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LITERATURE REVIEW

Common Herbal and Dietary Supplements for Patients with Type 2 Diabetes: Part 2

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In Part 1 of this literature review (appearing in the Aug. 15, 2021, issue of *Internal Medicine Alert*), we discussed *Aloe vera* and alpha-lipoic acid in detail. In this part, in-depth discussions on chromium, cinnamon, fenugreek, garlic, and *Gymnema sylvestre* are presented. These complementary and alternative medicine supplements include botanical and nonbotanical products for managing type 2 diabetes.

Chromium

Trivalent chromium, or chromium(III), is a trace element required for normal glucose metabolism. The benefits of chromium on blood glucose management have been linked to its potentiation of insulin action by increasing insulin sensitivity and improving glucose tolerance.[1]

Studies suggest chromium is a critical cofactor for insulin and important in preventing the development of diabetes mellitus in rare chromium deficiency situations.[1] The results of a 2014 meta-analysis of 25 randomized controlled trials with chromium monotherapy and combined supplementation suggested improved glycemic control, especially with chromium supplementation doses of more than 200 µg daily.[2] A 2016 meta-analysis revealed chromium supplementation significantly and positively lowered fasting plasma glucose levels and led to an overall decline of ≥ 0.5% in hemoglobin A1c (HbA1c) levels in patients with type 2 diabetes.[3] However, the reported trials featured high heterogeneity between treatment groups, study duration, forms of treatment, and analysis methods. Other studies failed to demonstrate any significant effects of chromium supplementation.[4,5] Some randomized, clinical trials addressed adverse events with chromium supplementation, which included skin rash, constipation, and other gastrointestinal symptoms.[4,5]

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Although higher chromium doses have been studied, 200 µg per day is the typical dose.[6] Overall, the information presented is mixed in determining chromium's efficacy in managing type 2 diabetes. The American Diabetes Association expressed no conclusive evidence supporting the use of chromium supplementation in diabetes.[7]

Cinnamon

Cinnamon is a preparation of the dried bark of specific evergreen trees. The proposed mechanism for diabetes use is the active ingredient, hydroxychalcone, which works as an insulin mimetic and increases insulin sensitivity by improving glucose uptake.[8] Certain studies have indicated some efficacy regarding reducing fasting serum glucose up to 29% when cinnamon is consumed daily.[9] The amount of cinnamon consumed in the studies ranged from 1 g to 6 g, showing modest improvement in fasting serum glucose.[9] However, a 2008 meta-analysis based on five prospective, randomized, controlled trials refuted the efficacy claims of cinnamon in decreasing HbA1c and fasting plasma glucose.[10] The authors of this meta-analysis concluded patients with type 1 or type 2 diabetes receiving cinnamon ranging from 1 g to 6 g did not demonstrate statistically or clinically significant changes in the endpoints compared to subjects receiving a placebo.[10]

In 2013, another meta-analysis included 10 randomized, controlled trials with 543 patients using cinnamon doses of 120 mg per day to 6 g per day for four to 18 weeks.[11] There was a significant reduction in fasting plasma glucose (-24.59 mg/dL, 95% CI, -40.52 to -8.67 mg/dL) but no statistically significant reduction in HbA1c.[11]

Cinnamon's role in patients with diabetes remains unknown. The conflicting available evidence includes a few studies with high heterogeneity where double-blinded procedures may not have been sufficient. Also, the amount of cinnamon used in studies varied widely; certain authors used amounts equivalent to about a half-teaspoon.

Fenugreek

Fenugreek is a common herb and condiment used in cooking. The purported mechanisms of its benefits in diabetes management include delaying gastric emptying, delaying carbohydrate absorption, and increasing peripheral glucose use.[12] Pooled results of a meta-analysis showed fenugreek significantly reduced fasting glucose values, two-hour postprandial glucose levels, and HbA1c.[12] Another randomized, single-blinded trial conducted in India at a single center also indicated significant reductions in fasting blood glucose and HbA1c; however, the authors noted a delayed occurrence of this effect at six months.[13] Fenugreek seeds also appear to be safe when consumed orally for up to six months at the typical doses.[14]

The small sample sizes and suboptimal quality of the studies reviewed limit any recommendations made on fenugreek used in patients with type 2 diabetes. Despite the few studies showing its efficacy in type 1 and type 2 diabetes, in the United States, fenugreek has been given generally recognized as safe (GRAS) status.[15] However, pregnant women should not take fenugreek, since uterine contractions are associated with its use.[16]

Garlic

Garlic is an herb consumed in many dishes. However, many do not realize its potential effect on a person's overall health. Garlic has been indicated as an alternative treatment for several disease states, including hypertension, hypercholesterolemia, coronary artery disease, vaginal candidiasis, atherosclerosis, and diabetes.[17] Multiple mechanisms have been proposed to explain its effects, mostly attributing to the antimicrobial, antioxidant, and antihypertensive properties of the herb. Garlic's glycemic effects seem to be caused by the increase in insulin secretion and sensitivity.[18] The authors of a 2015 meta-analysis reviewed seven clinical studies of patients with diabetes who consumed garlic in varying formulations.[19]

The studies included patients who were taking garlic powder 600 mg to 1,500 mg daily, garlic oil 8.2 mg daily, or aged garlic extract 1,000 mg daily. The results showed it reduced fasting blood glucose by 1.7 mg/dL vs. control groups.[19] Although the finding was statistically significant, a reduction of 1.7 mg/dL might not be considered clinically significant. The meta-analysis also did not include postprandial glucose or HbA1c outcomes because of only two studies reporting on these parameters. Older analyses also concluded garlic did not improve clinical outcomes in patients with diabetes.[20,21]

These results may have stemmed from the different preparations used, making it difficult to determine garlic's effectiveness on glycemic levels in people with diabetes. Although glycemic effect has not been established using garlic, it has been suggested garlic exerts mild effects in hyperlipidemia and hypertension through extracts in divided doses 600 mg to 1,200 mg per day.

Gymnema sylvestre

G. sylvestre is a well-known plant native to India that has been used in Ayurvedic medicine for treating diabetes by dulling the taste buds to sweetness.[22] Research suggests the leaf extract of G. sylvestre increases glucose absorption into the kidney, liver, and muscles as well as stimulates insulin release by increasing membrane permeability.[23,24] The leaves of *G. sylvestre* also may produce anti-glycemic effects by causing an increase in the number of pancreatic islets and beta cells.25

In a controlled clinical trial, 27 patients with type 1 diabetes were treated with 200 mg *G. sylvestre* in addition to their insulin for six to 30 months.[26] Study subjects reported a significant reduction in HbA1c from 12.8% to 9.5% after six to eight months of therapy vs. those treated only with insulin.[26] Another study included 22 patients with type 2 diabetes treated with 400 mg *G. sylvestre* daily for 18 to 20 months in addition to a sulfonylurea, and HbA1c significantly decreased, from 11.9% to 8.5%.[27]

In both type 1 and type 2 diabetes, *G. sylvestre* has been studied for up to 2.5 years. There have been few randomized trials demonstrating the efficacy of *G. sylvestre*, but current studies suggest a long-term effect on hyperglycemia. Future studies are warranted to confirm the findings because of the small samples in the studies identified.

Among the herbal and dietary supplements presented in Part 2, the role that chromium, cinnamon, fenugreek, and garlic can play in glycemic management for patients with type 2 diabetes is rather unclear because of the mixed data from the various clinical trials. *G. sylvestre*, on the other hand, has been shown in clinical trials to demonstrate some long-term hyperglycemic management effects in both type 1 and type 2 diabetes. Since these trials were small, further investigation is needed to confirm the observed efficacy of *G. sylvestre*. ■

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ABSTRACT & COMMENTARY

A Probiotic May Cause Sepsis and Death

By Joseph E. Scherger, MD, MPH

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SYNOPSIS: *Saccharomyces boulardii* is a probiotic yeast that may cause fungemia and other fungal infections.

SOURCE: Rannikko J, Holmberg V, Karppelin M, et al. Fungemia and other fungal infections associated with use of *Saccharomyces boulardii* probiotic supplements. *Emerg Infect Dis* 2021;27. doi: 10.3201/eid2708.210018.

Rannikko et al reviewed the medical records of patients with positive blood cultures for *Saccharomyces boulardii* at five university hospitals in Finland between 2009 and 2018. The authors identified 46 patients, at least 20 of whom were using a *Saccharomyces boulardii* probiotic. Compared with a control group, the odds ratio for using the probiotic was 14. A total of 37% of these patients died. In addition, the authors found 1,153 nonblood isolates of *Saccharomyces* species; most commonly, these were associated with gastrointestinal disease.

■ COMMENTARY

Probiotics are live organisms given to patients for health benefits, often to improve the gut microbiome. Usually, probiotics are a combination of several bacterial species, and most are safe. *Saccharomyces boulardii* is a yeast probiotic widely used to treat certain types of diarrhea, such as rotavirus infection in children and for ulcer prevention.[1,2] This report from Finland should remind clinicians that giving live organisms can be dangerous, especially to immune-compromised patients. ■

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ABSTRACT & COMMENTARY

Anticholinergic Use for Three Months or More Increases Dementia Risk

By Chiara Ghetti, MD

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SYNOPSIS: There is a significant increase in dementia risk associated with the use of anticholinergic medications for three months or longer.

SOURCE: Dmochowski RR, Thai S, Iglay K, et al. Increased risk of incident dementia following use of anticholinergic agents: A systematic literature review and meta-analysis. *Neurourol Urodyn* 2021;40:28-37.

The objective of this study was to determine the effect of three or more months of anticholinergic use and, specifically, medications used to treat overactive bladder (OAB) on the risk of dementia, mild cognitive impairment, and change in cognitive function. This was a systematic literature review and meta-analysis performed according to PRISMA guidelines and registered in the PROSPERO database. PubMed,

Embase, and Cochrane Library databases were searched for English-language articles published before August 2019. Studies eligible for this review included full-text articles of primary publications of randomized, controlled trials (RCTs), and cohort and case-control studies. Studies were reviewed by two reviewers and eligible if studies examined the effect of anticholinergic drug use for ≥ 3 months on dementia or cognitive function in adult patients and contained an adequate description of the methods used. Studies were excluded if they assessed only serum anticholinergic activity, used a combined scale of drug burden that did not specify the risk for exposure to anticholinergic agents only, or examined acute outcomes, such as delirium or acute cognitive dysfunction. Studies assessing anticholinergics used to treat OAB were considered for a separate meta-analysis.

Of 2,092 articles identified on search, 1,990 were screened based on title and abstract. Of these, 316 were assessed by full text; 21 met inclusion criteria and underwent qualitative analysis. A higher cognitive impairment risk was reported in the studies evaluated using a variety of endpoints (incident dementia, Alzheimer's disease, mild cognitive impairment, and change in cognitive function). Only the incident dementia category included sufficient studies (six of nine) to perform a meta-analysis. These comprised three case-control and three cohort studies and collectively included data from 645,865 patients. The six studies used varying anticholinergic exposure and dementia definitions. The authors reported an average relative risk for incident dementia using these six studies of 1.46 (95% CI, 1.17-1.81; 95% prediction interval, 0.70-3.04) and ranged from 1.05 to 2.63. Clinically, this translates into an average increased risk of dementia of 46% for anticholinergics vs. nonuse. Three studies reported anticholinergic dosing data; using these studies, any anticholinergic exposure was associated with increased incident dementia vs. no anticholinergic exposure. Two studies specifically examined the role OAB medications played in dementia. In these two studies, the risk of dementia from OAB medications appeared higher than the overall risk across all anticholinergic agents for most levels of exposure (adjusted odds ratios ranged from 1.21 to 1.65).

■ COMMENTARY

Urinary incontinence is defined as the involuntary loss of urine. It affects more than 50% of women.[1,2] Still, urinary incontinence remains frequently undertreated. Urgency incontinence, or OAB, is associated with a strong urge to void that is difficult to defer.[1] Although the evaluation of urinary incontinence is similar for all types, treatment options vary by diagnosis.

Guidelines for the evaluation of urinary incontinence consistently recommend characterization of symptoms, history, physical exam, and testing for urinary tract infection as well as an assessment of post-void residual, but guidelines vary in specific details and in testing recommendations.[1] Treatment for urge incontinence should begin with behavioral and lifestyle modification. Often simple, conservative measures can improve symptoms dramatically. Behavioral and lifestyle modifications include fluid management; limiting bladder irritant consumption (diet beverages, in particular), carbonated beverages, and caffeine; addressing and managing constipation, smoking cessation, and weight loss; and treating vaginal atrophy. In addition, pelvic floor physical therapy and pelvic floor exercises have shown efficacy.[3] Pharmacotherapy can be used concomitantly with these measures or used as the next step in women for whom conservative options have not fully resolved symptoms. Other treatments for urge incontinence include intradetrusor botulinum toxin injections, percutaneous tibial nerve stimulation, and sacral neuromodulation. Some insurance plans require a trial of pharmacotherapy before authorizing some of these additional procedural treatments.

Antimuscarinics are the most commonly prescribed medications to treat urge urinary incontinence. These include darifenacin, fesoterodine, oxybutynin, solifenacin, tolterodine, and trospium. Modest improvements have been seen in pharmacotherapy vs. placebo.[4] Combined therapy with behavior modification has shown more efficacy than medication alone.[5] Antimuscarinic agents are contraindicated in patients with untreated narrow angle glaucoma and supraventricular tachycardia. Nearly 50% of patients taking these medications report side effects; most commonly, these medications produce peripheral anticholinergic effects, including dry mouth and constipation. Thus, discontinuation is common. It is important to keep in mind these medications produce additive side effects with other medications, and patients often are on other medications with significant anticholinergic properties.

Importantly, the study by Dmochowski et al further adds to the growing literature linking anticholinergic drug use with the risk of dementia. Cognitive impairment is a significant public health issue. One in nine U.S. adults experience symptomatic cognitive decline.[6] There are an estimated 6 million people living with dementia in the United States today, and this number is projected to increase to 14 million by 2060.[7] Worldwide, more than 50 million people have dementia and 10 million new cases are added annually.[8] One of the studies included in the systematic review noted earlier is a nested case control study from the United Kingdom.[9] This study included 58,769 patients with a diagnosis of dementia and 225,574 matched controls. The authors found a significant dementia risk in patients with exposure to several types of strong anticholinergic drugs, including antimuscarinics. They found 50% increased odds of dementia with an exposure equivalent to three years of

daily use of a sole strong anticholinergic medication. They estimated 10% of dementias could be attributable to this exposure. Clinicians must strongly consider these associations before prescribing antimuscarinics. Although we may be most familiar with antimuscarinic bladder medications, patients often are taking other anticholinergic medications, such as antiarrhythmic medications, antihistamines, antidepressants, antiepileptics, antiemetics, antiparkinson agents, and antipsychotics. Alongside becoming more familiar with the broader class of anticholinergic medications, screening women for signs of cognitive changes and assessing their family history of dementia before prescribing antimuscarinics may aid in better understanding the risks and benefits of pharmacologic therapy for our patients. We should strive to maximize nonpharmacologic management of urge incontinence with behavioral and lifestyle modification and then refer for nonpharmacologic treatment with intradetrusor botulinum toxin injections or neuromodulation. Clinicians can affect the long-term well-being of women and help educate patients and colleagues as we work toward deprescribing antimuscarinic medications for the management of urge incontinence. ■

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ABSTRACT & COMMENTARY

Association of Sleepwalking and REM Sleep Behavior Disorder in Men with Parkinson's

By Daniel A. Barone, MD, FAASM, FANA

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SYNOPSIS: In this retrospective, cross-sectional study of men, both sleepwalking and rapid eye movement sleep behavior disorder were associated with the development of Parkinson's disease.

SOURCE: Zhang X, Molsberry SA, Pavlova M, et al. Association of sleepwalking and REM sleep behavior disorder with Parkinson disease in men. *JAMA Netw Open* 2021;4:e215713.

Rapid eye movement (REM) sleep behavior disorder (RBD) is one of the most well-known and extensively studied sleep features of Parkinson's disease, both in terms of risk and as a sleep-related symptom. The non-REM parasomnia, sleepwalking, is not as well understood or studied. Sleepwalking might exhibit a significant prevalence in patients with Parkinson's disease (approximately 10%), and the presence of non-REM parasomnias is associated with worse symptoms, cognitive impairment, and depression in those with Parkinson's disease. However, despite these observations and the fact sleepwalking is somewhat rare in adults (1% to 2%), no study comparing individuals without Parkinson's disease in direct comparison to those with Parkinson's disease for risk estimation has been conducted.

Zhang et al aimed to answer the question of whether the presence of sleepwalking in men, either alone or comorbid with RBD, is associated with higher odds of developing Parkinson's disease. To accomplish this, they surveyed a cohort of 25,694 men from the Health Professionals Follow-Up Study, which consisted of male health professionals in the United States followed from January 2012 until June 2018. The presence of probable sleepwalking and/or probable RBD was ascertained in

2012 via the Mayo Sleep Questionnaire. The diagnosis of Parkinson's disease was determined by a movement disorder specialist through a review of medical records. The mean age of this cohort was 75.6 years, and the authors found that 223 were probable sleepwalkers, 2,720 were probable RBD, and 257 had Parkinson's disease. The presence of confounders, such as age, smoking, caffeine intake, chronic disease status, and other sleep disorders, was adjusted for in a two-tailed logistic regression analysis. This led to the observation that those with probable sleepwalking, probable RBD, or both probable sleepwalking and probable RBD had higher odds of Parkinson's disease ($P < 0.05$): probable sleepwalking, OR = 4.80; probable RBD, OR = 6.36; both probable sleepwalking and probable RBD, OR = 8.44. Thus, it appears both probable sleepwalking and probable RBD, alone and in conjunction, were significantly associated with higher odds of developing Parkinson's disease. The authors noted arousal regulation during sleep is likely to be affected by Parkinson's disease-related neurodegeneration.

■ COMMENTARY

As the authors wrote, this is the first paper commenting on a non-REM parasomnia as a risk for Parkinson's disease. However, despite the novelty of this design, there were significant limitations. This was a questionnaire-based methodology for assessing the presence of sleep disorders and a medical records review for making a diagnosis of Parkinson's disease. However, this new line of thinking should open the doors to prospective evaluation of the risk for development of Parkinson's disease in other parasomnias and sleep disorders. For example, in an earlier study based on the Health Professionals Follow-Up Study, the presence of restless legs syndrome (RLS) was associated with higher odds of constipation and probable RBD, both of which are risk factors for Parkinson's disease.[1] Long-term studies evaluating the risk of neurodegeneration in those with non-REM parasomnias and other sleep disorders (such as RLS and periodic limb movements of sleep) are needed now. Perhaps this marks the beginning of a paradigm shift to a better understanding of the risk of neurodegeneration in patients with sleep disorders other than RBD. ■

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PHARMACOLOGY UPDATE

Finerenone Tablets (Kerendia)

By William Elliott, MD, FACP, and James Chan, PharmD, PhD

Dr. Elliott is Assistant Clinical Professor of Medicine, University of California, San Francisco.
Dr. Chan is Associate Clinical Professor, School of Pharmacy, University of California, San Francisco.

The FDA has approved the first nonsteroidal, third-generation, mineralocorticoid receptor antagonists to reduce risk of kidney and cardiovascular mortality and morbidity in patients with chronic kidney disease and type 2 diabetes. It received a priority review and fast-track designation.

INDICATIONS

Finerenone can be prescribed to lower the risk of sustained estimated glomerular filtration rate (eGFR) decline, cardiovascular death, non-fatal myocardial infarction, end-stage kidney disease, and hospitalization from heart failure in adults with chronic kidney disease associated with type 2 diabetes.[1]

DOSAGE

The recommended dose is 20 mg once daily if eGFR is > 60 mL/min/1.73m^2 and 10 mg if eGFR is ≥ 25 mL/min/1.73m^2 to < 60 mL/min/1.73m^2.[1] Withhold the dose if serum potassium is > 5.5 mEq/L. Serum potassium and eGFR should be measured before initiation of treatment and periodically during treatment.

POTENTIAL ADVANTAGES

Finerenone is a more selective antagonist vs. spironolactone and more potent than eplerenone.[2] It is the only FDA-approved mineralocorticoid for chronic kidney disease. It produces no activity on androgen, estrogen, or glucocorticoid receptors while still lowering the risk of hyperkalemia.[1-3]

POTENTIAL DISADVANTAGES

The most common adverse reaction (vs. placebo) is hyperkalemia (18.3% vs. 8%).[1] Finerenone is a substrate for CYP3A4; concomitant use with strong CYP3A4 inhibitors are contraindicated.[1] Avoid concomitant use with grapefruit or grapefruit juice or strong or moderate CYP3A4 inducers.[1]

COMMENTS

The efficacy of finerenone was evaluated in a randomized, double-blind, placebo-controlled study in adults with chronic kidney disease associated with type 2 diabetes.[1] The study population presented with a mean eGFR of 44 mL/min/1.73m^2, median urine albumin-

to-creatinine ratio of 852 mg/g, and 98.8% were treated with an angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB). Approximately 46% presented with a history of atherosclerotic cardiovascular (CV) disease. Subjects were randomized to finerenone (n = 2,833) or placebo (n = 2,841) and were followed for a minimum of 2.6 years. Those designated as New York Heart Association class II to IV were excluded. The primary composite efficacy endpoint was sustained decline in eGFR of ≥ 40%, progression to kidney failure, or renal death. The secondary endpoint was a composite of CV death, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for heart failure. Finerenone reduced the primary composite endpoint vs. placebo (17.8% vs. 21.1%; HR, 0.82; 95% CI, 0.73-0.93). This was driven by the decline in eGFR (HR, 0.81; 95% CI, 0.72-0.92). The secondary composite endpoint also was reduced (HR, 0.86; 95% CI, 0.75-0.99). None of the individual components reached statistical significance. The authors of a recently completed study assessed the efficacy and safety of finerenone vs. placebo for reducing clinically important CV and renal outcomes.[4] The results are pending.

CLINICAL IMPLICATIONS

Type 2 diabetes is a primary cause of chronic kidney disease. Mineralocorticoid receptor overactivation in type 2 diabetes appears to be the main pathophysiology resulting in cardiorenal disease. Established first-line treatments to prevent chronic kidney disease are renin-angiotensin system inhibitors (ACEI and ARB). More recently, sodium-glucose cotransporter 2 inhibitors, particularly dapagliflozin, have provided robust clinical benefit in patients with or without diabetes or cardiovascular disease.[5,6] Finerenone offers a potential alternative to spironolactone and eplerenone, with fewer side effects. Its ultimate role remains to be determined. The cost for a 30-day supply is $569.10. ■

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CME QUESTIONS

1. Which herbal supplement has been shown to produce a long-term effect on hyperglycemia?
a. Cinnamon
b. Fenugreek
c. Garlic
d. *Gymnema sylvestre*

2. What type of probiotic has been shown to cause bloodstream infections?
a. *Lactobacillus*
b. *Bifidobacterium*
c. Yeast species
d. *Streptococcus thermophilus*

3. Anticholinergic medications:
a. do not increase the risk of dementia in older patients.
b. prescribed for bladder symptoms are not associated with cognitive impairment.
c. should be prescribed after careful consideration of the benefits and risks of developing dementia.
d. can be prescribed safely without concern for dementia risk.

4. Which statement regarding sleepwalking and rapid eye movement (REM) sleep behavior disorder is correct?
a. Sleep disorders are common in the general population and not associated with other medical conditions.
b. Sleepwalking occurs only in children.
c. REM sleep behavior disorder may be a prodrome to Parkinson's disease.
d. REM sleep behavior disorder always occurs in sleepwalkers.