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SLEEP

ABSTRACT & COMMENTARY

The Disruptive Effects of Tablet Readers on Sleep Patterns

By William Haas, MD

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Dr. Haas reports no financial relationships relative to this field of study.

SYNOPSIS: The use of light-emitting tablet devices prior to bedtime negatively impacts sleep patterns through disturbances in circadian rhythms.

SOURCE: Chang AM, et al. Evening use of light-emitting eReaders negatively affects sleep, circadian timing, and next-morning alertness. *Proc Natl Acad Sci U S A* 2015;112:1232-1237.

With the advancement of technology, the printing press is slowly giving way to digital media, and consumers are spending increasing amounts of time assimilating knowledge from electronic devices. The tablet reader, a popular device for reading and entertainment, is frequently used in the evening hours prior to bed. Some researchers are concerned that such light-emitting devices may disrupt natural circadian rhythms and perpetuate sleep deficiencies. Through a randomized, crossover study, researchers at Brigham and Women's Hospital set out to determine the effect of light-emitting tablets on sleep patterns as compared to printed books when used prior to bed.

Twelve young adults (six females and six males) were recruited to live and sleep in separate light-controlled rooms for 14 days. Recruits were carefully screened with the following exclusion criteria: pre-existing chronic medical or psychological condition(s), pre-existing sleep disorder, use of prescription medication(s), history of night/shift work in the prior 3 years, travel across more than one time zone in the previous 3 months, or any vision abnormality

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Summary Points

- Tablet reading prior to bed increased time-to-sleep onset by 10 minutes compared to reading from a print book.
- Mornings after tablet reading were associated with increased levels of perceived sleepiness and decreased alertness.

preventing reading in a dimly light room. Three weeks prior to the study, the selected participants were instructed to refrain from use of medications, drugs, alcohol, nicotine, or caffeinated products, which was verified by toxicological testing. Additionally, participants were required to maintain a fixed 8-hour sleep schedule (10 p.m. to 6 a.m.) during the 3-week pre-study period, as verified by sleep/wake logs and wrist actigraphy.

After the initial 3-week acclimation period, participants were randomized to either: 1) reading from a light-emitting tablet (iPad; Apple Inc.) in a dimly light room for approximately 4 hours before bedtime or 2) reading from a printed book under similar dimly lit conditions for the same duration of time prior to bed. Each reading session took place for five consecutive evenings, after which participants crossed over to the alternative reading condition; the initial order was randomly assigned. The night prior to each 5-night reading block, as well as the final night of the study, participants completed a constant posture procedure, which consisted of sitting in a semirecumbent position for 4 hours before bed, with minimal activity and no reading. At the end of each reading session, sleeping periods occurred according to the same 8-hour block prescribed in the acclimation period (10 p.m. to 6 a.m.).

Details regarding the structure of reading sessions and lighting conditions were highly standardized and extensively outlined in the methods section. In short, tablets were set to the maximal brightness setting and placed stationary at a distance 30-45 cm from the participants' eyes. Books, on the other hand, were held at any distance desired and were restricted to printed text only (i.e., no pictures or illustrations) and were limited to topics of pleasure or leisure (i.e., no educational material). Participants were instructed to read while seated in a fixed location in their rooms. Approximately 3 hours into the reading sessions, participants were given a 15-minute break and completed the final hour of reading while seated in bed. Adherence to the treatment protocol was overseen by a trained technician.

Primary outcomes measured included sleep latency, timing and amount of melatonin secreted, and measures of sleepiness. Sleep latency was assessed using polysomnography (PSG) recordings on the fourth and fifth night of each reading block. Three other sleep measures, including total sleep time, sleep efficiency, and time spent in each sleep stage, were also obtained using PSG recordings. Melatonin was measured from blood samples collected hourly throughout the night via an indwelling IV catheter in the forearm. Both degree of melatonin suppression and time to dim light melatonin onset were calculated from samples drawn. Of note, due to lost blood samples, melatonin suppression and onset calculations were determined from 11 participants. Finally, subjective sleepiness measures were recorded using the Karolinska sleepiness scale (KSS) every evening and morning. Objective sleepiness was measured using electroencephalogram (EEG) measurements recorded on the final two evenings and mornings of each reading block.

As mentioned above, a total of six males and six females completed the study with an average age of 24.92 ± 2.87 years — no other demographic information was provided. With regard to sleep patterns, reading from a light-emitting tablet increased time-to-sleep onset by 10 minutes compared to reading from a print book (25.65 ± 18.78 min vs 15.75 ± 13.09 min; $P = 0.009$). Tablet reading also resulted in less rapid eye movement (REM) sleep compared to book reading (109.04 ± 26.25 min vs 120 ± 25.32 min, $P =$

0.03), but no difference was noted between total sleep time, sleep efficiency, or duration of non-REM sleep. Overall levels of melatonin were suppressed more while reading a tablet compared to reading a book (55.12 ± 20.12% vs -18.77 ± 39.57%, $P < 0.001$), with melatonin onset also occurring > 1.5 hours later on the day following the tablet sessions ($P < 0.001$). Both subjective KSS scores and EEG measurements revealed participants to be less sleepy within the hour before bedtime compared to book reading ($P < 0.01$). Similarly, participants felt sleepier in the morning following an evening of tablet reading compared to book reading ($P < 0.001$).

■ COMMENTARY

Through a well-designed and rigorous study, researchers at Brigham and Women's Hospital clearly demonstrate that the use of light-emitting tablets during the hours prior to bedtime negatively impacts sleep patterns. More specifically, reading from a light-emitting tablet decreases perceived sleepiness before bed and increases time-to-sleep onset, likely as a result of an acute alerting effect from light exposure and a delay in the circadian timing system. Additionally, tablet reading increases sleepiness in the mornings after use, which may be attributed to a decrease in REM sleep and a higher likelihood of spontaneous awakenings from deeper phases of sleep.

The results of the present study, while intriguing unto themselves, should be considered in the context of their general health implications. Despite the fact that melatonin secretion occurred 1.5 hours later with tablet reading, time-to-sleep onset only increased by 10 minutes compared to book reading. The researchers suggest that this may increase the risk of sleep-onset insomnia; however, if the time-to-sleep onset does not continue to lengthen with prolonged tablet use, the additional 10 minutes required to fall asleep is unlikely to result in a higher demand for hypnotics. On the other hand, the delayed secretion of melatonin does seem concerning for the development of a delayed sleep-phase disorder, thereby leading to a chronic sleep deficiency. Most concerning, perhaps, is the overall reduction in melatonin secretion while using a light-emitting tablet before bed. Chronic suppression of melatonin has been associated with an increase in several cancers, including breast, colorectal, and prostate cancer.[1] The important, yet unanswered question remains whether or not the degree of melatonin suppression with tablet use is large enough to confer any long-term health consequences. In the short-term, however, tablet use prior to bed may pose some safety concerns, especially with increased sleepiness and decreased alertness on the mornings after use. Decreased levels of morning alertness would certainly be hazardous in many professions (public transportation, medicine, construction, etc.).

Before settling on any final conclusions, the overall design of the study should be reviewed. The study was thoughtfully constructed with appropriate randomization and crossover between groups. A pre-intervention acclimation period attempted to minimize differences between the groups at baseline. The final sample size was arguably small, but was likely a result of the highly controlled environment required to ensure proper standardization of light exposure. The rigorous design of the study does raise some questions regarding generalizability. The exclusion criteria were so strict that the participants in the study are unlikely to represent the average tablet user, especially among those presenting in the clinic with complaints of a sleep disorder. Moreover, the average American's sleep schedule is not standardized to a set 8-hour period every night. Similarly, not every person remains fixed to their tablet for nearly 4 uninterrupted hours prior to bedtime. In a non-laboratory environment, tablet users also have greater control over settings, including brightness levels and the distance the device is held from a user's eyes. ■

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DIET

ABSTRACT & COMMENTARY

Live Longer: Substitute in Whole Grains

By David Kiefer, MD

SYNOPSIS: When adjusted for possible confounding variables, this analysis of U.S. men and women found an association between higher whole grain intake and lower mortality from all causes, including cardiovascular disease, but no association for cancer mortality.

SOURCE: Wu H, et al. Association between dietary whole grain intake and risk of mortality: Two large prospective studies in U.S. men and women. *JAMA Intern Med* 2015;175:373-384.

Summary Points

- For adult men and women eating the highest quintile of whole grains, their hazard ratio for all-cause morality was 0.91 and for cardiovascular mortality was 0.85.
- In terms applicable to diet, one serving of whole grains (or 28 grams) translated into a 5% lower total mortality or a 9% lower cardiovascular mortality.
- When analyses were done as if whole grains were substituted for refined grains or red meat, significant improvements in total mortality and cardiovascular mortality were seen.

The researchers of this analysis aimed to expand the literature showing a possible connection between dietary whole grains and chronic diseases, such as diabetes and coronary artery disease (CAD), as well as hypothesized benefits on mortality. The researchers analyzed two databases: the Nurses' Health Study (NHS) data on 121,700 female registered nurses and the Health Professionals Follow-up Study (HPFS), involving 51,529 male health professionals. Participants were excluded if they had baseline cancer, CAD, or stroke; < 500 kilocalories (kcal) or > 3500 kcal daily intake; or incomplete dietary data. After these exclusions, 74,731 participants from the NHS and 43,744 from the HPFS remained.

Food-frequency questionnaires every 2-4 years were used to estimate whole grain intake from all whole grain-containing foods, such as rice, bread, pasta, and breakfast cereals. Added wheat germ and bran were also factored in. Also, from the questionnaires an Alternate Healthy Eating Index (AHEI) score was calculated based on 10 foods and beverages with connections to chronic disease risk; a higher score means healthier eating and better diet quality. A variety of co-variates (i.e., body weight, lifestyle, and medical history) also were included in this analysis.

Study participants who consumed whole grains in the highest quintile were more likely to have a variety of characteristics (*see Table 1*). In both the NHS and the HPFS, a higher intake of whole grains was associated with a lower total and cardiovascular mortality; the hazard ratios (HR) were 0.91 (95% confidence interval [CI], 0.88-0.95; $P < 0.001$) and 0.85 (CI, 0.78-0.92; $P < 0.001$), respectively. The same analysis failed to find an association between whole grain intake and cancer mortality (HR, 0.97; CI, 0.91-1.04; $P = 0.43$). Quantifying these results, the researchers calculated that every daily serving of whole grains (28 grams = one serving) was associated with a 5% lower total mortality and 9% lower cardiovascular mortality.

Table 1: Characteristics of Higher Whole Grain Consumers

- More physically active
- History of elevated lipids
- Not current smokers
- Lower alcohol intake
- Higher AHEI score

The researchers found some other interesting results. Even refined grain intake was associated with a small reduction in total mortality (HR, 0.98; CI, 0.97-0.99), although there was no association with cardiovascular nor cancer mortality. More striking was the finding that replacing one serving of refined grains or red meat with one serving of whole grains led to 8% (HR, 0.92; CI, 0.88-0.97) and 20% (HR, 0.80; CI, 0.75-0.86) reductions in cardiovascular mortality, respectively. Total mortality reductions were 4% and 10%, respectively, whereas there were no effects on cancer mortality with such substitutions.

By collecting detailed information about specific whole grains, as well as added bran and wheat germ, the researchers were able to separate out the effects of dietary bran, added bran, and added germ. Total bran consumption across the quintiles was associated with lower total (HR, 0.94; CI, 0.90-0.99; $P < 0.001$ for the trend) and cardiovascular (HR, 0.80; CI, 0.73-0.87; $P < 0.001$ for the trend) mortalities. The effect of added bran was similar to that of naturally occurring bran, and there was no association between wheat germ intake and mortality.

■ COMMENTARY

In some respects, this methodologically sound analysis using datasets with information about large numbers of U.S. men and women corroborates what clinicians have been recommending for many years, namely that whole grains are good for our health. The authors of this analysis list some of the shortcomings and conflicting results from other studies. In some cases, dark bread was thought to be the healthiest; in other cases, specific demographics (elderly, diabetic, etc.) had cardiovascular benefits but not improvements in overall mortality. As is often the case, methodological nuances or flaws compromised painting a complete picture of the whole grain effect. That was true until this trial, which now seems to show that eating whole grains as a component of the diet, or when calculated as a substitute for less healthy dietary components, clearly benefits all-cause and cardiovascular mortality in this demographic.

The mechanism fits the results and conclusions. The

researchers tie their results into the fact that the bran component of some whole grains contains important phytonutrients (fiber, B vitamins, vitamin E, and magnesium) that have been shown in vitro and in vivo to have protective effects on cardiovascular disease risk and diabetes. The results of this study showed less positive effects with wheat germ, devoid of the above-mentioned bran components, supporting the proposed mechanism. In addition, there is little argument that fiber can benefit people with cardiovascular disease, but this study brings to light the positive effects on all-cause mortality, even if it is less of an effect than cardiovascular effects.

What remains as an important question not necessarily addressed by this study is teasing out how these results are affected by the relative quantity of fiber consumed by study participants. With concerns that grain intake is potentially too high for many people in the United States, is it possible to attain the benefits seen in this study by the phytochemicals and fiber contained in fruits and vegetables? Bran is full of healthy compounds, but for many people it may not be an option, such as in cases of gluten intolerance or celiac disease. The results from the substitution analysis are particularly compelling; any clinician can use these results to convince patients to swap out refined carbohydrates or red meat for whole grains, but a substitution with fruits and/or vegetables would likely convey similar positive effects; it's just not addressed here.

The researchers were not surprised by the lack of an effect on cancer mortality; many other studies have also failed to find an effect, probably attributable to the varied pathophysiology for each specific cancer as well as what the authors call "population characteristics," which can vary tremendously and affect results, even in large studies such as this one.

This is a useful study that arms clinicians with practical knowledge about the life-saving effects of one component of a healthy diet. Provided whole grains are an option for someone, the benefits can be pitched in percentages of risk reduction (the hazard ratio), the effect of one serving on mortality over time, or what might happen if refined grains or red meat are replaced with whole grains. This study provides convincing data for why conversations about healthy eating can weave in longevity as part of what we know when it comes to whole grains. ■

GASTROINTESTINAL DISEASE

ABSTRACT & COMMENTARY

Acupuncture and Moxibustion in the Treatment of Crohn's Disease

By Traci Pantuso ND, MS

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

SYNOPSIS: This randomized, placebo-controlled trial demonstrated that acupuncture and moxibustion treatment in patients with Crohn's disease (CD) significantly improved the patient's CD symptoms, quality of life, mucosal inflammation, serum hemoglobin, and C-reactive protein levels compared to the control group.

SOURCE: Bao CH, et al. Randomized controlled trial: Moxibustion and acupuncture for the treatment of Crohn's disease. *World J Gastroenterol* 2014;20:11000-11011.

This study used a randomized, placebo-controlled clinical trial design to investigate the effects of acupuncture and moxibustion treatment in patients with Crohn's disease (CD) three times per week for 12 weeks, with a follow-up period of 12 weeks. CD patients were recruited between January 2010 and April 2013, at the acupuncture outpatient center for inflammatory bowel disease (IBD) of the Shanghai Institute of Acupuncture and Meridian. The primary outcome of the study was the CD activity index (CDAI), which measures the following eight factors over 7 days: number of liquid stools, abdominal pain,

Moxibustion is a treatment that uses a traditional Chinese medicine herbal formula that is placed on a patient's acupuncture points, and a cone of moxa (mugwort) is then ignited on top of the herbal formula. This therapy is often used in conjunction with acupuncture.

Summary Points

- After 12 weeks of treatment, Crohn's disease activity index scores were significantly decreased in patients receiving acupuncture and moxibustion compared to the control group.
- Quality-of-life measurements were also significantly improved in the Crohn's disease patients receiving acupuncture and moxibustion compared to the control group.

general well being, extraintestinal complications, antidiarrheal drugs, abdominal mass, hematocrit, and body weight.[1] Secondary outcomes measured were quality of life (QoL) with the inflammatory bowel disease questionnaire (IBDQ), C-reactive protein and erythrocyte sedimentation rate (ESR) to evaluate inflammation, and hemoglobin (HGB) to assess anemia. In addition, 15 patients from each group were selected for enteroscopic exams and mucosal biopsies, which were evaluated by the CD endoscopic index of severity (CDEIS) and the D'Haens-Geboes intestinal histology scoring system.

Patients were included in the study if they had CDAI scores that were mild-to-moderate (151-350), had not been taking salicylic acid drugs and/or prednisone at a dose > 15 mg for at least 1 month, and had not been on immunosuppressants or used anti-TNF-α biological agents for 3 months prior to enrollment in the study. During the 12-week study period, patients maintained their CD medications at the same dosage. In the follow-up period, participants were allowed to adjust the dosage of their medication and were instructed to record such changes. Individuals with serious diseases of the heart, liver, brain, kidney or hematopoietic system, mental illness, and patients with other severe diseases were excluded. Pregnant and lactating women were also excluded.

A total of 146 patients were screened: 54 were excluded and 92 were included (*see Table 1*). Of that 92, 46 were assigned to the treatment group and 46 were assigned to the control group. The treatment group received moxibustion and acupuncture and the control group received a sham treatment of wheat bran moxibustion and superficial acupuncture for the 12 weeks. The sham treatments appear to the patient as the actual treatment, but have demonstrated significantly less treatment effects and are often used as a control arm in acupuncture studies. The treatment group received acupuncture with the acupoints selected from previous studies and herb-partitioned moxibustion, which contained *Coptis chinensis*, *Radix Aconiti lateralis*, *Cortex cinnamomi*, *Radix Aucklandiae*, *Flos carthami*, *Salvia miltiorrhiza*, and *Angelica sinensis* as the primary ingredients.

Table 1: Exclusion Rationale

Number Excluded (n = 54)	Reason for Exclusion
22	CDAI scores were too low
4	CDAI scores were too high
18	Refused to participate
10	Use of immunosuppressive drugs or traditional Chinese drugs

A total of 85 patients completed the study (43 patients in the treatment group and 42 in the control group). Three patients dropped out of the treatment group due to work and travel. Four patients in the control group did not complete the study for various reasons, including two who required prednisone > 15 mg/d, one who became pregnant, and the other due to unknown reasons. Seventy-seven patients completed follow-up: 37 in the control group and 40 in the treatment group.

There were no significant differences between groups at baseline with regard to gender or measurements of age, height, weight, Montreal classification, disease severity or duration, surgical history, CDAI, and QoL. Statistical analysis was performed using per-protocol (PP) and intention-to-treat (ITT) analysis for primary outcome of CDAI, and PP for subgroup and and secondary outcomes; the two-tailed *t*-test and Mann-Whitney test were also used to analyze secondary outcomes. *P* values < 0.05 were considered statistically significant.

Post-treatment CDAI scores were significantly reduced by PP analysis in both the treatment and control groups compared to baseline and to one another at 12 weeks ($P = 0.000$) (*see Table 2*). The treatment group demonstrated a significantly larger decrease in the CDAI scores compared to the control group ($P = 0.000$) (*see Table 2*). The CDAI scores remained significantly improved in the treatment group compared to the control group at follow up (*see Table 2*).

The ITT analysis demonstrated similar findings as the PP results except in the case of the CDAI score of the control group, as it was significantly improved during the follow-up period compared to baseline (*see Table 2*). The total treatment efficacy of the control and treatment groups was statistically significant and was 40.48% and 83.72%, respectively, through PP analysis ($P = 0.000$). The ITT analysis was also statistically significant, with a treatment efficacy of 78.26% and 36.96%, respectively, in the treatment and control

Table 2: PP and ITT analysis of CDAI scores in Control and Treatment Groups at Baseline, Post-Treatment, and Follow-up			
	Control	**Treatment**	***P* Value**
Baseline to post-treatment	PP = -35.68 ± 46.91 ITT = -32.58 ± 45.91	PP = -115.35 ± 55.05 ITT = -107.83 ± 60.47	PP = 0.000** ITT = 0.000**
Baseline to follow up	PP =-14.32 ± 52.09 ITT = -22.19 ± 55.31	PP =-128.93 ± 64.46 ITT =-117.85 ± 70.10	PP = 0.000** ITT = 0.000**
**= $P < 0.01$; *= $P < 0.05$			

Table 3: Secondary Outcome Measurement Changes at Post-Treatment compared to Baseline Between the Treatment and Control Groups			
Outcome measure	**Control**	**Treatment**	***P* Value**
IBDQ	9.93 ± 19.13	24.56 ± 34.15	0.017*
HGB (g/L)	-0.93 ± 10.07	5.09 ± 14.45	0.029*
CRP (mg/L)	1 .16 ± 12.11	-8.67 ± 20.04	0.008**
Histology scores	-0.53 ± 1.73	-2.2 ± 2.21	0.029*
**= $P < 0.01$; *= $P < 0.05$			

groups, respectively ($P = 0.000$).

Seventy-four percent of patients in the treatment group and 36% patients in the control group were considered to be in remission, with a CDAI score of < 150 after treatment. After treatment, 70% of patients in the treatment group and 14% of patients in the control group showed CDAI score reductions > 100 points, and 79% of patients in the treatment group and 21% of patients of the control group demonstrated CDAI score reduction > 70 points.

The QoL measurement IBDQ scores were significantly improved in both the control and treatment groups compared to baseline. However, the treatment group demonstrated a larger increase in IBDQ scores than the control group ($P = 0.017$) (*see Table 3*). The HGB levels of the treatment group were significantly increased from both baseline ($P = 0.026$) and the control group at 12 weeks ($P = 0.029$) (*see Table 3*). CRP levels in the treatment group were significantly decreased from both baseline ($P = 0.007$) and the control group at 12 weeks ($P = 0.008$) (*see Table 3*). ESR levels were decreased in both the treatment and control groups from baseline levels, but were not statistically significant. No significant changes were found on endoscopy after treatment. However, the histology scores from the intestinal tissue biopsies were significantly reduced in the treatment group compared to baseline ($P = 0.002$), and were not significantly different in the control group at 12 weeks. There was also a significant improvement in the histology scores in the treatment group compared to the control group at 12 weeks ($P = 0.029$) (*see Table 3*).

Two adverse events also occurred during the study: a subcutaneous hematoma and pain during acupuncture and a mild burn during moxibustion.

■ COMMENTARY

Both acupuncture and moxibustion are widely available in the United States and could be a potential treatment option for CD patients. Up to 60% of patients suffering from IBD are reported to use complementary and alternative medicine (CAM) therapies both to help treat their disease and also to treat side effects.[2] In a German study investigating CAM use in 413 IBD patients, 52% reported using CAM therapies, with 33% reporting use of acupuncture/traditional Chinese medicine.[3] In another study, acupuncture and moxibustion were reported to be 56% effective in the treatment of CD.[4] In two recent meta-analyses investigating the role of CAM therapies in the treatment of inflammatory bowel disease, the authors of both studies concluded that the evidence for using TCM and acupuncture has yet to be proven, as the quality of the studies has overall been low.[2,5]

This particular study was not included in either meta-analysis and offers some important data, as it not only included CDAI scores and QoL measurements but also endoscopic, histology, HGB, CRP, and ESR information. The results of this study demonstrate that acupuncture and moxibustion treatment improve CD symptoms, QoL, and HGB levels and decrease CRP levels and histology scores on intestinal biopsy samples in CD patients. These results expand on previous studies that demonstrated acupuncture and moxibustion treatments reduce CRP but were not statistically significant.[4]

A limitation of this study was the placebo effect, which has been seen in numerous other studies where sham acupuncture and moxibustion are used and may interfere with the statistical analysis. Despite this limitation, clinicians could weave the results of this study into their treatment plans by recommending acupuncture and moxibustion because they may improve both QoL and disease severity. Definitive use of acupuncture and moxibustion for IBD patients remains to be clarified, which is an important next step since a large number of IBD patients use CAM therapies.

In conclusion, it seems reasonable that recommending acupuncture and moxibustion to patients wanting to prevent flares could benefit mild-to-moderate CD patients as demonstrated in this study. Severe CD patients also may benefit from acupuncture and moxibustion as an adjunctive therapy; however, more research is required to further assess the role of acupuncture and moxibustion treatments in this demographic. ■

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ARTHRITIS

ABSTRACT & COMMENTARY

Lactobacillus casei Supplementation Improves Inflammatory Markers and Disease Activity Scores in Rheumatoid Arthritis

By Carrie Decker, ND

Founder and Medical Director, Blessed Thistle, Madison, WI

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

SYNOPSIS: In this randomized, double-blind, placebo-controlled study, the probiotic strain *Lactobacillus casei* 01 was provided to women with rheumatoid arthritis at a dosage of 10^8 colony forming units for a period of 8 weeks and compared to a placebo treatment. Disease activity score and levels of the proinflammatory cytokines tumor necrosis factor-α, interleukin-6, and interleukin-12 were found to be significantly decreased at the end of the intervention. Additional parameters of state and trait anxiety were also evaluated and were not significantly altered by therapies.

SOURCE: Vaghef-Mehrabany E, et al. Probiotic supplementation improves inflammatory status in patients with rheumatoid arthritis. *Nutrition* 2014;30:430-435.

Probiotics have been used in a variety of disorders for modulation of immune system function and inflammation. Some strains have been shown to stimulate immune system function,[1] while others moderate hyperactive function or type of immune response.[2,3] Studies have been performed to investigate the effect of various *Lactobacillus* spp. and other probiotics strains on immune response and inflammatory markers in animal models[4,5] and human studies[6,7] of rheumatoid arthritis (RA), a disease with pathology primarily attributable to immune system dysregulation and inflammation.

In this double-blind, placebo-controlled trial, 60 women with inactive to moderate RA were randomized to treatment with probiotics strain *Lactobacillus casei* 01 or a placebo (maltodextrin) for 8 weeks. Probiotic and placebo were provided in identical capsules and refrigerated, and participants were instructed to take the supplements once daily on an empty stomach. The dosage of *L. casei* provided was 10^8 colony forming units (CFU) daily.

Study participants were required to have been diagnosed with RA by the criteria of the American College of Rheumatology for more than 1 year and on a stable medication regime for more than 3

Summary Points

- Women with inactive to moderate rheumatoid arthritis (medication stable) were supplemented with 10^8 colony forming units of *Lactobacillus casei* 01 or a placebo daily for 8 weeks.
- Levels of proinflammatory cytokines tumor necrosis factor-α, interleukin-6, and interleukin-12 were observed to be significantly decreased from baseline in the intervention group at the end of the 8 weeks.
- The disease activity score (based on the number of tender and swollen joints, serum C-reactive protein, and visual analog scale questionnaire of global health) was found to be significantly decreased in the probiotic group at the end of the intervention.
- No change was found in state or trait anxiety with the intervention.

months prior to the intervention. Medications that individuals in the study were allowed to take were methotrexate, hydroxychloroquine, and prednisolone. Individuals were excluded from the study if they were using non-steroidal anti-inflammatory drugs or cytokine inhibitors, were pregnant or lactating, were using hormone therapies, had additional known inflammatory disorders such as inflammatory bowel disease, had digestive disorders including lactose intolerance, or had recent use of antibiotics or other vitamin or probiotic therapies.

Parameters assessed in the study included the levels of interleukin (IL) cytokines IL-1ß, IL-6, IL-10, IL-12, and tumor necrosis factor-α (TNF-α). Disease activity score (DAS), a calculated parameter, was determined based on the number of swollen and tender joints as assessed by a rheumatologist, serum high-sensitivity C-reactive protein (hs-CRP), and a visual analog scale (VAS) questionnaire for global health. State and trait anxiety were assessed using the Spielberger State-Trait Anxiety Inventory Form Y. All parameters were assessed at baseline and 8 weeks after the intervention.

No adverse effects were reported with the intervention. Thirty people were originally enrolled in each group, with 22 and 24 people completing the study in the intervention and placebo groups, respectively. Individuals did not complete the study due to reasons such as medication changes, altered activity level, vacation, and unwillingness to complete therapies.

Upon completion of the 8-week intervention, DAS was significantly decreased in the probiotic group compared to baseline ($P < 0.01$), but did not change significantly in the placebo group. The parameters used for the DAS calculation (number of tender and swollen joints, VAS score, and hs-CRP) were also all significantly decreased in the probiotics group ($P < 0.05$); however, values were not reported in this study. The serum levels of the inflammatory cytokines TNF-α, IL-12, and IL-6 significantly decreased ($P < 0.05$) in the probiotics group but increased (significance not assessed) in the placebo group (*see Table 1*). Confidence intervals associated with these changes were not assessed. No change was observed in state or trait anxiety in either group. No adverse effects were reported.

■ COMMENTARY

Probiotics have been the focus of a wide variety of research for conditions ranging from allergies[2] to metabolic syndrome[8] to reduction of occurrence of the common cold.[9] Within the species *Lactobacillus*, several strains of *L. casei* have been isolated, most commonly being found in plant materials, human gastrointestinal tracts, and cheeses.[10] Subspecies within the family *L. casei* have been found in animal studies of RA to reduce levels of proinflammatory cytokines[5] and alter the immune response,[4] hence the investigation of their use in this clinical study of RA.

The dosage of *L. casei* utilized in this study (10^8 CFU/day) is a relatively low dose for probiotic supplementation. Often, studies utilize probiotics dosages a level of magnitude, or even two levels, higher than this. The reasoning behind the low dosage was not discussed in this study, although it was mentioned that *L. casei* 01 has been reported to have greater adhesion to intestinal cells than the commonly used strain *L. casei Shirota*.[11] Other studies have found similar effectivity with lower and higher probiotics dosages,[12] suggesting that dosage may not be critical, or even that the effect can be variable, finding increased inflammation with higher doses.[13]

Neglected by the authors of this study was consideration for the difference between groups in baseline levels of a majority of the cytokines measured. Each of the cytokines that was found to be significantly decreased from baseline (within group changes) in the probiotics group initially was considerably higher than the placebo group. The baseline median values in the two groups with the 25th and 75th percentile ranges can be seen in Table 1.

Given the known relapse-remission course of autoimmune disease with disease flares, it may have been that more of the individuals randomized to

Table 1: Serum Levels of Inflammatory Cytokines in Placebo vs Probiotic Groups		
Parameter	**Placebo group (n = 24)**	**Probiotic group (n = 22)**
TNF-α (pg/mL)		
Baseline	3.60 (2.32, 5.10)	5.00 (2.75, 9.60)
Study End	3.65 (2.05, 5.40)	4.05 (1.60, 6.37)
IL-12 (pg/mL)		
Baseline	187.25 (106.40, 374.80)	422.85 (162.40, 574.80)
Study End	236.60 (121.00, 429.90)	342.25 (143.70, 555.50)
IL-6 (pg/mL)		
Baseline	8.80 (1.52, 122.67)	22.30 (1.65, 43.05)
Study End	11.55 (0.00, 141.02)	20.55 (0.90, 41.22)
Values expressed as median (25th and 75th percentile)		

the probiotic group initially were experiencing a greater amount of disease activity. Data utilized for the calculation of the DAS parameter, although not provided in this study but reported in an alternate publication,[14] also indicates that this may have been the case, as the serum hs-CPR at baseline was initially higher in the probiotics vs placebo group (3.10 mg/L [1.32, 18.01] vs 2.30 mg/L [1.23, 7.99]). A longer duration of study, with additional times when data were assessed, would have shed light on this.

As with many study protocols using nutritional therapies, the participants were on the standard treatments for disease control, in this case methotrexate, hydroxychloroquine, and prednisolone. The number of individuals in the placebo and probiotics group on each medication was not significantly different (P = 0.229, 0.725, and 1.00, respectively). Some individuals were also on combination therapies of these medications. Although the relative number of individuals in the placebo and probiotic group on each medication was similar, there are many reasons to anticipate the findings would be different depending on the specific pharmaceutical being utilized. Methotrexate has been shown to alter cytokine expression of IL-12 and IL-6, while other cytokines such as IL-18 (not assessed in this study) are not affected by methotrexate in the absence of corticosteroids but are reduced with combination therapies.[15] Additional mono and combinatory effects with the other medications participants were using are also anticipated.

In conclusion, although a beneficial effect was observed within the individuals taking the probiotics strain *L. casei*, the results of this study are at best suggestive that this therapy may improve inflammation and disease symptoms of RA. Other studies utilizing probiotics supplementation (*Bacillus coagulans* or *Lactobacillus rhamnosus* GR-1 with *Lactobacillus reuteri* RC-14) in RA have had similarly mixed results with improvements in pain and functional scores and some or no improvement in markers of inflammation.[6,7] However, as no adverse effects were seen with supplementation, it is acceptable for individuals with RA to take a form of probiotics as a supplement if they choose to. It may be that the various strains that have been studied for use in RA are better to select, as they have not been shown to have adverse effects; however, that does not eliminate the possibility that other strains may offer benefit. ■

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SHORT REPORT

Controversial Removal of Dietary Supplements from Retailers' Shelves

By David Kiefer, MD

This short report details an important series of events relevant to dietary supplement prescribing and purchasing. The controversy began in early February 2015, when the Attorney General of New York state sent cease and desist letters to Target, GNC, Walmart, and Walgreens after finding that four out of five supplements tested failed to contain any of the herbal medicines listed on the labels.[1] The Attorney General's office bought 78 bottles of leading brands from 12 stores across New York state, and then subjected the products to DNA barcoding analysis. DNA barcoding tests involve comparing extracts of a test sample to a library of known segments of DNA specific to a particular plant or animal.[2,3,4] Such analysis is a relatively new science, but not new to controversy, as detailed in a past issue of *Integrative Medicine Alert*;[5] certain extracts, purified phytochemicals, and/or tinctures would not be expected to contain DNA and, therefore, would be flagged in the testing, as done by the Attorney General's office. Such concerns were voiced by industry and educational organizations such as the American Botanical Council.[6]

Despite the concerns over the scientific method, the four retailers cited by the Attorney General agreed to remove the products from the shelves of New York state stores. Walgreens even went so far as to remove the relevant products from its stores nationwide,[7] and GNC announced plans to improve testing of its herbal medicines by using "advanced DNA testing" and allergen testing for tree nuts, soy, and wheat.[8] The media fallout of this 2-month ordeal has played into the hands of dietary supplement critics, including academicians and politicians who have been quoted emphasizing safety and quality concerns of the dietary supplement industry; there are less stringent controls for dietary supplements (considered "foods" by the Food and Drug Administration) than for pharmaceuticals. It is less clear, however, what the correct approach should be for differentiating safe and quality products from their lesser cousins. Recent requirements that all dietary supplement companies adhere to Good Manufacturing Practices, as well as the presence of third-party testing organizations such as ConsumerLab and the United States Pharmacopoeia, have made some strides toward improvement in dietary supplement quality and safety. Until sound testing methodology and retailer/government oversight is honed, what remains crucially important is a dialogue between clinician and consumer about the appropriateness of dietary supplement use and the choice of products from reputable companies. ■

Summary Point

- Until sound testing methodology and retailer/government oversight is honed, clinicians and consumers should discuss the appropriateness of dietary supplement use and the choice of products from reputable companies.

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CME INSTRUCTIONS

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CME QUESTIONS

1. **Which of the following is true regarding whole grain intake?**
   a. Higher whole grain intake was associated with higher cancer mortality.
   b. Higher whole grain intake was associated with lower cancer mortality.
   c. There was no association between whole grain intake and cardiovascular mortality.
   d. One serving of whole grains was found to be associated with a 5% lower total mortality in this cohort.
2. **In a recent study, acupuncture and moxibustion treatment demonstrated which of the following effects in Crohn's disease patients?**
   a. Increased HGB and increased CRP
   b. Improved QoL scores and CDAI scores
   c. Decreased HGB and increased CDAI scores
   d. Improved CDAI scores and decreased QoL scores
3. **In individuals with rheumatoid arthritis, probiotics supplementation with 10^8 colony forming units of *L. casei* was observed to**
   a. reduce tumor necrosis factor-α, interleukin-6, and interleukin-12, but not affect the disease activity score in the probiotics group.
   b. reduce disease activity score, but not levels of tumor necrosis factor-α, interleukin-6, and interleukin-12 in the probiotics group.
   c. reduce both disease activity score and levels of tumor necrosis factor-α, interleukin-6, and interleukin-12 in the probiotics group.
   d. reduce neither disease activity score nor levels of tumor necrosis factor-α, interleukin-6, and interleukin-12 in the probiotics group.
4. **Tablet reading prior to bed delays peak melatonin release by:**
   a. 30 mins.
   b. 60 mins.
   c. 90 mins.
   d. 120 mins.

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.

[IN FUTURE ISSUES]

- Types of medication and clinical use
- Spiritual interventions in oncology patients
- Glycemic index and cardiovascular disease
- Updates in integrative therapies for fibromyalgia