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DIET

ABSTRACT & COMMENTARY

Pediatrics: Diet Matters

By Ellen Feldman, MD

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Dr. Feldman reports no financial relationships relevant to this field of study.

SYNOPSIS: Specific diets show evidence of efficacy in the treatment of several common pediatric disorders.

SOURCE: Erlichman J, Hall A, Dean A, et al. Integrative nutrition for pediatrics. *Curr Probl Pediatr Adolesc Health Care* 2016;46:165-171.

These ancient words from Hippocrates still ring true today. In many disorders of children and adolescents, there is evidence that what a child eats — and also what a child does not eat — makes a difference in the outcome and management of disease states. However, there are many non-evidence-based claims and popular trends touting specific diets for childhood disorders, making it confusing for parents to choose a rational way to proceed.[1] Knowing the medical evidence for specific diets allows the practitioners to guide parents and children through this decision. The importance of recommending well-studied and medically sound nutritional interventions when considering diet modification in children cannot be understated considering, among other factors, the potential to harm the developing brain via malnutrition. Recognizing this, Erlichman et al chose to undertake a comprehensive review of dietary interventions for several common disorders of children. They chose to focus specifically on diet and not nutritional supplements; thus, the interventions do not include reviews of nutraceuticals.

Table 1 summarizes dietary interventions for common childhood disorders. Each row is devoted to one of the specified diets, contains major features of each diet, and notes disorders for which these diets can be useful (often in conjunction with conventional medication and interventions). A more in-depth discussion of each reviewed childhood disorder and the potential role of nutritional intervention follows.

ATTENTION DEFICIT HYPERACTIVITY DISORDER

Attention deficit hyperactivity disorder (ADHD) is a common neurodevelopmental disorder thought to affect about 11% of U.S. children between the ages of

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Summary Points

- The article focuses on evidence for use of specific diets in treatment of attention deficit hyperactivity disorder (ADHD), pediatric headaches, eczema, irritable bowel syndrome, celiac disease, and non-celiac gluten sensitivity.
- Diets include elimination diet for ADHD, eczema, and headaches; Mediterranean-type diet for headaches; low FODMAP for irritable bowel syndrome; and gluten-free diet for celiac disease and non-celiac gluten sensitivity.
- It's important to build a team that includes nutritionists and pediatric specialists, who can play especially important roles.

4 and 17 years. Psychostimulant medications remain the standard treatment, but an estimated 25% of parents look toward integrative therapies to provide non-pharmaceutical options. The most common interventions reside in the realm of nutrition, with either diet modification or the use of supplements (such as omega-3 fatty acids or vitamins).[8]

The Feingold Diet: Proposed in 1973 by pediatric allergist Ben Feingold, it is hypothesized that hyperactivity in children could be reduced by eliminating food additives and naturally occurring salicylates from food products. Although a large 1983 meta-analysis of 23 studies looking at this relationship was inconclusive,[2] research continues, and more recent studies have demonstrated a relationship between artificial food additives and hyperactivity.[9]

The Oligoantigenic Diet: Also known as the few-foods diet, this is an elimination diet in which common allergenic foods are removed (*see Table 1*) and then reintroduced in a challenge phase to see if/when symptoms re-emerge. Since 2007, several studies have demonstrated partial benefit in a subset of children with ADHD, particularly affecting specific symptoms, including sleep and hyperactivity. These effects do not appear to be IgG-mediated.[3]

There may be benefit to implementing a restrictive diet to improve symptoms of ADHD in children. The mechanism of action and likely responders still need to be identified. Erlichman et al recommended the assistance of a registered dietician if considering this as an option for intervention, given the need for "in-depth assessment, counseling, and support."

For families interested in adopting nutritional guidelines without intensive intervention or assistance of a dietician, an integrative practitioner with expertise in nutrition may be able to provide guidance and monitoring. Online resources (such as printable handouts from www.fammed.wisc.edu/integrative) can be helpful in supporting efforts to address nutritional intervention in the primary care physician's office.

PEDIATRIC HEADACHES

According to Erlichman et al, before recommending specific diets, most headache patients are advised about general dietary modifications that include avoiding fasting, preventing dehydration, limiting caffeine, and tracking and avoiding any specific food triggers through the use of a headache diary.

Oligoantigenic Diet (see above for details): Few studies have been conducted in children, but suggestive studies from adults look positive regarding efficacy of the IgG-based elimination diet (use IgG testing to determine which foods to avoid as opposed to non-IgG-mediated response in ADHD treatment).[3]

Ketogenic and Modified Atkins Diet: The ketogenic and modified Atkins diets are high-fat, low-protein, low-carbohydrate diets. The modified Atkins diet is less restrictive than the ketogenic diet.[4] Both of these diets are used to treat intractable epilepsy in children and adults. There are limited studies in children regarding these diets for treatment of headaches, but at least one study with low numbers shows promise in teenagers. Specifically, a 2010 prospective trial enrolling eight teenagers with migraines showed promising results in terms of headache amelioration, but the numbers involved make results difficult to generalize.

Table 1: Summary of Dietary Interventions for Common Childhood Disorders		
Diet	**Major Features of Diet**	**Childhood Disorders for Which the Diet May Be Useful**
Feingold Diet[2]	Avoidance of foods with naturally occurring salicylates, synthetic foods, colors, and additives	Attention deficit disorder (with or without hyperactivity)
Elimination-oligoantigenic Diet[3] "Few foods diet"	Remove foods that contain natural or potential allergens, such as dairy, wheat, soy, nuts, and citrus, and reintroduce in a "challenge" phase	Attention deficit disorder (with or without hyperactivity) Migraines Eczema
Ketogenic Diet[4]	High in fat, restricted proteins, very low carbohydrates	Intractable epilepsy Headaches (limited studies)
Mediterranean-style Diet[5]	Plentiful fruits and vegetables, whole grains, nuts, seeds, fish, olive oil, and beans Moderate poultry, seafood, eggs, and dairy Limited red meats and sweets	Headaches and migraines
Low FODMAP[6] (Fermentable oligosaccharides Disaccharides Monosaccharides and Polyols)	Decrease short-chain carbohydrates and sugar alcohols in diet, including wheat products, beans, sources of fructose and lactose, and artificial sweeteners	Irritable bowel syndrome
Gluten-free Diet[7]	Exclusion of gluten, a protein found in wheat, barley, rye, and products from these sources	Celiac disease Non-celiac gluten sensitivity

Additional large-scale studies are necessary before this intervention can be recommended.

Mediterranean-style Diet: The Mediterranean-style diet is becoming increasingly well-studied and shows promise in multiple areas of health and well-being.[5] Characterized by plentiful fruits and vegetables, whole grains, nuts, seeds, fish, olive oil, and beans; moderate poultry, eggs, and dairy; and limited red meats and sweets, this diet can be adapted and followed under many conditions. Erlichman et al noted a promising study with 23 adolescents following a Mediterranean-style diet for headaches, and they said in general this heart-healthy diet can be recommended for dietary intervention in most children. If working with very young children (younger than 3-4 years of age), it is important to consider the American Academy of Pediatrics guidance to avoid nuts because of swallowing concerns and to provide whole milk up to 2 years of age.[11]

Conclusion: A provider is safe to recommend avoidance of known triggers (or allergens) and a Mediterranean-style diet. If a family requests pursuit of a more restrictive dietary approach (such as ketogenic, modified Atkins diet, or oligoantigenic), providers should remember that evidence is limited for efficacy of these diets for headaches in children and should enlist the aid of a dietician to support and advise in more complicated cases.

ECZEMA

An estimated 9-18% of U.S. children younger than 17 years of age carry a diagnosis of eczema or atopic dermatitis; about one in three of these are considered moderate to severe in intensity.[12] There is evidence that food allergy and/or intolerance plays a role in development and severity of eczema. Erlichman et al noted there is heightened risk of food allergy when eczema occurs in infants younger than 6 months of age, in patients whose skin outbreaks cannot be controlled with standard topical therapies, and when parents report a food reaction (either immediate or delayed).

Under these conditions, Erlichman et al recommended an elimination diet with close observation after removal of the suspected food(s) for at least two weeks. If there is no remission of symptoms after two weeks, it is unlikely that the suspected food was a trigger. They also recommended a period of open challenge (under medical supervision in case of anaphylaxis) after the two-week elimination period to confirm the suspected relationship.

Conclusion: In specific cases, there is evidence that food allergies/intolerance contribute to pediatric eczema. A carefully conducted trial of an elimination diet followed by a challenge period can help confirm diagnosis. Consider enlisting the aid of a pediatric allergist if possible and if needed to manage or monitor the patient.

IRRITABLE BOWEL SYNDROME

Often presenting as recurrent abdominal discomfort or pain not associated with inflammation or other biological markers of disease state, irritable bowel syndrome (IBS) affects up to 20% of U.S. school-aged children.[13] Many parents look for suspected food triggers, such as high-carbohydrate foods, milk, and fatty foods. However, the most promising studies

regarding diet modification in children with IBS originate from adult trials.

Erlichman et al pointed to studies involving FODMAPs (fermentable oligosaccharides disaccharides monosaccharides and polyols); these are compounds (sugar alcohols and carbohydrates occurring naturally in or added to foods) that are poorly absorbed in the small intestine and fermented rapidly in the colon, producing gas and distention. Although medical evidence suggests use of a low-FODMAP diet in adults to lessen symptoms of IBS, studies involving children are less common. Two recent trials with school-aged children showed evidence of efficacy in this population, but long-term safety in terms of nutrient balance and efficacy has not yet been established.[14]

Conclusion: There is growing but incomplete evidence for use of a low-FODMAP diet in children and adolescents with IBS. If this course is desired, a registered dietician should assist with implementation. However, as with many of these disorders, an integrative practitioner with experience and knowledge in this area and age group also may be able to provide treatment.

CELIAC DISEASE AND NON-CELIAC GLUTEN SENSITIVITY

Celiac Disease: Affecting up to 1% of the non-Hispanic white population in the United States, celiac disease is a chronic inflammatory disorder of the small bowel caused by a genetically determined autoimmune response to ingestion of gluten products. Among other symptoms, patients present with diarrhea, poor growth, abdominal pain, and/or bone and joint pain.[15]

A gluten-free diet with absolute avoidance of wheat, barley, and rye (gluten is a protein found in wheat, barley, and rye) is the sole treatment for celiac disease. Erlichman et al noted that because of malabsorption issues, patients should be tested for iron and vitamin deficiencies and supplemented if necessary.

Non-Celiac Gluten Sensitivity: Defined as a syndrome "characterized by intestinal and extra-intestinal symptoms related to the ingestion of gluten-containing food, in subjects that are not affected with either celiac disease or wheat allergy," non-celiac gluten sensitivity originally was described in the 1980s. More recent research has investigated a link to neuropsychiatric disorders, and several interesting case reports involving children with autism and psychosis have been published.[16,17] At this point, additional research is needed before any conclusions can be drawn.

Conclusion: A gluten-free diet in children with celiac disease is essential to maintain health. There is less evidence of a relationship between a gluten-free diet and extra intestinal symptoms (including behavioral) in children with non-celiac gluten sensitivity.

SUMMARY

Overall, this review serves as a reminder of the importance of diet in healthcare and treatment of illness in the pediatric population. Additionally, the unique needs of children and the difficulty of conducting large-scale controlled studies makes dietary intervention challenging in this population.

It is worth stating that compliance with dietary changes can be difficult for any patient, but even more so for a young person who often is in the midst of a search for autonomy and independence. This drive (and many social factors) may make it difficult to take to heart dietary advice. Providers should remember the importance of a team approach — enlisting not only parents, a medical provider, and a dietician but also, and perhaps most importantly, making sure the young patient maintains a primary spot on the team. ■

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DIABETES

ABSTRACT & COMMENTARY

Zinc Supplementation for Prediabetes

By David Kiefer, MD, Editor

SYNOPSIS: Thirty milligrams of zinc sulphate over six months improved a variety of metabolic parameters in a Bangladeshi population with prediabetes.

SOURCE: Islam MR, Attia J, Ali L, et al. Zinc supplementation for improving glucose handling in pre-diabetes: A double blind randomized placebo controlled pilot study. *Diabetes Res Clin Pract* 2016;115:39-46.

Zinc may, in fact, not just be for the treatment of colds anymore. This essential mineral, a cofactor in many biological reactions, also has been found to nudge a variety of clinical conditions.[1] The researchers conducting this clinical trial were following up on previous studies that found a correlation between higher dietary zinc intake and a lower risk of type 2 diabetes. Furthermore, they cited work that shows a small, likely clinically insignificant, reduction in fasting glucose and hemoglobin A1c with zinc supplementation, although they posit that zinc supplementation might stave off the progression from insulin resistance or metabolic syndrome to overt diabetes. Islam et al attempted to add to some preliminary work on this hypothesis.

This study took place in Bangladesh, involving a collaboration of Bangladeshi and Australian researchers. Adults aged 30-65 years diagnosed with prediabetes within a "catchment area" of the Bangladesh Institute of Health Sciences hospital were screened (n = 224, n = 177 with phone numbers allowing contact) for randomization to either placebo (n = 27) or 30 milligrams of zinc sulphate (n = 28) daily for six months. Prediabetes was defined as fasting blood glucose concentration between 5.6-6.9 mmol/L.

Exclusion criteria were extensive and are detailed in Table 1. The zinc and placebo tablets were identical in size, taste, color, and smell, and study participants received a six-month supply of tablets upon recruitment for participation. Both groups received advice on diet and lifestyle activities (details not provided) and were called every two weeks to check on "compliance, adverse events, and morbid events." See Table 2 for a timeline of interventions and data collection during the study. Note that socioeconomic data, 24-hour diet information, and blood tests were obtained. The primary outcome of the study was any change in fasting glucose levels. Secondary outcomes included calculation of beta-cell function, insulin sensitivity, and insulin resistance by way of the Homeostasis Model Assessment (HOMA), and serum zinc and lipid values at baseline and six months.

Summary Points

- Researchers in Bangladesh randomized a small group of adults with prediabetes to either 30 mg zinc sulphate or placebo daily for six months.
- After six months, there were improvements in fasting glucose, lipids, C-reactive protein, and calculated measures of insulin and pancreas function (HOMA scale).
- Generalizability of these results is unknown, especially given that the population studied historically has had low dietary zinc intake, making them possibly more amenable to zinc repletion.

With respect to baseline characteristics, the placebo group was more affluent and had higher lipid values than the zinc group; other parameters were similar. Table 3 shows the results for primary and secondary variables for zinc vs. placebo over the course of the research trial. For fasting glucose and the three subsets of the HOMA calculation, the zinc group showed statistically significant improvements from baseline to six months; the placebo group improved slightly for fasting glucose and insulin sensitivity, although the beta-cell function and insulin resistance were unchanged (see *P* values in Table 3). Also interesting was the comparison between the zinc and the placebo group at the six-month mark. The zinc group showed statistically significant improvements compared to the placebo group for all four parameters (*P* values ranging from 0.01 to < 0.001). In addition, the zinc group showed a lower serum triglyceride, low-density

Table 1: Exclusion Criteria, Preempting Inclusion in This Trial

- Diabetes diagnosis
- Pregnancy
- Morbid obesity
- Renal insufficiency
- Cardiovascular disease
- Thyroid disease
- Liver disease
- "Any other known chronic diseases"
- Multiple comorbidities
- Physical inactivity (wheelchair bound)
- Psychiatric disorders
- Gastrointestinal disorders
- Taking vitamins, diuretics, or "complementary medicines"

lipoprotein, and C-reactive protein, and higher high-density lipoprotein (all *P* values < 0.001) than the control group after six months.

Of note, there were no dropouts during the six months, and no adverse effects nor side effects occurred. Furthermore, the authors reported that none of the participants progressed from prediabetes to type 2 diabetes over the six-month period.

■ COMMENTARY

This study is an interesting example of the effects of a single nutrient on a variety of metabolic parameters. These results should be somewhat predictable, given the range of physiological systems touched by zinc. For example, the authors provided a comprehensive review of how zinc might be involved with insulin and glucose regulation. However, it is important to remember the specific demographic studied here. The researchers mentioned the fact that Bangladesh has low dietary zinc intake and a high dietary phylate intake, further compromising zinc absorption. It is likely that the study participants were zinc-deficient, and there are examples of how zinc repletion in the context of zinc deficiency might lead to positive clinical outcomes;[1] it's less clear whether such results would be achieved if a person has adequate amounts of zinc. Hence, the results from this study may or may not apply to the typical patient in the United States.

Table 2: Data Collection and Interventions During the Six-month Study

Baseline	Every Two Weeks	Six Months
Home visit to confirm diagnosis Advice on "healthy eating and lifestyle" Face-to-face interview* 24-hour dietary recall Blood tests** Calculation of HOMA	Phone call: compliance, adverse effects, morbid events	Blood tests** Calculation of HOMA

* Face-to-face interview collected "… socioeconomic and other relevant information." (details not provided)
** Blood tests included fasting glucose, serum zinc, serum insulin, hemoglobin A1c, lipid profile, C-reactive protein

On a further note relevant to applicability, the exclusions seemed extreme enough that it's hard to believe there were any study participants left meeting the criteria. The authors justified the list, referencing prior work, as with exclusion criteria in general, that they wanted to minimize confounders and drug interactions. Nonetheless, it seems overly limiting and leaves clinicians wondering how to apply these results to their own patient population. Many patients with prediabetes probably are taking some vitamin or have even the most minor of gastrointestinal disorders (occasional gastroesophageal reflux disease or indigestion). It would be interesting to see a comparable study on "more normal" people with a mixture of conditions and medications or dietary supplements.

The lack of adverse effects or side effects almost seems too good to be true. Most placebo-controlled trials report side effects even for the placebo group, so the lack of this in the current study casts some doubt on the methodological rigor and data collection. The phrasing of the phone call query into adverse effects is not listed; perhaps leading questions dissuaded study participants from reporting their symptoms. We don't know.

Table 3: Study Results for the Zinc and Placebo Groups Over the Six-month Study Period

	Placebo		Zinc	
	Baseline	Six Months	Baseline	Six Months
Fasting glucose (mmol/L)	5.80	5.69 (*P* = 0.05)	5.80	5.37 (*P* < 0.001)
Beta cell function (HOMA mean)	75.8	78.7 (*P* = 0.14)	76.5	87.7 (*P* < 0.001)
Insulin sensitivity (HOMA mean)	86.4	88.6 (*P* = 0.001)	86.5	90.4 (*P* = 0.012)
Insulin resistance (HOMA mean)	1.15	1.13 (*P* = 0.10)	1.15	1.09 (*P* = 0.002)

The *P* values displayed compare the placebo and zinc baseline values with their own values at six months.

And how clinically relevant are these results? The authors mentioned a number needed to treat (NNT) of 12 for metformin in cases of prediabetes over three years, based on an approximate improvement in hemoglobin A1c of 1%. Meta-analyses estimate that zinc improves hemoglobin A1c by approximately 0.5%, so the authors postulated a NNT of 24 (this study didn't measure hemoglobin A1c). This is not a negligible effect, and given its safety profile (a few minor safety concerns, though, at higher doses, possible copper deficiency), perhaps clinicians might consider turning to zinc early in the prediabetes treatment algorithm. In some cases, a serum zinc level may also be helpful in guiding therapy, although there are nuances to interpreting the results.[2] A quick glance at the data showed marginal improvements in fasting glucose, but (not included above, but provided in the research article) more robust changes in lipids and C-reactive protein, both between groups and over the six-month study period. The mechanism is plausible, and these findings are believable. Now, the next step is to broaden the demographic and study size and see if the results translate to a wider audience, even if zinc deficiency is not present. ■

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URINARY HEALTH

ABSTRACT & COMMENTARY

Cranberries for Urinary Tract Infection

By Traci Pantuso, ND, MS

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Dr. Pantuso reports no financial relationships relevant to this field of study.

SYNOPSIS: Cranberry capsules containing 72 mg of proanthocyanidins administered by mouth daily to women residing in nursing homes for one year did not have a significant effect on bacteriuria plus pyuria.

SOURCE: Juthani-Mehta M, Van Ness PH, Bianco L, et al. Effect of cranberry capsules on bacteriuria plus pyuria among older women in nursing homes: A randomized clinical trial. *JAMA* 2016;316:1879-1887.

Urinary tract infection (UTI) is the most commonly diagnosed infection among nursing home residents and is the most common reason for antimicrobial use in older adults.[1] Cranberries contain numerous constituents, including A-type proanthocyanidins, which inhibit *Escherichia coli* adhesion to uroepithelial cells in vitro and ex vivo.[2] Juthani-Mehta et al conducted a double-blind, placebo-controlled, efficacy trial in women 65 years of age or older who resided in 21 nursing homes located within 50 miles of New Haven, Connecticut, between Aug. 24, 2012, and Oct. 26, 2015. Of 5,045 individuals screened for participation in this study, 185 were randomized into the study. Long-term care residents who were 65 years of age or older, female, and English-speaking were screened for participation.

The exclusion criteria for this study included individuals staying in the nursing home for less than one month, taking chronic or suppressive antibiotic or anti-infective therapy for recurrent UTI, with history of nephrolithiasis, undergoing dialysis for end-stage renal disease, receiving warfarin therapy, having pressure of an indwelling bladder catheter, with allergy to or current use of cranberry products, or unable to produce a baseline clean catch urine specimen.

Ninety-two participants were randomized into the treatment group and 93 into the control group. (*See Table 1.*) Two cranberry capsules containing a total of 72 mg of proanthocyanidins (equivalent to 20 ounces of cranberry juice) were administered to the treatment group, while the placebo group received two placebo capsules each day for one year. The primary outcome of this study was bacteriuria and pyuria measured every two months for one year. The secondary outcomes measured were numbers of symptomatic UTI, all-cause death, all-cause hospitalization, all multidrug antibiotic-resistant organisms, antibiotics for suspected UTI, and total antimicrobial prescriptions. Bacteriuria was defined as at least 10^5 colony-forming units per milliliter of one or two organisms. Pyuria was defined as any number of white blood cells in the urine. The statistical analysis performed

Summary Points

- Cranberries contain numerous constituents, including A-type proanthocyanidins, which inhibit *Escherichia coli* adhesion to uroepithelial cells in vitro and ex vivo.
- The study authors found no significant difference in the presence of bacteriuria plus pyuria over one year in patients administered cranberry capsules.

Table 1: Study Demographics			
Demographics	Total Participants (n = 185)	Treatment Group (n = 92)	Control Group (n = 93)
Age, mean (SD)	86.4 (8.2)	87.1 (8.4)	85.6 (8.0)
Hispanic ethnicity	6 (3.2)	3 (3.3)	3 (3.2)
White race	167 (90.3)	83 (90.2)	84 (90.3)

was intention-to-treat with a two-sided *P* value of 0.05, which was considered statistically significant.

The overall adherence to the administration of the oral capsules was 80.1%, with 77.5% in the treatment group and 82.6% in the control group. No significant difference was found between the treatment and control groups on the percentage of urine specimens that were positive for bacteriuria and pyuria during the study (adjusted rates, 29.1% vs. 29.0%; odds ratio, 1.01; 95% confidence interval, 0.61-1.66; *P* = 0.98). No significant differences were found between the cranberry and placebo groups among the secondary outcomes: symptomatic UTI (10 vs. 12 episodes), mortality (17 vs. 16 deaths), or hospitalizations (33 vs. 50 episodes). The authors also found no significant differences between the placebo and cranberry group on the bacteriuria associated with multidrug-resistant gram-negative bacilli, antibiotics administered for suspected UTIs, or total antimicrobial utilization.

A total of 3,830 adverse events occurred during the study period, which is to be expected with the study population. Of these adverse events, only 14 were considered to be protocol-related and non-serious; they included altered mental status, gastrointestinal disturbance, weight loss, oral cavity disturbance, and/or a skin and soft tissue event. These 14 adverse events were similar between the placebo and treatment groups.

■ COMMENTARY

In this study, Juthani-Mehta et al found no benefit to women taking two cranberry capsules containing 72 mg of proanthocyanidins on bacteriuria or pyuria. The strengths of this study include the double-blind, randomized, controlled trial design with cranberry capsules that were standardized to proanthocyanidin concentration. The dose of 72 mg of proanthocyanidins is comparable to the amount of proanthocyanidins in 20 ounces of cranberry juice.

The authors also used the objective outcome of bacteriuria and pyuria and the use of the National Healthcare Safety Network criteria for symptomatic UTI. The limitations of this study were that participants were unable to be catheterized to obtain urine samples, so only patients who could provide a clean catch urine specimen were randomized. Only 65% of the planned urine specimens were able to be collected. Another important variable that was not controlled in this study was hydration status, which may reduce bacteriuria and urinary symptoms in older women. Anti-adhesion of *E. coli* to uroepithelial cells was not tested in the urine samples of the participants; this may have been an objective measure of not only adherence to the treatment but also evaluation of mechanism of action. Lavigne et al previously demonstrated that adhesion by *E. coli* to a uroepithelial cell line can be measured ex vivo in urine collected from participants taking cranberry products orally.[3] There is limited generalizability of this study to non-white older women and women not residing in nursing homes as the participants in this study were older than 65 years of age and predominately white.

The evidence for the use of cranberry products to prevent UTIs is a controversial topic, with some studies showing benefit and others demonstrating no effect.[4] The most recent 2012 Cochrane Review, which included 24 studies with 4,473 participants, investigating cranberry products and the prevention of UTI found no benefit and concluded that cranberry products should not be recommended for the prevention of UTI.[5] The previous Cochrane review, published in 2008, included 10 studies with 1,049 participants and found that there was some evidence that cranberry may decrease the incidence of symptomatic UTI.[6] This study is important in that it used a narrow UTI definition and objective measures (bacteriuria plus pyuria) as the primary outcome compared to a number of previous studies.

Although Juthani-Mehta et al reported no conflict of interest, the cranberry and the placebo capsules used in this study were manufactured and donated by Pharmatoka, which manufactures and sells Ellura, a cranberry capsule standardized to 36 mg of proanthocyanidin per capsule, in the United States. Ellura is marketed as "helping to maintain a clean urinary tract" and is a cranberry juice extract. It is unclear whether the cranberry capsules in this study were a cranberry juice extract. There are numerous compounds in cranberries, such as flavonoids, phenolic acid, triterpenoids, and anthocyanins.[2] These other compounds also may prevent UTIs, and cranberry juice extract may not provide the complex mixture of bioactive components that are found in whole cranberry fruit.[2] Although this study did not find benefit in the incidence of bacteriuria and pyuria or symptomatic UTI in this population consuming cranberry capsules, cranberry still may have benefit in other demographics as per past research. ■

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ABSTRACT & COMMENTARY

Free Probiotics for Winter Infections and Reducing Antibiotic Prescriptions

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Dr. Merry reports no financial relationships relevant to this field of study.

SYNOPSIS: A randomized, controlled trial of recommendations that asthmatics (5 years of age and older) take free daily probiotics over a winter season failed to show any benefits in terms of antibiotic usage or overall respiratory health.

SOURCE: Smith TD, Watt H, Gunn L, et al. Recommending oral probiotics to reduce winter antibiotic prescriptions in people with asthma: A pragmatic randomized controlled trial. *Ann Fam Med* 2016;14:422-430.

Resistance to antimicrobial agents is considered a major threat to global health security.[1,2] Antimicrobial resistance has been described as a "problem without borders" and has been identified as a key health priorities in the United States.[3] Ongoing efforts to stem the emergence of antimicrobial resistance include antimicrobial stewardship, new regulatory approaches, enhanced antimicrobial surveillance, increased research funding, and the elimination of non-judicious use of antibiotics in animals, plants, and marine life.[4] Little, if anything, has been said about looking at integrative health approaches to reducing antibiotic prescribing. Respiratory tract infections account for the vast majority of antibiotics prescribed in the primary healthcare setting.[5] People with asthma are particularly susceptible to viral respiratory tract infections and receive a disproportionate number of unnecessary antibiotics.[6]

Smith et al sought to determine whether access to free probiotics could reduce winter respiratory tract infections and antibiotic use in people with asthma older than age 5 years. The rationale for the use of probiotics was twofold. First, a 2011 Cochrane review suggested that probiotic use can reduce upper respiratory tract infections and antibiotic use.[7] The Cochrane review focused on children younger than 8 years of age and did not select out children with asthma. Second, a small pilot study that looked at acupuncture plus probiotics showed a reduction in the rates of respiratory tract infections in people with asthma.[8] The pilot study was underpowered and the differences in infection rates were not statistically significant.

Summary Points

- There is growing interest in the possible roles of the gastrointestinal microbiota and probiotics in immune mediated disorders such as asthma.
- This aim of this study was to see if free probiotics could reduce winter infections and associated antibiotic prescribing in asthmatics over the age of 5.
- The study failed to show any benefit of free probiotics in this patient population in terms of respiratory health or antibiotic prescribing.

The science behind the use of probiotics in asthma relates to a growing interest in a possible role for intestinal microbiota in the development of immune-mediated disorders such as asthma.[9] The working hypothesis is that the gut microbiota influence immune stimulation and tolerance. U.K. researchers conducted a community-based study in a semi-urban practice caring for 23,000 patients that examined the use of probiotics alone for reducing antibiotic use in asthmatics over a single winter between October 2013 and March 2014. Patients attending the Ashfields Primary Care Centre who were ≥ 5 years of age and who had a current diagnosis of asthma were included. All practice patients who met the study inclusion criteria were enrolled in the study and were randomly allocated to a control or intervention arm.

All U.K.-based asthmatic patients are entitled to receive the annual influenza vaccine. In this study, all patients received an invitation to come in for the seasonal influenza vaccine along with other helpful wellness tips via the U.K. postal service. This pragmatic study design essentially piggybacked onto the existing clinical care and randomized study participants to either receive standard of care clinical practice or to receive an additional leaflet offering them free probiotics to try to reduce winter respiratory infections and antibiotic use.

Households in the intervention arm received information about probiotics and three tokens, each of which entitled the households to receive a two-month supply of a patented probiotic free of charge. The probiotic contained 2.5 billion colony-forming units per capsule (containing two different strains of *Lactobacillus acidophilus* plus *Bifidobacterium bifidum* and *Bifidobacterium animals*). The probiotic used is a commercially available patented brand; none of the investigators disclosed any conflict of interest. The participants were instructed to take one capsule daily. The study did not have a placebo comparison arm.

The primary outcome for the study was the proportion of patients who received antibiotics for respiratory tract infections over the course of the winter. The secondary outcome for the study was overall respiratory health as defined by consultations for respiratory tract infections, exacerbations of asthma, and the number and cost of antibiotic courses prescribed during the six-month intervention period.

Both intention-to-treat and per-protocol analyses were carried out with an anticipated 20% loss of outcome data and a 5% contamination rate in the control group. A total of 1,270 study participants were enrolled in the study. The probiotic was accessed by 121 (19%) participants in the intervention group at least once. This means that 19% of households in the study used the token to get free probiotic capsules. The study design did not factor in any assessment of compliance, specifically whether the household member with asthma actually took the probiotics. There was a supplement to the study, which mentioned that one patient who was randomized to the intervention arm contacted the study team to request probiotics for her daughter.

The results of the study showed that there was no significant difference in the primary outcome measure. Smith et al reported 27.7% of children in the intervention group received antibiotics compared to 26.9% of children in the control group in the intent-to-treat analysis (odds ratio, 1.04; 95% confidence interval [CI], 0.82-1.34) or the per-protocol analysis (adjusted odds ratio, 1.08; 95% CI, 0.69-1.69). There was no evidence of any effect on respiratory tract infections or asthma exacerbations. There was no significant difference in serious adverse events between the intervention and control groups.

■ COMMENTARY

The results of this study do not support the use of leaflets and free access to probiotics to reduce antibiotic prescriptions or improve respiratory tract health in asthmatics older than 5 years of age. These results differ from the 2011 Cochrane review, which showed that probiotics reduce the risk of antibiotic use for acute upper respiratory tract infections.

To try to reconcile the apparent contradictory results between the British study and the Cochrane review, it is worth noting the key differences between the study designs. The British study focused on people with asthma aged 5 years or older. The authors of the British study suggested that the younger age of the children included in the Cochrane review may have affected the results, as younger children may be more sensitive to the immunological changes in the gastrointestinal tract triggered by taking probiotics. Additionally, the probiotic strains and formulation used in the British study were different from the ones included in the Cochrane review. Specifically, the British study used intact probiotic capsules rather than a liquid formulation. It is unclear whether probiotics prevent respiratory tract infections via local effects in the mucosa of the upper respiratory tract, in which case liquids may be superior to capsules.

In summary, free probiotics were not effective in preventing winter antibiotic prescribing, upper respiratory tract infections, lower respiratory tract infections, or asthma exacerbation rates in patients older than 5 years of age. This study provides real-world data, which show that free probiotics cannot be recommended to prevent winter infections and reduce antibiotic use in older children and adults with asthma.

Given the limitations of the study, including the lack of a placebo control arm and the inability to ascertain who (if anyone) within the household took probiotics, it is not possible to extrapolate from this study to make any generalizations about probiotics in asthma. Although this study failed to show any benefit of probiotics at either the individual patient level or at the public health level in terms of global antibiotic consumption, the investigators get top marks for the trial design and innovative integrative health style approach to address the growing concern about antimicrobial resistance. ■

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SHORT REPORT

Mind-Body Intervention for Neurofibromatosis

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Dr. Maltz reports she is a speaker for the Texas Medical Association Physician Health and Wellness Committee.

SYNOPSIS: Participants in a randomized, controlled trial of a videoconferencing mindfulness intervention for neurofibromatosis experienced improvement in measures of physical and psychological quality of life when compared to placebo.

SOURCE: Vranceanu AM, Riklin E, Merker VL, et al. Mind-body therapy via videoconferencing in patients with neurofibromatosis: An RCT. *Neurology* 2016;87:806-814.

Neurofibromatoses (NF; NF1, NF2, and schwannomatosis) are a set of progressive, genetic neurologic conditions for which there is no known cure. The severity of illness varies greatly from person to person; however, most patients experience some discomfort at the site of these non-cancerous growths. Some will experience debilitating symptoms and a rare set will develop life-threatening symptoms. All patients with NF may experience pain, anxiety, depression, and other factors leading to a decreased quality of life (QoL).[1]

Mindfulness techniques have shown positive results in lowering patients' levels of anxiety, depression, and chronic pain in various populations.[2,3] The intervention in this study was structured around elicitation of the relaxation response — a state of calm awareness first documented by Harvard physician researcher Herbert Benson in 1975.[4] Vranceanu et al studied a videoconferencing mindfulness intervention in patients with NF for these symptoms. The authors randomized 63 patients with NF to one of two videoconferencing mind-body programs — the Relaxation Response Resiliency Program for neurofibromatosis (3RP-NF) or an attention placebo control (Health Enhancement Program for NF [HEP-NF]).

The intervention consisted of eight videoconferencing sessions with study participants via Skype. The intervention group received instruction in three core components: 1) 15 mindfulness and relaxation techniques; 2) appraisal and coping — cognitive coping techniques for stress and medical symptoms; and 3) growth enhancement, which included acceptance, positive psychology, and problem-solving techniques that foster resiliency in the face of new symptom development and uncertainty of prognosis. The control group used an adapted program called the HEP-NF that focused on educating patients with NF about symptoms and stress related to NF. The modules taught nutrition, exercise, and communicating with medical providers. Primary outcome measures of the study included physical health and psychological QoL. These measures were assessed with the World Health Organization Quality of Life abbreviated instrument at time 0, within one week after completion of the intervention, and six months after the study was completed. Secondary outcome measures were social relations and environment QoL, depression, anxiety, pain intensity, and pain interference.

Compared to the placebo control group, the intervention group experienced a trend toward greater improvement in physical (95% confidence interval [CI], 0.29-15.10; $P = 0.04$) and psychological health QoL (95% CI, 0.17-11.34; $P = 0.056$). Participants in the intervention group also experienced significantly greater improvements in social relations QoL and environmental QoL (95% CI, 4.10-17.24; $P = 0.002$ for social relations QoL, and 95% CI, 3.50-11.15; $P < 0.001$ for environmental QoL). Their anxiety scores also significantly decreased in comparison to the control group (95% CI, -3.96 to 0.69; $P = 0.006$).

Post-treatment effects on physical and psychological QoL were maintained six months after the intervention by the 3RP-NF group; however, *P* values were not specified for this analysis. These results were unchanged from post-test analyses. Post-treatment effects on secondary outcome measures were maintained after six months; however, the results were also unchanged from the post-test analysis. Patients in the 3RP-NF group showed a significant decrease in pain interference over those in the control group after six months (95% CI, -2.44 to -0.20; $P = 0.02$). No adverse effects were reported for the intervention.

These findings are extremely promising for patients suffering from NF, regardless of type. It is a low-cost, safe, and effective modality to reduce negative physical and psychological aspects in this population, and there were no adverse effects associated with the intervention. Given the small sample size and homogeneity of the sample, the data cannot be extrapolated to larger populations. However, patients suffering from chronic pain and anxiety may experience a benefit in QoL measures if the intervention is applied. More research with larger numbers of participants across a variety of chronic illnesses is warranted. ■

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CME QUESTIONS

1. Diet plays a role in many disorders of children. Which of the following is most true?

a. In ADHD, the standard of treatment is shifting from psychostimulant medication to dietary intervention.

b. A low FODMAP diet may be used for children with IBS, but long-term safety remains to be established.

c. In pediatric headaches, a strict elimination diet often is first-line treatment.

d. A Mediterranean-style diet is very difficult to implement for most children.

2. After six months of zinc supplementation, which of the following metabolic changes was seen in the treatment group?

a. An increase in HDL cholesterol

b. No significant change in beta cell function (as measured by HOMA)

c. A slight increase in fasting glucose

d. A decrease in insulin sensitivity

3. Which of the following is true regarding cranberry and urinary tract infections (UTIs)?

a. Cranberry capsules prevented bacteriuria and pyuria in women residing in nursing homes.

b. Cranberry capsules prevented symptomatic UTIs in women residing in nursing homes.

c. Cranberry contains proanthocyanidin A (PAC), which is a compound that has been found to prevent adhesion of *E. coli* to uroepithelial cells in vitro and ex vivo.

d. Cranberry is an effective treatment for UTIs.

4. Participants in a Relaxation Response Resiliency Program for neurofibromatosis intervention group improved significantly in all of the following measures when compared to the control group, *except*:

a. psychological quality of life.

b. pain interference.

c. depression.

d. physical quality of life.

[IN FUTURE ISSUES]

Omega-3 fatty acids and dietary retinopathy

Social media activity and mortality risk

Biotin and multiple sclerosis

Beetroot juice and endurance