

Integrative Medicine

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AGING

Influencing Telomere Length: The Long and Short of It

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

Telomeres are nucleoprotein complexes found at the extreme ends of eukaryotic chromosomes. They consist of repeats of a six nucleotide sequence and specialized telomere-binding proteins that form a stable T-loop structure, essentially capping the chromosome ends and protecting the genome from degradation during replication and the cell cycle.¹ Since Elizabeth Blackburn elucidated the nature of telomeres in her Nobel Prize winning work in the mid-1970s, an explosion of research has followed focusing on interventions to preserve or enhance telomere length as anti-aging and chronic disease prevention strategies. Lifestyle interventions have been examined in both cross-sectional and longitudinal studies. A few nutrients have emerged as essential for telomere preservation in basic science research. One proprietary extract of astragalus has been widely commercially promoted to enhance telomere length. This article reviews recent research on factors affecting telomere length and examines marketing

claims promoting telomere-preserving, anti-aging products.

UNDERSTANDING TELOMERES

Telomeres have been likened to the plastic caps at the ends of shoelaces in the way that they protect the ends of chromosomes. DNA replication is a tightly regulated process involving semi-discontinuous DNA synthesis. As DNA “unwinds” in regions to allow replication, both parent strands replicate at the same time but DNA polymerase, the replicating enzyme for this function, can only work in a 5’ to 3’ direction. This means that one strand (the “leading strand”) will replicate completely and continuously in one direction from beginning to end, but the other strand (the “lagging strand”) has to replicate in short fragments. RNA primers attach to the lagging strand segments and initiate replication by DNA polymerase, and these RNA primers later have to be removed and “back filled” with DNA nucleotides, a process that takes DNA polymerase, RNA nuclease,

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Summary Points

- Telomeres are nucleoprotein complexes that protect the ends of chromosomes from progressive loss of genetic material during DNA replication.
- Telomeres shorten with age, oxidative stress, and psychological stress until critical shortening leads to cell senescence and cell death; but telomerase, the RNA transcriptase responsible for adding nucleotides back on to telomeres, is also highly active in cancer cells and contributes to cancer cell immortality.
- Several dietary habits and supplements have shown a correlation with preserved or enhanced telomere length, but more research is needed before strong recommendations can be made promoting these as interventions solely based on their effects upon telomere length.

and DNA ligase. Once the RNA primer is placed on the last piece of the 5' end of the lagging strand, there is no additional DNA on the parent strand to initiate this "back filling" process. This last RNA primer is eventually destroyed and the genes at this end of the parent strand fail to replicate in the daughter strand. Thus, these terminal genes are vulnerable to deletion with each replication, threatening loss of codons with each cell cycle (See Figures 1 and 2).²

The telomere gene sequences at the ends of chromosomes solve this problem by "taking the hit" — telomere gene loss of about 50 nucleotides and subsequent telomere shortening occur with every cell replication until the telomeres reach certain critical lengths that first result in senescence and finally result in the death of the cell (apoptosis).³ Telomeres also keep the ends of chromosomal DNA from being perceived as double-stranded DNA breaks during cell cycle damage control checkpoints, preventing loss of chromosomal material. Telomere DNA is able to serve this protective function as it is highly stable compared to chromosomal DNA, is not subject to recombination or fusion with other chromosomal DNA, and is not detected by systems of damage recognition of DNA.

Telomere shortening is attenuated to a degree by telomerase, an RNA transcriptase that adds base pairs to the telomeric DNA. Telomerase is present in germ cells, stem cells, and hematopoietic cells, but is inactive in most somatic

cells. High levels of telomerase activity correlate with longer telomeres and prevention or postponement of cell senescence, theoretically resulting in cells and tissues with more youthful behavior in terms of health and phenotype. Shorter telomeres have been associated with aging, earlier all-cause mortality, and several chronic diseases, including cardiovascular disease, Alzheimer's disease, Parkinson's disease, diabetes, and depression.^{4,5} Telomere shortening is enhanced by free radicals and oxidative stress as well as psychological stress.⁴

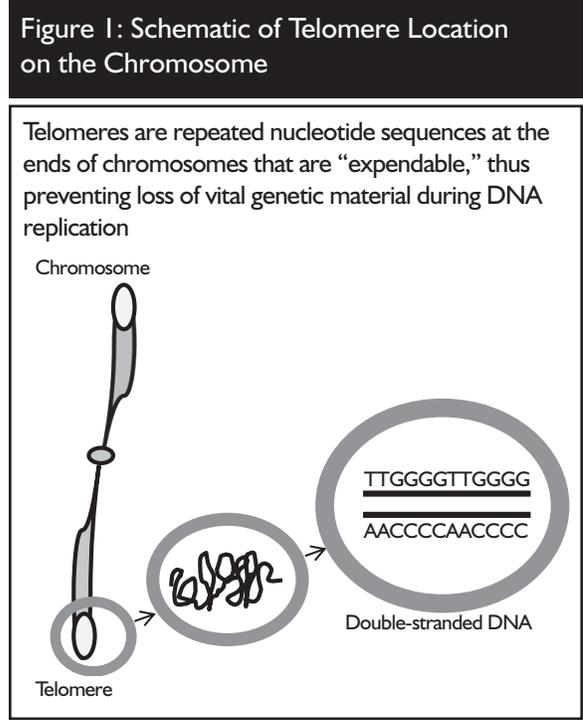
On the surface, it would seem desirable to find ways to preserve and increase telomere length and telomerase activity in healthy somatic cells as an age- and mortality-prevention strategy. However, increased telomerase activity is also present in 90% of cancers and is one of the biological keys to cancer cell line immortality; telomerase inhibition has become a potential target for anticancer drug research. Some researchers hypothesize that telomeric shortening may be an adaptive mechanism: Planned cell senescence and death may play a role in suppressing cancer emergence, despite the association of short telomeres with increased risk of disease progression and premature mortality in several cancers including breast, prostate, head and neck, and colorectal. Thus, the relationships between telomere length, telomerase function, longevity, and susceptibility to cancer remain complex and unclear.^{3,4}

RECENT RESEARCH

Caloric restriction appears to extend

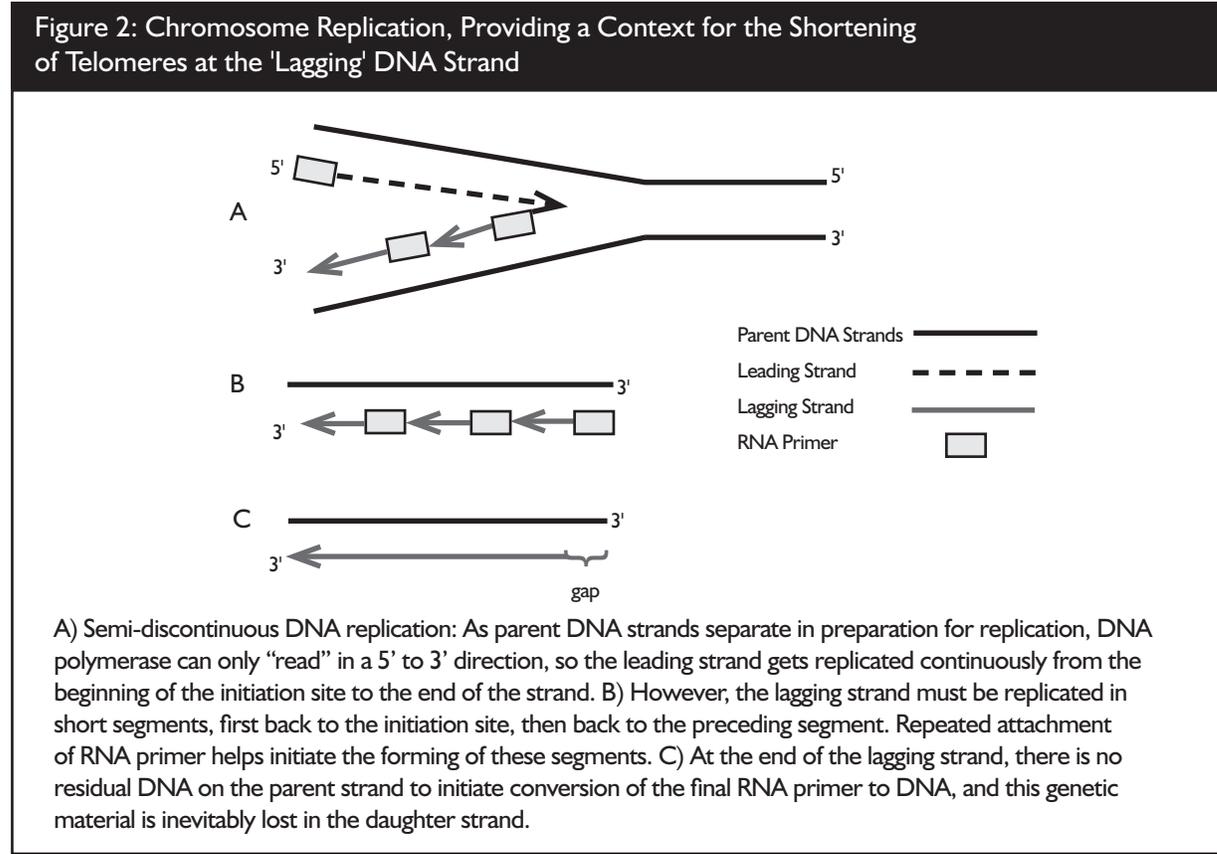
lifespan in mammals. Kark et al performed a longitudinal study of a cohort of Israeli men (n = 405) and women (n = 204) assessing leukocyte telomere length over time correlated with caloric intake and polyunsaturated fatty acid intake. Dietary intake was assessed at baseline (mean age 30.1

years) by food questionnaire and telomere length was assessed by Southern Blot at baseline and follow up (mean age 43.2 years). This study found an inverse relationship between baseline energy intake and telomere length in men ($P = 0.0005$) but not in women. Between the highest and lowest quintiles of energy intake, telomere length was different by about 244 base pairs (95% confidence interval [CI], 59-429). Between the highest and lowest quintiles of telomere length, caloric intake difference was about 440 kcal (95% CI, 180-700).⁶



Mason et al assessed telomere length at baseline and after 12 months in 439 overweight menopausal women randomized to one of four arms: dietary weight loss, diet and aerobic exercise, aerobic exercise, or control. At baseline, measures of telomere length were inversely related to age ($P < 0.01$) and positively related with fitness measured by maximal oxygen uptake ($P = 0.03$) but not with body mass index (BMI) or percentage body fat. About 48% of the study cohort experienced a net increase in telomere length and this increase was greatest in subjects with lower telomere lengths at baseline. However, there was no change in telomere length in any intervention group compared to controls.⁷

Kiefer et al studied cohorts of premenopausal (n = 36) and postmenopausal (n = 20) women to determine if telomere length was linked to self-



A) Semi-discontinuous DNA replication: As parent DNA strands separate in preparation for replication, DNA polymerase can only “read” in a 5' to 3' direction, so the leading strand gets replicated continuously from the beginning of the initiation site to the end of the strand. B) However, the lagging strand must be replicated in short segments, first back to the initiation site, then back to the preceding segment. Repeated attachment of RNA primer helps initiate the forming of these segments. C) At the end of the lagging strand, there is no residual DNA on the parent strand to initiate conversion of the final RNA primer to DNA, and this genetic material is inevitably lost in the daughter strand.

reported dietary restraint, defined as chronic pre-occupation with weight and repeated attempts to reduce food intake. They hypothesized that this kind of dietary restraint creates physical and psychological stress and should be associated with shorter telomeres. In both of these small cohorts, higher levels of self-reported dietary restraint were associated with shorter telomere length independent of age, BMI, or smoking status ($P < 0.01$ for the younger cohort; $P < 0.001$ for the older cohort).⁸

Using data from 840 Hispanic, white, and black adults from the Multi-Ethnic Study of Atherosclerosis (MESA) in a cross-sectional study, Nettleton et al evaluated the relationship between telomere length and known dietary patterns, foods, and beverages associated with markers of inflammation. Only processed meat intake was inversely associated with telomere length ($P = 0.006$).⁹

Bocardi et al studied the effect of different levels of adherence to a Mediterranean diet in 217 elderly subjects on telomere length and telomerase activity. The high adherence group had longer leukocyte telomere length and higher telomerase activity ($P = 0.003$ and $P = 0.013$, respectively) than medium and low adherence groups. The correlation of the Mediterranean diet with telomere length and telomerase activity was independent of age, gender, and smoking status. Higher telomerase levels were associated with increased healthy status as measured by the Barthel Activities of Daily Living Index, a validated questionnaire to assess physical function ($P = 0.022$).¹⁰

Ornish et al studied the effects of 3 months of intensive lifestyle changes on telomerase activity in peripheral blood mononuclear cells in 30 men with biopsy-proven, low-risk prostate cancer. This lifestyle intervention consisted of a very low fat, whole foods, plant-based diet, 30 minutes of walking 6 days per week, a stress management program 60 minutes daily 6 days per week, and a 1-hour group support session per week. Diet was supplemented with soy (tofu plus soy protein powder), 3 g of fish oil daily, 100 IU of vitamin E daily, 200 mcg of selenium daily, and 2 g of vitamin C daily. Telomerase activity increased significantly from baseline ($P = 0.031$), and increases in telomerase activity were associated with decreases in low-density lipoprotein cholesterol ($P = 0.041$) and psychological distress ($P = 0.047$).¹¹ In a follow-up study 5 years after the original data were collected, blood samples from 10 men in the intervention cohort were evaluated for relative telomere length and telomerase activity again and compared to baseline. They were compared to a control group of 25 men with low-risk prostate

cancer who underwent only active surveillance during the study period. The degree of change in telomere length and telomerase activity was studied in relationship to the degree of lifestyle change over this 5-year interval. Relative telomere length increased in the intervention group and decreased in the controls ($P = 0.03$). Adherence to the lifestyle intervention was determined using a “lifestyle adherence score” and for each percentage increase in this score, relative telomere length increased by 0.07 T/S units (telomere to single copy gene ratio) with a 95% CI of 0.02-0.12 and P value of 0.005. Telomerase activity decreased from baseline in both the intervention and control groups, but significantly less so in the intervention group: average decrease of 0.25 units in the lifestyle intervention group vs 1.08 units in the control group. This difference was not statistically significant ($P = 0.64$) and was independent of adherence to lifestyle changes.¹²

Several supplements have been studied for their effects on telomere length and telomerase activity. In a randomized, double-blind, placebo-controlled study of 106 healthy sedentary, overweight, middle-aged, older adults, Kiecolt-Glaser et al found that telomere length increased with decreasing dietary omega-6:omega-3 ratios ($P = 0.02$).¹³ In a longitudinal study of 608 subjects with stable coronary artery disease, Farzaneh-Far et al showed that patients with higher omega-3 eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) levels had the slowest rate of telomere shortening over 5 years. For each standard deviation of increase in DHA+EPA levels, there was a 32% decrease in the odds of telomere shortening (adjusted odds ratio [OR], 0.68; 95% CI, 0.47-0.98).¹⁴

Xu et al performed a cross-sectional analysis of data from 586 participants in the Sister Study, a prospective cohort study of healthy sisters of breast cancer patients, correlating multivitamin and nutrient intake to leukocyte telomere length. Multivitamin use was associated with an average increase in telomere length of 5.1% compared to nonusers ($P = 0.002$). Higher intakes of vitamins C and E from foods were also associated with greater telomere length independent of multivitamin use.¹⁵

Using data from the Long Island Breast Cancer Study project, Shen et al assessed telomere length in 1067 cases and 1110 controls. Breast cancer risk was moderately increased in women with the shortest telomere length and low dietary and supplemental intakes of beta-carotene, vitamin C, and vitamin E (OR [95% CI], 1.48 [1.08-2.03], 1.39 [1.01-1.92], and 1.57 [1.14-2.18], respectively).¹⁶

Two recent studies have shown that higher serum

Table 1: Summary of Interventions Purported to Influence Telomere Length

Intervention	Research
Calorie restriction	Kark et al: longitudinal study in men and women; telomere length inversely associated with caloric intake in men only. Kiefer et al: higher levels of self-reported dietary restraint in pre- and post-menopausal women correlated with shorter telomere length.
Mediterranean diet	Bocardi et al: high adherence to a Mediterranean diet in elderly subjects correlated with longer telomere length independent of age, gender, and smoking status.
Intensive lifestyle changes	Ornish et al: an intensive lifestyle program consisting of very low-fat, plant-based diet, 30 minutes of walking 6 days per week, a stress management program 60 minutes daily 6 days per week, and a 1-hour group support session per week correlated with increased telomerase activity after 3 months and a slower decrease in telomerase activity after 5 years; relative telomere length positively correlated with degree of adherence to intensive lifestyle program.
Omega-3 fats	Keicolt-Glaser et al: lower omega-6:omega-3 ratios correlated with longer telomere length. Farzaneh-Far et al: highest omega-3 levels correlated with slowest rates of telomere shortening in subjects with stable coronary artery disease.
Multivitamin use	Xu et al: multivitamin use correlated with an average increase in telomere length of 5.1% compared to nonusers in healthy sisters of breast cancer patients.
Vitamin D	Richards et al: higher 25 OH vitamin D levels correlated with longer telomere length. Liu et al: also noted longer telomere length correlated with higher serum 25 OH vitamin D levels but not higher 1,25-dihydroxy vitamin D levels.
Astragalus	Harley et al: astragalus root extract activated telomerase activity in vitro in human keratinocytes, fibroblasts, and immune cells; in study subjects provided a proprietary supplement pack including an astragalus root extract, mean telomere length was stable after 1 year, though percent of short telomeres was decreased compared to baseline.
Curcumin	Khaw et al: curcumin inhibited telomerase activity and induced telomere shortening in brain cancer cells in vitro.
Genistein	Khaw et al: genistein inhibited telomerase activity and induced telomere shortening in brain cancer cells in vitro.
Epigallocatechin gallate (EGCG)	Sheng et al: EGCG reduced heart weight indices and inhibited telomere attrition in cardiomyocytes in rats with induced cardiac hypertrophy as well as quercetin and carvidilol.
<i>Chlorella vulgaris</i>	Makpol et al: pre- and post-treatment of cells with <i>Chlorella vulgaris</i> prevented peroxide-induced telomere shortening and reduction of telomerase activity in human fibroblasts in vitro.

25-hydroxyvitamin D concentrations correlate with longer leukocyte telomere length. Richards et al found that this positive correlation persisted after adjustment for age and other covariates ($P \leq 0.003$) in a cohort of 2160 women aged 18-79.¹⁷ Liu et al drew their sample of 1424 from participants of the Nurses' Health Study, further noting that longer telomeres were not associated with 1,25-dihydroxyvitamin D.¹⁸

Harley et al reported data from 114 subjects (age 63 ± 12 years; 72% male) on a commercial health maintenance program consisting of a comprehensive dietary supplement pack including a proprietary extract of astragalus root. In their study, the astragalus root extract was shown to activate telomerase in vitro in cultured human keratinocytes, fibroblasts, and immune cells. In addition, study subjects demonstrated a reduction in percent of short telomeres compared to baseline after 1 year,

though mean telomere length was stable in the cohort. No adverse effects of the proprietary formula were noted at doses of 10-50 mg daily. Several of the authors were subjects in the study and/or had financial interests in the product at the time of publication.¹⁹ The proprietary product is marketed by the developers in a 6-month supply package that includes blood work and biomarker tests assessed at baseline and after 6 months of product use, and consultation with an expert age management doctor (ta-sciences.com). The full package is expensive, advertised at \$6000 for 6 months, not including the physician consultation or Quest Lab costs.

A few in vitro and basic science studies suggest that additional supplements may affect telomere length in both healthy and cancerous cells. In vitro studies have shown that curcumin and genistein (a soy isoflavone) inhibit telomerase activity and induce telomere shortening in cultured brain tumor cells.^{20,21} Epigallocatechin gallate (EGCG) compared favorably to quercetin, losartan, captopril, and carvedilol in its ability to reduce heart weight indices and cardiomyocyte apoptosis in rats with induced cardiac hypertrophy. However, only EGCG, quercetin, and carvedilol inhibited telomere attrition.²² Carly et al present convincing biochemical information that folate deficiency induced hypomethylation of DNA and elevated homocysteine levels have a deleterious effect on telomerase activity and telomere length.⁴

Makpol et al noted that DNA damage, telomere shortening, and reduction of telomerase activity could be induced in human fibroblasts subjected to free radical oxidative stress induced by peroxide. Pre- and post-treatment of the cells with *Chlorella vulgaris* prevented these effects ($P < 0.05$).²³

CONCLUSION

It is hard to interpret cross-sectional studies on telomere length because of the large degree of inter-individual difference in telomere length at any given age. Longitudinal studies comparing measures to baselines are better at compensating for these natural differences in telomere length, but still only tell us about correlations. As can be seen, most research to date describes correlations between habits, dietary status, or supplement use and telomere length, and few randomized, controlled trials have been conducted for interventions. Correlations simply don't tell us about causation and don't give us enough information to make decisions for our patients or ourselves.

What we know about telomere biology lends testimony to the amazing adaptive nature of the multitude of checks and balances that contribute

to cell homeostasis and our health. Because of the complex relationships between telomerase activity, longevity, cell senescence, and cancer biology, it is unwise to say that enhancing telomere length by any pharmacological or nutraceutical means is advisable. However, there are a number of lifestyle habits that appear to positively influence telomere length and are supported by other research as health promoting. Enjoying a Mediterranean diet, avoiding eating too many calories, and consuming fruits and vegetables with high antioxidant levels can all be endorsed, and if these strategies happen to increase telomere length as part of their gift to longevity and health, so much the better. Omega-3 fish oil supplementation, adequate folate through diet, and maintaining high vitamin D serum levels also have proven health-promoting effects and can similarly be endorsed. Until further research is done assessing long-term effects on carcinogenesis, substances specifically taken to increase telomerase activity should be viewed with caution. ■

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SPIRITUALITY

ABSTRACT & COMMENTARY

Intercessory Prayer: A Narrower Lens, but Clarity is Still Elusive

By *Howell Sasser, PhD*

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

SYNOPSIS: Tested under rigorous conditions, the benefit of intercessory prayer is a small step, not a giant leap.

SOURCE: Olver IN, Dutney A. A randomized, blinded study of the impact of intercessory prayer on spiritual well-being in patients with cancer. *Alt Ther Health Med* 2012;18:18-27.

Researchers in Australia recruited 999 patients with a diagnosis of cancer. No restriction was placed on the type or stage of cancer, although one inclusion criterion was an expected survival time of more than 6 months. Participants were assigned to intercessory prayer (the active intervention) or a comparison group that received standard care and support. Study group assignment was triple-blinded — it was unknown to participants, their physicians, and study staff (except those who made the assignments).

The names and limited personal information of those in the intervention group were provided to an existing Christian intercessory prayer group. This group prayed for the well-being of those whose names they were given, but the study report does not describe how often or for how long they prayed.

The main outcome of the study was assessed using the FACIT-Sp, which combines a general quality-of-life scale with questions designed to measure a number of dimensions of well-being. It includes 12 items for spiritual well-being that are reported as a summary score and as subscale scores for peace, meaning, and faith. All study participants completed the FACIT-Sp at baseline and again 6 months later.

Of the original 999 participants, 665 (66.6%) provided follow-up data. Of the 334 participants lost from the study, 117 (11.7% of the original

Summary Points

- Intercessory prayer delivered in a carefully blinded fashion on behalf of cancer patients led to small improvements in self-reported spiritual well-being.
- Participants in the intervention and control arms of the study showed similar changes in emotional and functional well-being.
- A majority of participants in both study groups showed no reliable change on any measure.

total) died before completing the follow-up period. There were no significant differences in demographic characteristics between the original study groups. A comparison of those who completed the study with those who dropped out or died showed that completers had significantly higher physical, emotional, and functional — but not spiritual — well-being scores at baseline. No information is provided as to how those lost from the study scored in any of the outcome dimensions at the time they were lost, so it is not possible to assess how they responded to the study intervention as compared with those who remained.

Comparing the 6-month follow-up with baseline, the

intervention group showed a statistically significantly larger increase in overall spiritual well-being than did the control group ($P = 0.03$). Differences in the spirituality sub-scales (peace, meaning, and faith) and in the other domains of well-being did not reach statistical significance, with the exception of spiritual well-being, in which the intervention group also showed a larger gain ($P = 0.04$).

COMMENTARY

The field of prayer research has faced considerable skepticism both from believers and agnostics (however each may be defined). Prayer is difficult to define in measurable units. It is not a practice in which cause and effect can be reproduced reliably. Supporters and detractors have an almost equal interest in not delving too deeply into its underlying mechanism(s). This has not forestalled a succession of larger and more rigorous studies of the subject. Recent studies have shown little or no benefit of prayer by any measure.^{1,2} Their use of careful study methods, such as random assignment, blinding, and at least some attempts at standardization of the intervention, lends credence to this, at least from a scientific perspective.

The present study uses these methods too, and comes to a different conclusion. There are a number of potential explanations. The rate of attrition was quite high (33.4%). Perhaps those who survived had a better outlook on life and this either contributed to or resulted from the success of their treatment. It is conceivable that this was manifested in their sense of well-being. The study's outcome — spiritual well-being — was more narrowly, and arguably more modestly (because limited to spiritual well-being), focused than in prior studies. It may be that the field is continuing to evolve toward a cause-and-effect model that more accurately reflects the true “state of nature.” In addition to, or despite, these possibilities, the observed benefit was negligible. The effect size, as measured by the eta-squared statistic, was very small (0.01). It may represent a chance finding that will not stand up to replication.

Whatever the truth of this and other studies, the issue remains that patients — and their physicians — struggle to find ways to talk about hope. The spirit of medical care is grounded in pragmatism and its language is heavy on percentages and probabilities. The constant, necessary search for what works can distract from what the patient wants and expects. Finding meaning in illness may seem to run counter to the dominant narrative in which illness is to be eliminated or at least minimized (such that the patient can live a “relatively normal life”). Yet with chronic and progressive diseases, the definition of “normal life” must be expanded to include the disease state, its management, and the consequences of both. This makes well-being, and the hope of achieving it or returning to it, of great importance.

What studies of prayer share is an understanding that patient goals such as hope for the future and a sense of whole-person well-being are influenced only imperfectly by anything a physician does. Instead, they are driven in large part by the beliefs and attitudes that the patient brings into the medical encounter. Some early studies of prayer tried to make the most of this, by informing study participants that they would (or would not) be prayed for, thereby recruiting the patients' own capacity to participate in building or rebuilding their lives.³ This plainly violated the usual practice of minimizing bias in scientific assessment. But it may be that more recent studies have erred in seeking to treat intercessory prayer as a therapeutic intervention, and thus under medical control, rather than as a means of bridging the gap between what medicine can provide and what the patient needs. ■

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ALLERGIES

ABSTRACT & COMMENTARY

Is Acupuncture for Allergies Worth It?

By David Kiefer, MD, Editor

SYNOPSIS: Acupuncture improved symptoms of seasonal allergic rhinitis, but it is expensive.

SOURCE: Reinhold T, et al. Cost-effectiveness for acupuncture in seasonal allergic rhinitis: Economic results of the ACUSAR trial. *Ann Allergy Asthma Immunol* 2013;111:56-63.

The researchers of this randomized, controlled trial attempted to determine the clinical and cost effectiveness of acupuncture for seasonal allergic rhinitis (SAR) sufferers in Germany. This study was an additional analysis of the ACUSAR (Acupuncture in Seasonal Allergic Rhinitis) trial in which study participants with at least 2 years of moderate-to-severe allergic rhinitis were randomized to 12 sessions of acupuncture plus antihistamine, 12 sessions of sham acupuncture plus antihistamine, or just antihistamine. With respect to the antihistamine, the participants were allowed to take up to two doses of cetirizine daily. There were numerous exclusion criteria as listed in Table 1.

The treatments continued for 8 weeks, and then participants were followed for an additional 8 weeks during which the control group also received acupuncture. Quality of life (QOL) as assessed by the Medical Outcomes Study 36-Item Short Form Health Survey was measured at baseline, 8 weeks, and 16 weeks. The QOL score was converted to a “health utility” score that the researchers had used previously; a perfect QOL equates with a utility score of 1, whereas a 0 represents the absence of full QOL, or death. All costs associated with the treatment of the study participants’ SAR were calculated using estimates of either out-of-pocket acupuncture costs or third-party payer reimbursements (the former was labeled “society’s perspective,” the latter “third-party payer’s perspective”), as well as patient questionnaires at baseline and weeks 8 and 16 about clinic visits and hospitalizations, days off of work (only included in “society’s perspective”), and medication costs. The researchers used a series of calculations to arrive at

Table 1: Inclusion and Exclusion Criteria for the Acupuncture in SAR Study

Inclusion criterion
<ul style="list-style-type: none"> ■ Moderate-to-severe SAR for at least 2 years
Exclusion criteria
<ul style="list-style-type: none"> ■ Perennial allergic rhinitis ■ Allergic asthma ■ Moderate-to-severe atopic dermatitis ■ Autoimmune disorders ■ Severe chronic inflammatory disease ■ History of anaphylactic reactions ■ Hypersensitivity to cetirizine ■ Specific immunotherapy in the last 3 years or planned in the upcoming 2 years ■ Pregnancy or breastfeeding ■ Previous acupuncture treatment for SAR ■ Any use of complementary or alternative treatment

Summary Points

- Acupuncture, compared to sham acupuncture and a control group, improved symptoms of seasonal allergic rhinitis.
- Both acupuncture and sham acupuncture were costly treatments, leading to some doubt about the cost-effectiveness of this treatment modality for seasonal allergic rhinitis.

an Incremental Cost-Effectiveness Ratio (ICER), which was the cost for gaining one additional Quality-Adjusted-Life-Year (QALY). An ICER threshold of \$67,575 (50,000 euros) per QALY gained was used, an acceptable level as compared to past international research.

A total of 422 participants were randomized to the three arms, and cost and QOL data were available for analysis for 364 participants. The baseline cost results, essentially the estimates of what was spent in the 8 weeks before randomization, for the three arms are listed in Table 2. The two acupuncture groups had more outpatient visits and more work lost than the control group, accounting for most of the observed differences at baseline. After the first 8 weeks of the study interventions, costs listed in the three study arms are also shown in Table 2, as were health utility scores, the QOL representation. No *P* values were given for the health utility scores, making it difficult to determine if any of these trends were statistically significant. However, from this table it does appear that the sham acupuncture group had the most costs (presumably from ineffectual treatment and more outpatient visits, more medication use, etc.), that the acupuncture group had the highest utility score, and that the control group showed almost no improvement in health utility.

The researchers also computed costs and QOL results after 16 weeks of treatment, but pointed out that inter-group comparisons were complicated due to the control group also receiving acupuncture during this time. The 16-week mark was considered most interesting for an “observation” period to determine the persistence of the results from the original 8-week intervention. On that note, the utility health score at week 16 for the acupuncture group was 0.821, for the sham acupuncture group was 0.800, and for the control group was 0.832. Again, without *P* values, it is difficult to determine statistical significance, but one read of these data is that the acupuncture and sham acupuncture groups continued to improve during the 8-week

“observation” period, while the control group, now receiving acupuncture, showed similar, if not higher, health utility scores, than the original acupuncture groups.

With respect to cost-effectiveness, from baseline to week 8, only acupuncture showed statistically significant higher QALY ($P = 0.01$); QALY for the sham acupuncture group did not change from baseline to week 8 ($P = 0.40$). However, both the acupuncture and sham acupuncture groups accrued more costs than the control group, as would be expected due to the costs of the treatments themselves; apparently even sham acupuncture costs money. A range of ICER values were calculated (see Table 3) for the two treatment groups vs the control group; as a reminder, the threshold per QALY gained was \$67,575 in order to justify, from a cost-effectiveness standpoint, a particular intervention. Sham acupuncture, for all intents and purposes, did not meet the criteria for a justifiable intervention, whereas normal acupuncture, the researchers posit, had 1.3% probability (from the society’s perspective) and 22% probability (from the third-party payer’s perspective) of being “worth its money.”

Two other points are interesting in this analysis. First, no one needed to be admitted to the hospital for SAR, not a surprise, but important to know in the cost calculations. And, secondly, the three arms of this study had varying visits to outpatient clinics because of SAR, the differences of which weren’t analyzed statistically in terms of significance and P values: 4.3% of patients in the acupuncture group

went to a clinic because of their SAR vs 4.7% of the sham acupuncture group and 16.7% of the control group.

COMMENTARY

This was an ambitious research endeavor. It would have been a worthy effort had the researchers simply created a tested and testable research protocol for studying acupuncture; the creation of sham acupuncture points, where needles are used to pierce the skin at sites not associated with any meridian, is complex in and of itself. But then, in addition to this, the researchers created a complex methodology for calculating costs and cost-effectiveness, addressing the important question of whether or not the benefit received from this integrative therapy is worth the extra cost. For many of us, mixing economics with clinical care is walking a fine line between compromising adequate care on one hand vs overspending on the other. How many clinicians know, for instance, the cost of a rapid throat test for *Streptococcus*, and does that matter?

A few interesting conclusions can be drawn from this research study. The first is that both acupuncture and sham acupuncture are costly, but only correctly administered acupuncture passes a cost-effectiveness evaluation, though not 100% of the time (rather 1.3-22% of the time). Part of this makes sense, as we wouldn’t expect sham acupuncture to achieve therapeutic goals. However, even the acupuncture group wasn’t universally cost-effective, especially when factoring in society’s seasonal allergic rhinitis costs, including days off work and out-of-pocket

Table 2: Society’s Cost (Using Out-of-pocket Acupuncture Cost and Days of Work Lost) and Third-party Payer’s Cost at Baseline and After 8 Weeks for the Three Arms of the Research Trial

	Acupuncture group		Sham acupuncture group		Antihistamine only group	
	Baseline	8 weeks	Baseline	8 weeks	Baseline	8 weeks
Society’s cost	\$219.93	\$580.10	\$278.99	\$765.96	\$84.17	\$78.88
Third-party payer’s cost	\$41.95	\$333.83	\$24.44	\$336.96	\$20.77	\$21.04
Health utility score, from 0-1	0.750	0.798	0.744	0.770	0.762	0.768

Table 3: Incremental Cost-Effectiveness Ratio (ICER), Which is the Cost for Gaining One Additional Quality-Adjusted-Life-Year (QALY), for the Two Treatment Groups vs the Control Group

	Acupuncture Group vs Control	Sham Acupuncture Group
Society’s cost	\$42,222-160,678	\$134,580-717,690
Third-party payer’s cost	\$28,121-100,802	\$66,441-344,022

acupuncture expenses. Perhaps the gentle nudge from acupuncture in this scenario can't overcome such a significant cost burden in this research methodology. It makes one wonder, though, how these analyses would change if "intangibles," such as psycho-social-mind-body benefits from the provider-patient encounter itself, were factored in. A hint to this effect exists in the health utility (QOL) scores: Even sham acupuncture showed a benefit in this scale. Sham acupuncture fell behind regular acupuncture in accrued costs, leading it to be cost-ineffective, but it may agree with other studies showing a clinical benefit beyond the acupuncture itself.¹

There are some perplexing aspects to this study. A fairly large number of study participants (58 of 422) did not have cost or QOL data available, and there were no reasons given for these "dropouts" nor was there any indication whether they were included in an intention-to-treat analysis. Presumably they weren't included in this way, compromising the results. Furthermore, the extensive exclusion criteria may leave clinicians scratching their heads, wondering how generalizable these results are to their patient population. And, of course, cost-effectiveness thresholds create controversy and disagreement about QALY: When, based on cost, do we deny a treatment for someone? It would have been helpful to see other calculations relevant to clinicians, such as the number-needed-to-treat.

Should clinicians now turn to acupuncture as a first-line therapy for people with SAR? Perhaps the answer is "Yes, if you can get a third-party payer to pick up the tab." This study is anything but the final word on the topic, but it is helpful to see a research group taking on the difficult task of blending clinical effectiveness and cost, using terms such as ICER and QALY that we will all surely be seeing more of as health care costs rise and the push for evidence-based medicine only intensifies. ■

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- Vickers AJ, et al; Acupuncture Trialists' Collaboration. Acupuncture for chronic pain: Individual patient data meta-analysis. *Arch Intern Med* 2012;172:1444-1453.

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CARDIOVASCULAR DISEASE

SHORT REPORT

Yoga Improves Paroxysmal AF

By David Kiefer, MD

SOURCE: Lakkireddy D, et al. Effect of yoga on arrhythmia burden, anxiety, depression, and quality of life in paroxysmal atrial fibrillation: The YOGA My Heart Study. *J Am Coll Cardiol* 2013;61:1177-1182.

This study evaluated the effect of yoga on 52 people with paroxysmal atrial fibrillation (AF).

The research subjects served as their own control by comparing a 3-month observation period with a subsequent 3-month intervention period during which the people participated in 60 minutes of structured Iyengar yoga at least twice weekly. The primary outcome variables were any change in symptomatic AF, asymptomatic AF, or symptomatic non-AF episodes (using self report and cardiac non-looping event recorders). Also measured were quality of life (Short Form 36), anxiety (Zung self-assessment anxiety score), and depression (Zung self-assessment depression score). Three patients withdrew from the study, and it is unclear whether they were included in an intention-to-treat analysis. Of note, the results of the Short Form

Summary Point

- Three months of twice weekly Iyengar yoga helped some of the symptoms experienced by people with paroxysmal atrial fibrillation.

36 varied depending on the domain; for example, yoga benefited physical functioning, general health, vitality, social functioning, limitations stemming from emotional problems, and overall mental health, but not limitations due to physical health nor bodily pain. Due to these results, the researchers tout the utility of yoga for paroxysmal AF, and mention the prior research into the multisystem benefits of yoga that could explain its effects here. ■

CME QUESTIONS

1. Which of the following is *true* about telomere biology?

- Activating telomerase is an unequivocally desirable anti-aging strategy.
- Curcumin has been shown to activate telomerase in brain cancer cells.
- A Mediterranean diet is associated with preservation of telomere length.
- Astragalus root extract is a proven safe telomerase activator.

2. To date, the consensus of the published evidence for intercessory prayer shows:

- small evidence of improvement in quality of life.
- no benefit when compared with usual care.

- improvement in somatic symptoms among those who self-identify as religious.
- a clearer effect in women than in men.

3. Which of the following is *true* about acupuncture for seasonal allergic rhinitis?

- Both acupuncture and sham acupuncture alleviated the symptoms of seasonal allergic rhinitis.
- The control group was as costly as sham acupuncture.
- None of the treatments met the cost-effectiveness threshold to justify their use.
- The control group showed no improvement in quality-of-life scoring over the first 8-week treatment period.

[IN FUTURE ISSUES]

Acupuncture and infertility

Yoga and low back pain

Microbiota and gut flora

Fruit and type 2 diabetes

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