be evaluated for deficiency and corrected to normal levels with oral vitamin D supplementation.

15.7 S-Adenosylmethionine (SAMe)

Background SAMe is a natural substance involved in methyl donation that is synthesized in and supports the liver, supports neurotransmitter metabolism, and may be helpful in two common problems in the elderly: depression and arthritis. There are mixed studies on antidepressant effects [50, 51, 52], Adjunctive S-adenosylmethionine (SAMe) in treating non-remittent major depressive disorder: An 8-week double-blind, randomized, controlled trial. SAMe appears to have analgesic and anti-inflammatory properties equivalent to NSAIDs, but with less side effects. It may stimulate cartilage growth helpful for joint support (preliminary evidence), with studies showing benefit for osteoarthritis of the knee, hip, hand, and spine (moderate evidence, Natural Medicines database SAMe, accessed 9/5/19).

Indications SAMe has evidence for use in three disparate clinical conditions:

1. Osteoarthritis
2. Possibly for Depression can be used as an alternative or adjunct to conventional antidepressant medications
3. Possibly as an adjunct in liver disease [53], and also in fibromyalgia [54], though the evidence is less strong than for the above two conditions

Important note For supplements not derived from plants, being cognizant of how processing occurs is still important. Here there are parallels with pharmaceuticals, where a single molecule is relevant, ensuring that such active principle is bioavailable and in correct formulation. For instance, SAMe is sensitive to heat, moisture, and stomach acid, so only use enteric-coated tablets in blister packs. In addition, SAMe products have stabilizing compounds such as tosylates, so only ~1/2 of the total ingredients of a pill are actual SAMe – it's important to verify that any formulation is delivering the actual amount of active SAMe intended. Like herbal supplements, ConsumerLab.com can be a guide on high-quality and least expensive brands. SAMe is utilized in the body with cofactors folate, B12, and B6, so consider supplementing these if there is concern of low nutritional status (ConsumerLab.com, SAMe, accessed 8/18/19).

Dose/practical considerations Doses shown to be effective, reflective of the actual SAMe component, (which can be higher than what is often listed on the bottle) for osteoarthritis are 800–1200 mg as a total daily dose, divided two to three times per day; and for depression 400–1600 mg/day, in divided doses. Again, these doses should be reflective of the actual active SAMe component taken orally, which can be higher than what is often listed on the bottle. For fibromyalgia, 800 mg/day may be helpful. It can take a few weeks for SAMe to reach its full effect, and so the provider can "front-load" the dose for quicker effect but then might increase the chance of side effects. Thus the recommendation in the elderly is to start low and gradually titrate up the dose.

Adverse effects SAMe side effects are generally minimal but at higher doses can be associated with GI upset, headache, and agitation. Counseling patients to avoid taking it in evening can help mitigate any insomnia risk. SAMe has not been found to cause weight gain or sexual dysfunction (Natural Medicines database, accessed 8/18/19).

Contraindications As SAMe may have an antidepressant effect, it should not be used in elders with bipolar disorder, as it could trigger a manic phase.

Interactions SAMe does interact with a few medications. Levodopa (L-dopa) used in Parkinson's disease treatment may deplete brain SAMe levels; thus, supplementation may improve depression in Parkinson's disease. SAMe might however decrease L-dopa effectiveness. Serotonin syndrome when combined with selective serotonin reuptake inhibitors (SSRIs) and other anti-depressants appears rare, but it is prudent to not use SAMe in patients taking monoamine oxidase inhibitors (MAOIs) (Natural Medicines database, accessed 9/5/19).

15.8 Turmeric/Curcumin

Background *Curcuma longa* is a culinary herb that, when standardized to the curcumin content, has been found to have anti-inflammatory and antioxidant properties. When turmeric is ingested in cooking, curcumin content is less, and so effects described below are in the context of more processed turmeric [55–58]. In this botanical, curcumin is believed to be the main active principle, and so here curcumin will be used when talking about medicinal benefits; turmeric is the plant from which it is derived.

Indications Curcumin has been shown to be beneficial in various conditions affecting the geriatric population. Curcumin in multiple small randomized controlled trials (mid-level evidence) demonstrates efficacy in knee osteoarthritis with preliminary evidence of benefit in other sites (e.g., hand, hip) and other forms of arthritis such as rheumatoid arthritis [57]. Benefit has been found for curcumin alone or when taken with other dietary supplements such as boswellia, glucosamine, etc. [36, 59–71]. In addition to the pain relief benefit found in arthritis, there is preliminary data that curcumin may have other beneficial effects, such as in:

- Improving the hyperlipidemia profile [58, 72]
- Decreasing progression of pre-diabetes to diabetes mellitus type 2 (DM2) [73]
- Preliminary evidence that curcumin benefits a multitude of other inflammatory conditions [58, 74, 75]

Dose/practical considerations A typical dose for the 95% curcumin standardized extract for arthritis is 500 mg three times a day. The supplement should be taken with healthy fat and black pepper (ConsumerLab.com accessed 9/5/2019) – this improves the bioavailability. Use of high bioavailable curcumin is important, since little is absorbed from the GI tract otherwise. Curcumin products complexed with piperine (the active enhancer in black pepper) are also on the market. These complexed products have better bioavailability, and so dose would be lower [55–57].

Contraindications/cautions Turmeric/curcumin generally is well tolerated. Caution the patient about theoretical increased risk of bleeding with curcumin if on anti-platelet drugs and anti-coagulants such as DOACs or warfarin, though antiplatelet agents such as aspirin probably don't need to be avoided. Patients with a history of active biliary colic should also avoid curcumin, as it can stimulate gallbladder contraction. While there is some evidence that curcumn appears to protect the liver, for example in non-alcoholic fatthy liver disease (NAFLD), there are uncommon reports of elevated liver enzymes and very rarely auto-immune hepatitis that possibly could have been due to the botanical. In addition, turmeric has small amounts of oxalates which theoretically could exacerbate risk of stone formation in patients with a history of calcium oxalate kidney stones (ConsumerLabs.com and Natural Medicines database accessed 9/5/2019).

Interactions Avoid the use of curcumin with critical drugs metabolized by the P450 3A system such as tacrolimus. Theoretically curcumin could bind iron, so monitor iron levels in those deficient or with marginal stores and take curcumin at a different time than iron supplements. Piperine extract (BioPerine) theoretically could alter some drug levels, so if it is part of the curcumin complex, take curcumin at different times from pharmaceuticals. Lastly, as mentioned above, curcumin may provide a mild hypoglycemic effect when patients are already on diabetic medications. Diabetics who opt to take this supplement should have their glucose levels closely monitored (Natural Medicines database accessed 9/5/19).

Summary Turmeric/curcumin may offer elderly patients a well-tolerated means of decreasing arthritis pain, with a safe side effect profile. It also has an intriguing anti-inflammatory profile that plays a role both in pain benefit and broader anti-inflammatory conditions. However, bioavailability can be limited without the correctly processed product, and caution should be taken with patients who are on polypharmacy.

15.9 Coenzyme Q10 (CoQ10)

Background CoQ10 is an essential cofactor in the human mitochondrial electron transport pathway that generates cellular ATP. It acts as a powerful lipid-soluble antioxidant to reduce free radical damage from this energy production. It is endogenously synthesized via the mevalonate pathway (which is blocked by statin drugs) and can also be obtained from the diet in small amounts from fish, organ meats, and wheat germ. CoQ10 is in virtually all cells, with especially high concentrations in the heart. CoQ10 levels are highest during the first 20 years of life and decline with age, so deficiency is relatively common in the elderly. Statins may aggravate this deficiency, and CoQ10 serum levels can be assessed for deficiency. It may be used with other nutrients such as selenium (Se) and other antioxidant vitamins, omega-3 fatty acids, ribose, carnitine, and taurine to support the "energy chain," especially in heart function [76–80].

Indications Ingestion of CoQ10 is helpful to prevent or correct deficiency. Its safety and freedom from drug interactions make it useful in many conditions suffered by the elderly:

- Cardiovascular disease: typically 50–200 mg per day. Preliminary to mid-level evidence supports the following benefits:
  - Coronary artery disease (CAD) – improved function and reduced cardiac events [81], reduced cardiovascular mortality in elderly with CoQ10 and selenium [82], and better lipid goals with nutraceuticals containing CoQ10 [83]. Of note, evidence is conflicting in the use of CoQ10 in prevention of statin-induced myopathy. A typical dose used in this context is 50–200 mg per day [84, 85].
  - Congestive heart failure (CHF) – mainly positive results in later trials. The Q-SYMBIO trial demonstrated improved key CHF endpoints including lower mortality, using CoQ10 100 mg TID for 2 years [86]. Other studies largely support the use in CHF, whether in preserved or reduced ejection fraction subtype [87–89].
  - CoQ10 may also decrease atrial fibrillation in heart failure [90] and may improve blood pressure in hypertensive patients, the latter through a possible related anti-inflammatory and vascular function [91].
- There is some suggestion that CoQ10 can be helpful in neurodegenerative diseases such as in Parkinson's disease. Mild cognitive impairment possibly may be improved in Parkinson's disease, as an example [92]. Doses in this context appear to be higher, at anywhere from 300 mg up to 2400 mg per day [93].
- Hospital-free days and maintenance of healthcare quality of life in elderly with CoQ10 and selenium (Se) [94].
- DM – 100–200 mg per day modestly decreases A1C (mixed evidence).
- Preliminary evidence of benefit of CoQ10 alone or with other supplements such as selenium (Se) for many other medical problems such as metabolic syndrome and hyperlipidemia [95–98], diabetic retinopathy [99, 100], skin aging [101, 102], nonalcoholic fatty liver disease (NAFLD) [103], chronic fatigue [104, 105], cancer-related fatigue [106] and depression (in MS patients [107]), oxidative stress in hemolysis patients [108], and migraines [109].

Dose/practical considerations As a lipid-soluble supplement, bioavailability of CoQ10 can vary among supplement products. Softgel or chewables have better bioavailability than tablets. Doses for heart failure are typically 200–600 mg/day. It is worth noting that, on average, the monthly cost for 100 mg per day is approximately $30 and for 1200 mg per day of CoQ10 is approximately $300. As such it is important to discuss cost with patients.

Adverse effects CoQ10 is very well tolerated and has minimal adverse effects. There is a theoretical risk that it can decrease PT/INR on warfarin, so this should be monitored [110]. In addition, as mentioned above, CoQ10 can mildly lower blood pressure and blood sugar – monitoring may be prudent.

Contraindications/cautions No specific contraindications have been identified in the geriatric population.

Interactions No clinically significant interactions known. As mentioned above, CoQ10 can slightly lower blood sugar and BP, so monitor with medications used for these purposes.

Summary CoQ10 may be useful for elderly with heart disease, statin-induced myopathy, and possibly neurodegenerative and some other disorders. It is a more expensive supplement, and so counseling about cost is prudent with patients.

15.10 Magnesium (Mg)

Background As a mineral, magnesium is present and available in many whole food sources; however, these food sources are not present in a more processed diet. That is, magnesium ingestion may be low in patients who are not ingesting much of the following whole foods: legumes, nuts, dark leafy greens, halibut, unprocessed grains, and fortified cereals, meat, and dairy.

Indications Magnesium supplementation is indicated for the prevention or correction of magnesium deficiency, which is common [111, 112]. As stated above, many Americans including especially the elderly consume less than the RDA of about 320 (Females) – 420 (Males) mg/day, mainly due to a lack of eating the whole foods rich in magnesium. In addition, there are select groups at risk for Mg deficiency, and these include patients with the following conditions [112]:

- Regular alcohol use (esp. spirits), predisposing to stroke, sarcopenia, cardiomyopathy, steatohepatitis, and cirrhosis. Even moderate alcohol use promotes magnesiuresis.
- GI disorders: malabsorption, chronic diarrhea, inflammatory conditions, short bowel syndrome, and intestinal resection.
- Elderly (especially hospitalized): due to decreased GI magnesium absorption, increases in urinary excretion, use of certain medications (e.g., diuretics, proton-pump inhibitors (PPIs)), and poor dietary intake, elders are at risk of low total magnesium levels.
- Diabetes mellitus: approximately 33% of diabetes have low Mg intake, which is significant, since hypomagnesemia impairs glucose handling [113].

It's important to have a high suspicion for Mg deficiency in any of the above clinical settings, especially if serum values are low or low normal or if there is unexplained/persistent low potassium (which is found in ~40% of low Mg cases) or low calcium, phosphorus, or sodium serum levels. Expected beneficial effects of correcting Mg deficiency include [112]:

- Cardiovascular: May lower BP modestly and may reduce risk of stroke and atrial fibrillation and may improve prognosis in CHF and MI. Improves risk of digitalis toxicity/side effects.
- Metabolic: Adequate Mg intake is associated with improved metabolic syndrome, diabetes mellitus control, and HDL levels.
- Musculoskeletal: Adequate Mg is associated with improved bone density and is required for proper vitamin D function.
- Renal: Correcting Mg deficiency likely lowers risk of calcium oxalate nephrolithiasis. Chronic low Mg is associated with kidney disease [114].

Dose/practical considerations All nutrients ideally should be gained from whole foods; however, if need to supplement Mg, it is best to take magnesium in divided doses, since gut absorption is slow and most of a high single daily dose will be wasted leading to osmotic diarrhea. Avoid prolonged supplementation that exceeds the upper tolerable limit (UL) of 360 mg/day unless in special clinical situations. Various Mg salts are roughly equivalent, but magnesium citrate in a slow absorbed formulation has reasonably good bioavailability. Severe hypomagnesemia would require IV MgSO4 and is outside the scope of this chapter.

Adverse effects Excess doses of Mg can lead to osmotic diarrhea, since the body can only absorb a small amount at a time. Magnesium needs to be given cautiously in patients with chronic kidney disease (CKD).

Contraindications/cautions Mg appears safe if sensibly dosed to correct deficiency; however, because both low and high serum Mg levels are associated with increased hospital mortality [115, 116], supplement with magnesium only if suspecting deficiency, and follow levels to make sure they are not excessive. Advanced CKD impairs excretion of Mg – use caution in dosing and monitor levels if CKD stages 4 or 5.

Interactions Medication classes that can lead to Mg loss or impaired function include diuretics and PPIs (though the Mg impairment effect of PPIs may not be that clinically significant) [117, 118].

Summary Magnesium deficiency is common but often missed. In addition, common medical conditions and medications used in the elderly put them at risk for lower magnesium levels. Correcting Mg deficiency is important for health, especially relating to healthy cardiovascular, neuromuscular, and metabolic function. However excess Mg may also be hazardous and should be avoided.

15.11 Summary

Supplements, like all therapeutics, need to be used based on solid evidence, careful selection, and thorough communication and have a legitimate place in the proper treatment of elderly patients. A shared decision-making approach with open dialog helps elderly patients make the best decision around supplement use, and proper documentation of supplement use in the medical record enhances surveillance for potential side effects and botanical/pharmaceutical interactions, thus optimizing benefit/risk ratio.

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