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DIABETES

LITERATURE REVIEW

The Safety and Efficacy of Common Herbal and Dietary Supplements in Patients with Type 2 Diabetes Mellitus: Part 1

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Diabetes mellitus (DM), especially type 2 DM, is a major public health concern that affects about 34.1 million people in the United States.[1] This chronic health condition, if not properly managed, can cause long-term complications as well as considerable morbidity and mortality in the affected population.[2] In 2018, an estimated 1.5 million new cases of diabetes were diagnosed in U.S. adults aged 18 years or older, with more than half of these new cases in adults aged 45 to 64 years old.[1]

With an increasing number of diabetes cases, clinicians also are encountering more patients who are turning to complementary and alternative medicine (CAM) to help control their glucose levels. In a 2015 National Consumer Survey on the Medication Experience and Pharmacist Roles, 35% of 26,157 respondents in the study reported the use of at least one herbal medicine.[3] In all, 3,050 respondents had diabetes, and 41.2% of the respondents reported the use of a dietary supplement.[3] The data revealed that respondents with diabetes were associated with higher herbal medicine use when compared to respondents without chronic diseases (41% vs. 34%, $P < 0.001$).[3] The results also showed that herbal medicine use increased as age increased among the respondents.[3]

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Summary Points

- The authors reviewed the current literature on the effectiveness and safety of commonly used herbal supplements in people with diabetes.
- A search was performed on the American Diabetes Association website to gather recommendations from the American Diabetes Care and Education Specialists about herbal products relating to diabetes management. Search results were cross-referenced with the Natural Medicines Database and Complementary & Alternative Medicine Supplement Use in People with Diabetes: A Clinician's Guide for available studies regarding the identified herbal supplements' safety and effectiveness.
- The available evidence for each supplement was inconclusive because of inconsistent results across studies, and very few studies reported adverse effects.
- There is insufficient evidence to make definitive recommendations on the role of herbal and dietary supplements used in people with diabetes. The current data warrant further research to produce high-quality results from randomized controlled trials. The inconsistent data on herbal and dietary supplements should be relayed to people with diabetes seeking alternative strategies as adjunctive options to manage diabetes.

Since CAM products are regulated as dietary supplements by the Food and Drug Administration, the effectiveness and safety of these products are regulated after they are available in the market, which means the quality and safety of these supplements can be highly variable.[4] As more people with diabetes are reporting their use of CAM products in conjunction with prescription medications, it is important that clinicians understand what role these products play in diabetes management with the available evidence. By reviewing the current evidence behind these alternative therapies, medical practitioners will be better equipped to distill information for their patients and address the utility of these proposed diabetes supplements. This review will try to explore and present the current literature on commonly used herbal and dietary supplements among people with diabetes.

METHODS

An electronic literature search was performed on the American Diabetes Association website based on the recommendation from the American Association of Diabetes Educators (now named Association of Diabetes Care and Education Specialists) to discover what had been written about herbal products relating to diabetes management.[5] These findings were cross-referenced with the Natural Medicines Database and Complementary & Alternative Medicine Supplement Use in People with Diabetes: A Clinician's Guide regarding the identified products' safety and effectiveness.[6] Keywords included dietary supplements, herbal supplements, type 2 diabetes mellitus, *Aloe vera*, alpha lipoic acid, chromium, cinnamon, fenugreek, ginseng, ginger, gymnema, magnesium, nopal, and psyllium. The search was limited to studies published in the English language and searched from date of inception until 2019. We included systematic reviews, meta-analysis, and randomized controlled trials. We excluded abstract-only articles, conference presentations, editorials, and studies with fewer than five participants. Articles were screened independently by the authors and included based on relevancy

RESULTS

The most popular supplements taken by patients are herbal supplements that come from natural sources, as opposed to other forms, such as vitamin or mineral mixtures.[7] The authors have identified eleven herbal and dietary supplements — *Aloe vera*, alpha-lipoic acid, chromium, cinnamon, fenugreek, garlic, ginseng, magnesium, psyllium, gymnema, and nopal — that are commonly used among patients with diabetes.

However, because of limited quality control in dietary supplements, it is difficult to make firm recommendations without reviewing the current evidence on efficacy and proposed mechanisms in which these products work in patients with diabetes. This review article is

divided into three parts, with parts 2 and 3 to be published in subsequent issues of *Integrative Medicine Alert*. *Aloe vera* and alpha-lipoic acid are included in this part.

ALOE VERA

There are more than 300 species in the Aloe genus, and one is extremely well-known worldwide. *Aloe barbadensis*, otherwise known as *Aloe vera*, is a renowned plant of the Liliaceae family, known for its many medicinal properties.[8] The spiky succulent plant contains gel and juice, which has become a commercial supplement and cosmetic. It is believed that *Aloe vera* possesses antioxidant, anticancer, anti-inflammatory, laxative, and anti-atherosclerotic properties.[9]

There are multiple existing hypotheses on why *Aloe vera* can have potential benefits in diabetes management. One hypothesis states that *Aloe vera* lowers blood glucose levels through its anti-inflammatory effects. Type 2 DM is an inflammatory disease associated with oxidative stress of the pancreas, which leads to beta-cell dysfunction and insulin resistance.[10] Clinical research shows that *Aloe vera* can reduce fasting blood glucose levels by 30 mg/dL to 46.6 mg/dL and hemoglobin A1c (HbA1c) by 0.41% to 1.05% in adults with prediabetes and diabetes.[11-13] Another hypothesis proposes that a constituent of the *Aloe vera* plant, glucomannan, is the agent that possesses the hypoglycemic effects.[14] Glucomannan is a hydrosoluble agent believed to promote satiety and delaying intestinal absorption becuase of its increased viscosity.[15] There has been a variety of doses and dosage forms, ranging from 100 mg to 1,000 mg of its powder to 15 mL to 150 mL of its juice formulation, suggested to be efficacious in lowering blood glucose.[11-13] However, because of the heterogeneity of the available studies, the mixed evidence on *Aloe vera*'s effectiveness hinders the validity of the reported findings.

ALPHA-LIPOIC ACID

Alpha-lipoic acid (ALA) is an antioxidant that has been hypothesized to improve carbohydrate disturbances.[15,16] ALA is a naturally occurring antioxidant that promotes the transport of glucose into cells of muscles.[16] Additionally, its use has been suggested to have beneficial effects in peripheral neuropathy in patients with type 2 diabetes.[17] The suggested effective dose to improve insulin sensitivity and fasting blood glucose is 600 mg to 1,800 mg/day orally for four to eight weeks.[16] However, conflicting evidence does exist, which suggests no effect on insulin sensitivity.[12] Dosages of 600 mg to 1,800 mg daily have been shown to be beneficial for patients experiencing pain, numbness, and prickling of extremities associated with neuropathy.[18]

Table 1 summarizes the common dosages and adverse effects of the two supplements included in this part of the review. Table 2 includes meta-analyses, systematic reviews, and major clinical trials pertinent to the two supplements. For more information on the specific studies analyzed in Table 2, visit https://bit.ly/3eRfp3g.

■ DISCUSSIONS

Compared to patients without diabetes, patients with diabetes are 1.6 times more likely to include CAM as a component of their diabetes management plans, thus more prone to negative consequences — e.g., side effects and drug interactions — resulting from herbal and dietary supplement usage.[19] These products often are purchased over the counter or through mail order, so the consumers/patients with DM might be confused about the product contents and labels, adding to the list of safety concerns. For that reason, patients might be at risk of purchasing products that do not match their stated claims if the products have not gone through a third-party verification/testing process.

Table 1. Common Dosages and Adverse Effects of Herbal and Dietary Supplements*

Supplement	Typical Dosages	Adverse Effects	Drug Interactions
Aloe vera	• *Aloe vera* powder 100 mg to 1,000 mg daily • *Aloe vera* juice 15 mL to 150 mL daily	• Hypokalemia • Abdominal pain • Diarrhea • Renal complications	• Digoxin • Antiplatelets • Laxatives
Alpha-lipoic acid	• Alpha-lipoic acid capsules 300 mg to 1,800 mg daily • Alpha-lipoic acid 600 mg IV daily for two weeks	• Bitter taste • Headaches • Nausea/vomiting • Abdominal discomfort • Change in urine odor • Skin rash • Allergic reaction (IV) • Intoxication at extremely high doses (2,400 mg/day) can lead to seizures, lethargy, and unconsciousness	• Alkylating agents/chemotherapeutic agents • Thyroid agents

IV: intravenous
*Information in this table was acquired from the Natural Medicines Database

Table 2. Common Dosages and Adverse Effects of Herbal and Dietary Supplements*

Supplement	Notable Studies	Type of Study	Participants	Measurements	Findings
Aloe vera	Zhang et al 2016[9]	Meta-analysis of five RCTs	415 participants with prediabetes and untreated diabetes	HbA1c and FBG	• Significant decrease in FBG ($P = 0.02$): WMD, -30.05 mg/dL; 95% CI, -54.87 to -5.23 mg/dL • Significant decrease in HbA1c ($P < 0.001$): WMD -0.41%; 95% CI, -0.55% to -0.27%
	Dick et al 2016[10]	Meta-analysis of nine RCTs	283	HbA1c and FBG	• Significant decrease in FBG by -46.6 mg/dL ($P < 0.0001$) • HbA1c by -1.05% ($P = 0.004$)
	Suksomboon et al 2016[11]	Meta-analysis of eight RCTs	470 participants with pre-diabetes and type 2 diabetes	HbA1c and FBG	• Significant decrease in: - Pre-diabetes: FPG (MD -0.22 mmol/L; 95% CI, -0.32 mmol/L to -0.12 mmol/L, $P < 0.0001$); no effect on HbA1c. - Type 2 diabetes: FPG (MD, -1.17 mmol/L; 95% CI, -2.35 mmol/L to 0.00 mmol/L, $P = 0.05$); HbA1c (MD, -11 mmol/mol; 95% CI, -19 mmol/mol to -2 mmol/mol, $P = 0.01$)
Alpha-lipoic acid	Ziegler et al 1995[15] (ALADIN study)	RCT with three doses (1,200 mg, 600 mg, and 100 mg ALA) and placebo	260 non-insulin-dependent patients with diabetes and symptomatic peripheral neuropathy	Neuropathic symptoms; Hamburg Pain Adjective List; Neuropathy Symptom and Disability Scores	• Scores captured at baseline and at each visit (days 2-5, 8-12, 15-19): • Decrease in total symptom score in feet from baseline to day 19
	Reljanovic et al. 1999[21] (ALADIN II Study)	RCT	65 patients with type 1 or 2 diabetes and who experienced symptomatic polyneuropathy	Neuropathy Disability Scores; nerve measurements	• See Table 2E at https://bit.ly/3eRfp3g.
	Ziegler et al 1999[22] (ALADIN III Study)	RCT	509 patients with type 2 diabetes and symptomatic polyneuropathy	Total Symptom Score for neuropathic symptoms in the feet; Neuropathy Impairment Score	• See Table 2F at https://bit.ly/3eRfp3g.

RCT: randomized controlled trial; FBG: fasting blood glucose; WMD: weighted mean difference; CI: confidence interval; FPG: fasting plasma glucose; MD: mean difference

To ensure safety from the standpoint of clinicians, it is crucial to ask patients at every visit whether any herbal or dietary supplements were added since the last medical appointment to identify potential drug-supplement interactions, side effects, or additive effects when used with antidiabetic medications if new agents were added.

Although *Aloe vera* has been used for skin treatment and incorporated into drugs as laxatives, there is no long-term evidence yet to suggest its effectiveness in diabetes management. ALA — functioning similarly to B-complex vitamin — has been used in peripheral neuropathy treatment, even secondary to diabetes.[20,21] In Part 2 of

this review article, discussions will focus on chromium, cinnamon, fenugreek, garlic, and ginseng, summarizing common dosages and adverse effects, as well as pertinent studies. ■

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OBESITY

ABSTRACT & COMMENTARY

Does Combined Obesity and Depression Treatment Result in Better Quality of Life and Psychosocial Functioning?

By Ellen Feldman, MD

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SYNOPSIS: This study tracked measures of quality of life and psychosocial functioning in patients participating in a randomized clinical trial with the goal of reducing symptoms of obesity and depression. The authors found that both quality of life and psychosocial functioning significantly increased at six months compared to patients with "care as usual," but not at 12 months.

SOURCE: Rosas LG, Azar KMJ, Lv N, et al. Effect of an intervention for obesity and depression on patient-centered outcomes: An RCT. *Am J Prev Med* 2020,58:496-505.

Summary Points

- A 2017 randomized controlled trial compared a 12-month collaborative care intervention for patients with comorbid obesity and depression to care as usual. The authors found that patients in the intervention arm had significantly more weight loss and improvements in measures of depression than patients in the "care as usual" arm.
- This study investigated the same population to see if the intervention was associated with improvements in health-related quality of life and psychosocial functioning, as measured by several different scales at baseline, six months, and 12 months.
- At six months (but not 12 months), intervention participants reported significantly greater improvements in measures of mental health-related quality of life, sleep-related impairments, functional disability, and obesity-specific quality of life compared to the "care as usual" arm.

Social stigma, low self-esteem, and exacerbation of chronic medical problems are a sampling of the factors complicating treatment of either obesity or depression. Because obesity is a risk factor for depression, and depression elevates the risk of obesity, these disorders frequently appear as comorbid conditions.[1,2]

Recent estimates reveal both of these conditions are common, with obesity occurring in 40% of U.S. adults and depression affecting 21% at some point during a lifetime.[3] Few studies have looked at rates of comorbidity among these two disorders, but there is suggestive evidence that this association is most pronounced in women. Evidence also points to poorer health-related quality of life and more significant functional impairment in patients with comorbid obesity and depression (compared to either condition alone or to neither condition).[1-3]

Rosas et al, looking from a different vantage point, were interested in investigating if patients with improvements in depression and comorbid obesity endorse parallel improvements in quality of life and psychosocial functioning. They reviewed data from a cohort of patients enrolled in a study of a collaborative care intervention designed to treat patients with both conditions: I-CARE (Integrated Coaching for Better Mood and Weight.) This intervention took place over 12 months, during which participants enrolled in an obesity/weight-loss group (Group Lifestyle Balance) and an additional program targeting depressive symptoms (Program to Encourage Active, Rewarding Lives). At the conclusion of 12 months, Cohen d effect scores for the intervention group were 0.28 for reduced body mass index (BMI) and 0.23 for depressive symptoms, representing a small but significant effect associated with the interventions.

The two therapies were timed to produce synergistic results with nine health coach-directed in-person sessions followed by 11 home video sessions over the first six-months, and monthly phone sessions with the health coach over the last six months.

The Short Form-8 Health Survey (SF-8), measuring both physical and mental health quality of life, and the Obesity-Related Problem Scale were used to evaluate health-related quality of life. The SF-8 asks questions such as, "Over the past four weeks, how often have you been bothered by emotional problems such as irritability, anxiety, depression?" and, "During the past four weeks, how often did your physical health limit your social activity?"[4] The Obesity-Related Problem scale asks specifically about weight-related concerns, such as how bothered by obesity a respondent feels when going shopping for clothes or attending a community activity.[5]

Sleep-related impairment questionnaires and the three-item Sheehan Disability scale were used to measure the level of psychosocial functioning. All measurements were taken at baseline, month 6, and month 12.

RESULTS

Out of an initial 409 study participants, 317 individuals (78%) completed the evaluations measuring quality of life and psychosocial functional level. At six months, respondents in the intervention arm reported significantly greater improvements in all but one measure of quality of life as well as all psychosocial function measurements compared to the control arm, but none of these improvements remained statistically significant at the 12-month mark. (*See Table 1.*)

The first step of analysis looked at quality of life and functional improvement in the intervention vs. control arm at six and 12 months. The second step looked at a relationship between these measures and an improvement in BMI and/or reduction of depressive symptoms. At six months, improvements in the mental component of SF- 8, the Obesity-Related Problem Scale, measures of sleep disturbance, and the Sheehan Disability Scale all were associated with improved measures of depression, but not with lower BMIs. At 12 months, all these factors were associated with both lower BMI and lower measures of depression.

Table 1. Results at Six and 12 Months

	Obesity-Related Problem Scale (Lower Scores Reflect Higher Quality of Life)	SF-8 Physical Component (Higher Scores Reflect Higher Quality of Life)	SF-8 Mental Component (Higher Scores Reflect Higher Quality of Life)	Sleep Disturbance (Lower Scores Reflect Less Sleep Disturbance)	Sheehan Disability Scale (Lower Scores Reflect Less Functional Impairment)
Intervention arm: six-month mean value (SD)	55.8 (25.8)	47.6 (91.0)	44.5 (10.6)	53.2 (8.6)	7.3 (6.8)
Usual care: six-month mean value (SD)	60.3 (26.4)	45.8 (9.6)	41.8 (9.7)	56.7 (8.2)	8.9 (6.8)
Difference between the two arms (95% CI)	-5.3 (-9.5 to 1.0)	1.5 (-0.3 to 3.2)	2.9 (0.7 to 5.0)	-3.5 (-5.3 to -1.6)	-1.5 (-2.9 to -0.1)
P-value: six months	0.02*	0.11	0.01*	< 0.001*	0.03*
Intervention arm: 12-month mean value (SD)	54.3 (25.9)	47.1 (8.7)	45.0 (9.6)	53.4 (9.3)	6.8 (6.7)
Usual care: 12-month mean value (SD)	56.1 (27.2)	46.3 (8.6)	43.3 (9.5)	55.1 (8.5)	8.4 (6.2)
Difference between the two arms (95% CI)	-4.7 (-9.8 to 0.3)	0.9 (-0.9 to 2.7)	1.7 (-0.4 to 3.9)	-1.6 (-3.6 to 0.5)	-1.3 (-2.8 to 0.1)
P-value: 12 months	0.06	0.32	0.11	0.13	0.07

SF-8: Short Form-8 Health Survey; SD: standard deviation; CI: confidence interval
*Statistically significant values

In multi-variable analysis, several interesting relationships were noted. Improvements in Obesity-Related Problem Scale results and sleep disturbance were associated with decreased BMI at 12 months. Improvements in all measures of quality of life and psychosocial functioning were associated with a clinically significant reduction in measures of depression at 12 months.

■ COMMENTARY

Rosas et al shed new light on an investigation looking primarily at the effect of a collaborative care intervention targeted for treatment of patients with comorbid obesity and depression. Although the primary findings from the initial study are impressive (with improvement in BMI and depressive symptoms at 12 months from study entrance), this team wanted to understand whether patient-reported outcomes, such as quality of life and functional improvement, follow the trend in clinical improvement. In this work, improvements in mental health-related quality of life, obesity-related quality of life, sleep disturbances, and functional status were significantly improved at six months when compared with patients in the treatment as usual group, but not at 12 months. In part, this may have to do with the change in intervention during the study, since the second six months of treatment was more of a maintenance phase approach with monthly phone check-ins.

Interestingly, this drop-off in effect does not appear to be because of a decrease in scores in the intervention group, but rather an increase in such measures in the "care as usual" group. For example, at six months, the difference between the mean values of the intervention and control groups in the mental component of the SF-8 was significantly different at 2.9. At 12 months, this difference narrowed to a non-significant 1.7, largely because of improvement in the control arm patients, since there was little movement in scores in the intervention group. Future studies may help clarify these relationships, but there seems to be a suggestion that active intervention post-six months may be needed for continued response.

Multi-variable analysis pointed to another interesting finding. Improvement in obesity-related quality of life and sleep disturbances were associated with weight loss, while improvement in other measures of health-related quality of life and functional impairment measures were more strongly associated with decreased depressive symptoms. The inference here is that both depression and obesity need to be targeted to reach maximum measurable improvements in patient-defined measures of quality of life and functional impairment.

The primary care provider can expect to see many patients with comorbid depression and obesity. This study, while preliminary, can serve as a reminder of the importance of evaluating patient perception of improvement while also collecting and measuring clinical data. The results from this study also imply that treatment of both obesity and depression may yield more patient-perceived

benefits than focusing on either one condition alone. ■

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CME OBJECTIVES

Upon completion of this educational activity, participants should be able to:

- present evidence-based clinical analyses of commonly used alternative therapies;
- make informed, evidence-based recommendations to clinicians about whether to consider using such therapies in practice; and
- describe and critique the objectives, methods, results, and conclusions of useful, current, peer-reviewed, clinical studies in alternative medicine as published in the scientific literature.

CME INSTRUCTIONS

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CME QUESTIONS

1. Which of the following diabetes-related complications has shown benefits in its management from using alpha-lipoic acid?
a. Diabetic retinopathy
b. Diabetic peripheral neuropathy
c. Diabetic nephropathy
d. Diabetic autonomic neuropathy

2. In the investigation of obesity and depression:
a. measures of quality of life and functional impairments were improved significantly at six and 12 months compared to treatment as usual.
b. measures of quality of life and functional impairments were improved significantly at six months, but not at 12 months, compared to treatment as usual.
c. improvement in measures of quality of life and functional impairments were correlated with improvements in depression but not obesity at 12 months.
d. improvement in measures of quality of life and functional impairments were correlated with improvements in obesity but not depression at 12 months.

[IN FUTURE ISSUES]

Ultraviolet Exposure and Melanoma Risk

Vitamin D and Mental Health

Long COVID