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DEPRESSION

ABSTRACT & COMMENTARY

A Null Finding: Vitamin D3 Supplementation Not Associated with Depression Prevention

By Ellen Feldman, MD

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SYNOPSIS: This randomized clinical trial involving more than 18,000 nondepressed adults at baseline and followed for five years concludes that supplementation with vitamin D3 (vs. placebo) is not associated with a decrease in symptoms of depression.

SOURCE: Okereke OI, Reynolds CF, Mischoulon D, et al. Effect of long-term vitamin D3 supplementation vs. placebo on risk of depression or clinically relevant depressive symptoms and on change in mood scores: A randomized clinical trial. *JAMA* 2020;324: 471-480.

In 2010, former U.S. Surgeon General **David Satcher**, MD, PhD., said, "The nation is now poised to take the next step toward realizing the vision of integrating mental health and public health described a decade ago in the Surgeon General's report. Spiraling healthcare costs and the rising number of uninsured Americans have built momentum for healthcare reform, and it is clear that a population-based, public health approach — one that encompasses mental health — will be needed as a foundation for that reform."[1]

It has been more than 10 years since Dr. Satcher accurately predicted the integration of mental health with public health efforts.[1] Today, fighting depression is recognized as a public health priority, but depression in the elderly presents unique challenges. Often, providers and patients perceive symptoms of depression in this population as a normal reaction or component of aging, rather than a treatable condition.

Unfortunately, untreated depression may have devastating effects in this vulnerable age group, with a decline in cognitive and physical functioning that is difficult to reverse. Although rates of major depression are less frequent among older adults than the younger population, suicide rates by age are highest in persons aged 85 years

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Summary Points

- In all, 18,353 nondepressed adults older than 50 years of age participated in this five-year randomized controlled trial investigating a role for vitamin D3 in the prevention of depression.
- Half of subjects received placebo while participants randomized to the intervention arm received 2,000 IU/day of cholecalciferol and daily omega fatty acids.
- There was no statistically significant difference between incidence of depression, clinically relevant symptoms of depression, and mood scores when comparing these outcomes in participants in the active intervention arm to those in the placebo arm.

and older, and higher in the ≥ 50-year-old demographic than any younger age group.[2,3]

Investigations into interventions to prevent depression in this older age group are ongoing. Observational studies have shown an association between low serum 25-hydroxyvitamin D and later life depression.[4] Okereke et al noted these findings have spurred efforts to understand if supplementing with vitamin D3 can prevent depression.

For background, Okereke et al cited 13 randomized controlled trials (RCTs) looking into use of vitamin D3 during middle to later life to prevent development of depression and noted all but one of these studies were unable to confirm a role for vitamin D3 in depression prevention.

However, few of the studies used robust doses of vitamin D3, some participants had subclinical levels of depression at the onset of the studies, and none of the studies were adequate in length to draw firm conclusions.

In contrast to these previous studies, this investigation lasted five years, included 18,353 adults without symptoms of depression at study entrance, and used high-dose vitamin D3 (2,000 IU/daily). Participants were recruited from a larger study of 25,871 men and women enrolled in the vitamin D and omega-3 trial (VITAL) investigating the use of high dose vitamin D and omega-3 fatty acids in the prevention of cancer and cardiovascular disease.

This ancillary trial looking at development of depression, recurrence of depression (in patients with such a history), and mood trajectory over the five years is known as VITAL-DEP.[5]

Exclusion criteria for participation in VITAL-DEP included any of the following:

- having current symptoms of depression (defined as a Patient Health Questionnaire [PHQ-8] score of > 10);
- having a core symptom of depression for more than two weeks over the previous two years;
- receiving current treatment for depression;
- abusing alcohol or substances within the past year;
- having a current diagnosis of another psychiatric illness, such as schizophrenia or bipolar disorder.

All participants were followed annually with questionnaires about symptoms until study end, with a median time in the study of 5.3 years and an impressive 90.5% completion rate. Baseline and end of study serum levels of 25-hydroxyvitamin D were collected from a representative sample of the participants and confirmed expected increase in levels of vitamin D3. Another subset of the participants underwent in-person psychiatric interviews to validate findings from the questionnaires.

Identified outcomes included a self-report of a diagnosis of depression from a medical provider, treatment of depression, and/or a PHQ-8 score > 10 on an annual questionnaire. At study onset, participants were randomized into either an active treatment or placebo group with efforts to balance each arm according to age, sex, and race.

The active treatment consisted of the 2,000 IU of vitamin D3 as well as fish oil or alpha omega-3 (1 g/day of 465 mg of eicosapentaenoic acid and 375 mg of docosahexaenoic acid).

RESULTS

Relevant characteristics of the study population included:

- 49% female
- 27% racial minority
- Mean age of 67.5 years at study onset

Table 1 shows the results of primary outcome (development of depression, including incident and recurrent episode) during the five-year study period. There were no statistically significant differences between development of depression (either incident or recurrent) between the active treatment and placebo groups. When PHQ-8 scores were compared between the two groups, there was a mean difference of 0.01 points with a 95% confidence interval of 0.04 to 0.05 points (essentially, the difference between group PHQ-8 score was 0 throughout the study period).

■ COMMENTARY

This ambitious study, including more than 18,000 nondepressed, older U.S. adults followed for five years, found no measurable evidence supporting prevention of depression with supplementation of daily vitamin D3 2,000 IU and alpha omega-3 fish oil.

This study was rigorous, with adequate numbers and length and built-in redundancy to double-check accuracy of measures (for example, in-person psychiatric interview in a subset of participants to validate questionnaire results and serum monitoring to verify vitamin D3 compliance.) Maintaining racial and ethnic diversity during randomization adds to the strength of the study, given that cultural influences may affect questionnaire results and that baseline 25-hydroxyvitamin D3 levels tend to vary among racial lines.

One study limitation was that the population was limited to older adults. There is no evidence that findings may be extrapolated to a younger age group. In addition, although serum levels of 25-hydroxyvitamin D were measured in a subset of participants (to check compliance), the majority of participants in both arms of the study had adequate levels of this vitamin at baseline.

Since randomization did not occur according to vitamin D serum level, there is no indication from this study that supplementation can or cannot prevent depression if an individual is deficient in this vitamin. This is an avenue ripe for exploration in future studies.

Additionally, this study was limited to a nondepressed population at baseline, and conclusions regarding patients with existing depression cannot be drawn at this time. Furthermore, the effect of vitamin D3 on individuals taking antidepressants remains unclear and open for future study.

For now, it does seem that this study reinforces past investigations finding a lack of evidence that vitamin D3 is associated with depression prevention. However, the results contrast with observational studies noting that low levels of vitamin D3 are associated with depression. It may be that these later studies can be re-examined now in light of the findings from this study and with a consideration that confounding factors may have affected original findings.

The clinical implications from this study are simple: There is no association found between supplementation of vitamin D3 and depression prevention in a nondepressed older adult population. This certainly does not extend to the potential for vitamin D3 in maintaining and improving skeletal health — there remains a well-established place for vitamin D3 in this realm. In addition, use of vitamin D3 in other populations (including younger age groups and in depressed patients) remains to be explored. ■

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Table 1. Number of Patients Developing Depression During the Study Period

Study Arm	Number of Participants	Depression or Clinically Relevant Depressive Symptoms	New-Onset Depression	Recurrent Depression
Vitamin D3 and omega-3	9,181	609	150	
Placebo	9,172	625	164	
		Hazard ratio = 0.97; *P* = 0.62	Hazard ratio = 0.99	Hazard ratio = 0.95

ABSTRACT & COMMENTARY

Dietary Influences on Rheumatoid Disease

By Shiva Maharaj, MB BCh, MSc, and Nancy Selfridge, MD

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SYNOPSIS: An extensive systematic review of research exploring the relationship between diet and the risk of rheumatoid arthritis as well as disease activity concludes that some dietary patterns and supplements may be protective enough to be recommended as part of the holistic management of rheumatoid disease.

SOURCE: Gioia C, Lucchino B, Tarsitano M, et al. Dietary habits and nutrition in rheumatoid arthritis: Can diet influence disease development and clinical manifestations? *Nutrients* 2020;12:1456.

Chronic autoimmune inflammatory diseases, such as rheumatoid arthritis (RA), cardiovascular diseases, and adiposity-based chronic diseases, such as type 2 diabetes mellitus, constitute a global healthcare burden of pandemic proportions. They all share systemic inflammation in their pathophysiology and environmental factors, such as diet, as potentially enabling conditions.[1] RA has a global age-adjusted prevalence of 0.24%, is twice as prevalent in females compared to males, and is ranked as the 42nd-highest contributor to global disability.[2] Higher prevalence has been noted in Australia, Western Europe, and North America and lower prevalence noted in Eastern Asia, Southeast Asia, North Africa, and the Middle East. Higher prevalence also has been associated with high income.[2] Global variation in disease burden and association of RA with higher income support the premise that environment and diet may play a role in this disease risk and disease severity.

Gioia et al offer a systematic review of more than 200 publications (from 1979-2020) exploring the relationship between diet and RA in the following categories:

- pro- and anti-inflammatory influences of specific dietary constituents;
- diet as an epigenetic risk factor for RA development, disease activity, and outcomes;
- dietary effects on the gut microbiome and subsequent effect on inflammatory cascade;
- the influence of specific nutrients on disease activity in established RA;
- dietary recommendations for RA patients.

Studies included in the review encompass bench in vitro and animal research on food and nutrient biochemistry and immunology, epidemiologic studies, longitudinal cohort studies, cross-sectional studies, randomized controlled trials, and systematic reviews and meta-analyses.

The ability to measure inflammatory markers, such as C-reactive protein, interleukin-6, and tumor necrosis factor-alpha, has enabled the assessment of the proinflammatory and anti-inflammatory effects of dietary patterns and individual nutrients. Given the geographic differences in the prevalence of RA, comparison between the standard Western diet and the Mediterranean diet (MD) and their inflammatory potential seems intuitive. The former, characterized by relatively high intake of red meat, saturated/trans fats, refined sugars, and high glycemic index carbohydrates and low omega-3/omega-6 fatty acid ratios, has been associated with increased RA risk through documented pro-inflammatory marker responses and induction of insulin-resistance and obesity.

Trans-fatty acids found in manufactured (hydrogenated) cooking oils and margarines have demonstrated pro-inflammatory effects when compared to polyunsaturated fatty acids (PUFAs), such as omega-3 fatty acids, found in fish oils, nuts, and eggs. The Mediterranean Diet emphasizes consumption of plant-based unprocessed foods and PUFAs, and its nutrient-dense profile has been associated with reduced overall mortality, reduced cardiovascular mortality, and reduced incidence of cancer as well as reduced incidence of Alzheimer's and Parkinson's disease. Biochemical analyses of components of the MD have identified the antioxidative properties of polyphenols and lycopenes in red wine and tomatoes, respectively, and the anti-inflammatory influences of flavonoids and carotenoids found in fruits and vegetables.

The proven immunomodulatory effects of the active metabolite of vitamin D are well known and highlight the challenges of connecting this metabolite with disease processes.[3] Vitamin D deficiency has been observed in patients with autoimmune conditions, but its actual role has not been well defined because of confounding variables within studies, such as sunlight exposure, and an absence of global consensus on defined deficiency levels. Table 1 (online at https://bit.ly/3q6HMi1) summarizes findings from two large prospective cohort studies (EPIC-Norfolk and NHS) and a cross-sectional multicenter study

Summary Points

- An autoimmune inflammatory process underlies the pathogenesis of rheumatoid disease.
- Certain dietary patterns and profiles have proven pro- and anti-inflammatory effects.
- Dietary habits influence gastrointestinal physiology, including the gut microbiome, and systemic inflammatory cascades.
- Dietary modifications, when integrated into holistic management of patients with rheumatoid arthritis, can mitigate disease activity, modify pharmacological intervention, and reduce disease morbidity.

examining diet and the risk of developing RA. Results from these studies are conflicting and inconclusive despite what is known about the pro-inflammatory and anti-inflammatory potentials of the listed foods and nutrients.

Studies of milk consumption and the risk of RA have been similarly mixed and inconclusive. The association between fruit and vegetable consumption and RA risk also has been inconclusive. Despite the abundant anti-inflammatory and antioxidant components of plant-based foods, it is possible that consumption of "nightshade" vegetables (potatoes, tomatoes, and eggplant) and their known association with increased RA risk confounds study results. These vegetables contain solanine, an alkaloid that increases intestinal permeability. Some evidence suggests that "excessive" consumption of red meat (more than two servings/month) has been associated with an increased risk of inflammatory polyarthritis in rat models possibly mediated through the pro-inflammatory metabolite trimethylamine-N-oxide found in blood and synovial samples.

Sound biochemical evidence exists to implicate the pro-inflammatory additive effects of salt and smoking through the induction of glucocorticoid kinase-1 and anti-citrullinated protein antibodies. High-caloric diets resulting in obesity, increased body mass index (BMI), and waist circumference are established risk factors for RD development. The authors posit that white adipose tissue is an "endocrine organ" able to release inflammatory mediators, thus promoting the development of autoimmune and other inflammatory diseases. A population-based study of more than 500,000 subjects found an association between increased waist circumference (even after BMI correction) and heightened risk of RA development. Similar associations were found in a Danish cohort, which showed an increased risk of RA development and higher total body fat and waist circumference, especially in women. Consumption of sugary drinks appears to increase the risk of RA development, as does consumption of > 4 cups of coffee daily, although when cigarette smoking was considered as a confounding factor in coffee consumption, the association was lost.

Alternatively, omega-3 fatty acid intake and consumption of fatty fish appear to confer protection, as does olive oil and drinking tea. Moderate alcohol consumption (three to five drinks/week) also appears to confer protection, although studies have been hampered by confounders and other limitations. Green tea appears to suppress inflammation in mouse models of arthritis. Disruption of normal gut microbiota may be associated with the pathogenesis of RA, via alteration of gut epithelial integrity with increased intestinal mucosal permeability, allowing immunogenic substances from ingested food to trigger a systemic inflammatory cascade. Studies suggest that RA is associated with significant modification of gut microbiota and that specific bacteria may directly influence the development of the disease. MD may have a beneficial effect on the gut microbiota in RA, if maintained for longer than three months.

Calorie restriction, fasting, and a ketogenic/low carbohydrate diet have shown anti-inflammatory effect with reduction in inflammatory markers, although these interventions have not been studied for effects on RA disease activity and symptoms. Studies of antioxidant supplementation (selenium, ascorbic acid, vitamin A, vitamin E, zinc) in RA have been mixed, with clinical disease activity corresponding poorly to any salubrious changes in measured oxidative stress. Although genistein, a compound found in soybeans, has demonstrated in vitro and in vivo ability to inhibit inflammatory cytokines and growth factor expression, its clinical efficacy is unknown. Gluten has known immunogenic properties. Elimination of gluten (plus a vegan diet) was associated with decreased RA disease activity and athero-protection. Alcohol consumption has shown mixed effects on RA symptoms. Probiotic supplementation appears to consistently reduce pro-inflammatory cytokines in patients with RA but has demonstrated mixed effects on patient symptoms and disease activity.

The authors conclude that dietary patterns influence both the risk of developing RA and disease activity in patients diagnosed with RA. Current research supports a MD for primary prevention and for adjunctive treatment for RA. Additional reduction in red meat, refined sugar, gluten, salt, trans fatty acids, and coffee, as well as solanine-containing "nightshade" family vegetables is advised. Dietary substances to be encouraged include omega-3 fatty acids (fatty fish), mono-unsaturated fats (olive oil), fruits and

vegetables, and probiotics. Figure 1 (online at https://bit.ly/3j4MPOH) illustrates the effects of various foods and nutrients on joint health and rheumatoid arthritis and their complex interactions.

■ COMMENTARY

Although in-vitro and rodent-model studies reveal compelling biochemistry supporting the pro- and anti-inflammatory effects of a wide variety of foods and nutrients, the clinician's challenge lies in determining how well these effects translate into in vivo ecosystems and associated complex homeostatic processes toward creating recommendations for patient dietary practices and interventions.

Strengths of this analysis include its comprehensive database, wide thematic scope, and types of studies reviewed. Although incredibly edifying, this broad spectrum of information simultaneously limits the ability to arrive at consistent data-supported specific clinical recommendations for dietary interventions for RA. No reasonable statistical meta-analysis of the research data was possible, given the diversity of study designs. Additional large clinical controlled trials of dietary interventions are technically difficult but necessary to amass the practical data needed to support inclusion of dietary and nutritional advice in therapeutic guidelines. Nonetheless, clinicians may consider the following advice in caring for their RA patients, based upon this review:

- An MD can be recommended to confer beneficial effects on risk, related comorbidities, and RA disease activity.
- Limited consumption of salt, sweetened drinks, alcohol, milk, and red meat and avoidance of smoking tobacco may help reduce the harmful pathophysiological processes of inflammation in RA.
- Maintenance of optimum vitamin D levels via dietary intake or ultraviolet exposure is important for RA management.
- Regulation of body weight as an imperative because of its demonstrated adverse effect on disease activity.

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DIABETES

ABSTRACT & COMMENTARY

Chamomile and Diabetes

By Charla Corbin, MBBS, and Nancy Selfridge, MD

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SYNOPSIS: A systematic review of recent studies of the effects of chamomile on metabolic profiles suggests a positive effect on glycemic control, lipid profiles, and diabetic complications.

SOURCE: Hajizadeh-Sharafabad F, Varshosaz P, Jafari-Vayghan H, et al. Chamomile (*Matricaria recutita* L.) and diabetes mellitus, current knowledge and the way forward: A systematic review. *Complement Ther Med* 2020;48:102284.

Diabetes mellitus is one of humankind's top 10 leading causes of death and disability.[1] Affecting more than 400 million people worldwide, including more than 30 million Americans, diabetes prevalence continues to rise — disproportionately more rapidly in low- and middle-income countries.[1,2]

Despite breakthroughs in pharmacotherapy and strong evidence of efficacy for lifestyle interventions, diabetes remains a major cause of blindness, amputations, chronic kidney disease, and cardiovascular events, such as myocardial infarction and stroke.[2] Oxidative stress and systemic inflammation appear to be the common pathophysiologic conditions linking diabetic macrovascular and microvascular complications. Chamomile has been used as an herbal medication for thousands of years in many healing traditions and still is included in the natural pharmacopoeia of many countries.[3] The plant has been found to contain sesquiterpenes, terpenoids, flavonoids, coumarins, and polyphenols, many of which have been shown to demonstrate anti-inflammatory, antioxidant, antiseptic, and antihyperglycemic effects.[3]

The authors of this systematic review wished to review, analyze, and report evidence of chamomile's effects on metabolic markers and complications of diabetes from animal and human studies. After a broad literature search of common electronic databases, including PubMed, Sco-

Summary Points

- Chamomile, a plant that is rich in polyphenols, flavonoids, and other antioxidant and anti-inflammatory chemicals, has a long history of medicinal use worldwide and across healing traditions and practices.
- In this systematic review, results from various research studies suggest that chamomile may improve glycemic control, improve lipid metabolism, and reduce oxidative stress in diabetes.
- Some weaker evidence suggests that chamomile use may affect diabetic complications positively.

pus, Embase, ProQuest, and Google Scholar, the authors applied the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) protocol.[4] Of 208 initial articles retrieved in the literature search, nine animal studies and six human clinical trials met inclusion criteria for review. In eight of the animal studies, diabetes was induced by streptozotocin or alloxan. A variety of chamomile preparations were used in the animal trials, including ethanolic extract (n = 3) and aqueous extract (n = 4), both at doses between 20 mg/kg to 500 mg/kg for two to 14 weeks, and chamomile tea (n = 2) at a dose of 500 mg/kg for four weeks or 1 g for eight weeks. Studies also varied in the part of the chamomile plant used for the aqueous and ethanolic extracts. All human trials employed chamomile tea, 2.5 g to 10 g for four to 12 weeks.

Outcome measures varied by trial but included blood glucose and insulin, hemoglobin A1C levels (HbA1c), lipid profiles, liver enzymes and liver function, renal function, measures of oxidative stress and inflammation, and body weight fluctuations. Animal studies typically employed gavage or gastric cannula to deliver doses; one study administered the chamomile in the rat's drinking water. All animal studies showed improvement in various measures of glycemic control and glucose intolerance, sustained over time. Improvements in plasma glucose levels in rats with diabetes ranged from 14% to 59% and was dose-dependent in studies that included different dosing regimens. Where measured, insulin levels and insulin sensitivity increased.

In one study, histopathologic assessment of sacrificed animals showed that rats with diabetes treated with chamomile demonstrated increased insulin positive B cells in pancreatic islets compared to untreated controls. Animal studies also demonstrated positive results of chamomile on lipid profiles in two studies, with statistically significant reductions in total cholesterol, triglycerides, low-density lipoproteins (LDL), and very-low-density lipoproteins, as well as increases in high-density lipoproteins in rats with diabetes.

In the four animal studies that addressed chamomile's effects on oxidative stress markers in both normal rats and rats with diabetes, the levels of various antioxidant enzymes were increased consistently. In three studies of the effects of chamomile on diabetic complications, statistically significant positive effects on renal profiles, reductions in hepatic enzymes (alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase), and weight reduction were noted. Human study results were less consistent. Only three of the six human studies included in the review examined the effects of chamomile in patients with diabetes. One study using chamomile tea (10 g/100 mL boiling water) twice daily for four weeks in both patients with diabetes and controls demonstrated reductions in fasting and post-prandial blood glucose of 8% and 7%, respectively, although the changes were not statistically different between the treatment and control groups.

In another trial, 64 patients with type 2 diabetes received three cups daily of chamomile tea (3 g/150 mL of hot water) or placebo for eight weeks. The chamomile tea group demonstrated significant decreases in HbA1c, insulin levels, and insulin resistance, as well as an 11% reduction in serum glucose levels compared to the placebo group. A third study of 64 depressed patients with diabetes receiving three cups daily of chamomile or black tea for 12 weeks demonstrated significant reduction in HbA1c in the chamomile users compared to the black tea group. Again, three of the six human studies investigated the effects of chamomile supplementation on dyslipidemia.

All of these studies demonstrated significant reductions in total cholesterol, triglycerides, and LDL. In the chamomile vs. black tea study mentioned previously, there were no between-group differences in the post-treatment lipid profiles of the patients with diabetes in the study. Only three human trials included measures of oxidative stress and inflammation. Two of the trials yielded inconclusive results. However, one trial noted significant increases in antioxidant enzymes and reductions in malondialdehyde (MDA — a marker of oxidative stress) levels, as well as decreases in tumor necrosis factor and C-reactive protein measures of systemic inflammation. The single clinical trial that evaluated the effects of chamomile on diabetic complications demonstrated significant decreases in serum creatinine over the four-week treatment period.

■ COMMENTARY

Chamomile tea appears to have positive effects on glycemic control and hyperlipidemia, based on the human

clinical trials included in this systematic review. Animal studies of different extracts of chamomile more strongly support chamomile's positive effects on insulin resistance, blood glucose, dyslipidemia, and disease complications in rats with diabetes. A major strength of this systematic review is the application of the PRISMA protocol, a standardized checklist for systematic reviews and meta-analyses that aligns with Cochrane Collaboration standards and procedures and helps minimize bias in reporting.

A significant weakness is that the streptozotocin- and alloxan-induced diabetes in rats in the animal studies may be a poor model for human type 2 diabetes mellitus. These chemicals destroy pancreatic islet cells within a short timeframe after exposure, unlike the lengthy evolution of type 2 diabetes mellitus involving predisposing increased adiposity, insulin resistance associated with elevated insulin levels, and multiple associated metabolic disturbances long before reduction of pancreatic islet cells occurs.

Nonetheless, preliminary results from small human trials is encouraging, and chamomile tea is accessible and has no known adverse effects, although patients who are allergic to the Asteraceae/Compositae family of plants (e.g., dandelions, daisies, asters, ragweed, and goldenrod) may need to exercise caution in using chamomile. In one report, 3.1% of a general population of subjects developed Asteraceae-related allergic reactions, and of those subjects, more than 50% demonstrated an allergic response to chamomile.[5] Chamomile is contraindicated in patients taking warfarin because of an increased risk of bleeding mediated through cytochrome P450 enzyme inhibition, although case-based evidence for this drug-herb interaction is not strong.[6] Because of its effects on P450 enzymes, chamomile should be used with caution in patients taking aspirin and platelet inhibitors, cyclosporine, tricyclic antidepressants, some antipsychotics, propranolol, theophylline, and tacrine. Use in patients taking insulin may place the patient at an increased risk of hypoglycemic episodes.

However, outside of these caveats, and while awaiting larger human randomized controlled clinical trials of chamomile for the management of type 2 diabetes, physicians can recommend daily use of chamomile tea for patients with type 2 diabetes because of its known anti-inflammatory and antioxidant effects and for its potential value in improving the disease's glycemic control, lipid profiles, and renal and hepatic consequences. ■

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To view the references for this article, visit https://bit.ly/2TIbL3Q.

CME QUESTIONS

1. **Which of the following best describes the likely first effect of altered gut microbiota in the pathophysiology of rheumatoid arthritis?**
   a. Disruption of intestinal epithelial integrity
   b. Impaired systemic innate and adaptive immunity
   c. Generation of inflammatory mediators by gut bacteria
   d. Impaired intestinal absorption of nutrients
2. **In a single human trial assessing the effects of chamomile on systemic inflammatory markers, which of following was reduced significantly in subjects drinking chamomile tea?**
   a. Erythrocyte sedimentation rate
   b. Interleukin-6
   c. Tumor necrosis factor-alpha
   d. Procalcitonin
3. **Supplementation with 2,000 IU daily of vitamin D3 over five years:**
   a. was shown to be associated with a decreased risk of depression in young adults, but not in adults older than 55 years of age.
   b. was shown to have no effect on prevention of depression or exacerbation of depression in a population of depressed older adults (ages 55 years and older).
   c. was shown to have no effect on prevention of depression or depressive symptoms in a population of nondepressed older adults (ages 55 years and older).
   d. was shown to be associated with a decreased risk of depression but increased risk of mood instability in adults ages 21 and older.

[IN FUTURE ISSUES]

Ultraviolet Exposure and Melanoma Risk

Supplements and Type 2 Diabetes

Long COVID