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SPIRITUALITY

ABSTRACT & COMMENTARY

Spiritual Care at the End of Life: Who Defines a Good Outcome?

By Howell Sasser, PhD

Associate, Performance Measurement, American College of Physicians, Philadelphia, PA

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

SYNOPSIS: Those receiving spiritual support from medical personnel rather than community-based religious organizations were more likely to receive hospice care at the end of life.

SOURCE: Balboni TA, et al. Provision of spiritual support to patients with advanced cancer by religious communities and associations with medical care at the end of life. *JAMA Intern Med* 2013;173:1109-1117.

Between 2002 and 2008, researchers in New England and Texas recruited 670 adults (age ≥ 20 years) with advanced cancer diagnoses who had an "informal" (i.e., unpaid) caregiver. Baseline interviews recorded demographics, diagnosis-related details, and information related to participants' sources of spiritual care, the importance of religion in their lives, and their quality of life (QoL). Participants were asked to rate on a five-point scale the extent to which their spiritual needs were being met by their religious communities (clergy, lay visitors, congregation members) and the extent to which the same needs were being met by the "medical system" (including chaplains as well as physicians and nurses). The results of each question were dichotomized (the lowest three levels as low and the highest two levels as high) for analysis. Religious coping was measured with the 21-point Brief RCOPE scale, and the results were also dichotomized at the median (a score of 12) as low or high for analysis. QoL was assessed using the McGill QoL and SUPPORT questionnaires. Important aspects of QoL that were measured included the quality of the patient-physician relationship, patient reports of having had end-of-life (EoL) discussions with their physicians, and patients' preferences for aggressive vs comfort care.

The main outcome was the nature of EoL care received by each participant. Medical records

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were reviewed to determine whether a participant was treated in inpatient or outpatient hospice in the last week of life, whether s/he received "aggressive" care measures (treatment in an intensive care unit [ICU], ventilation, or resuscitation) in the last week of life, and whether s/he died in an ICU. QoL also was included as an outcome. Caregivers were interviewed to assess participants' psychological, physical, and overall QoL at the time near death.

Because the study focused on EoL care, only those participants who died during the study period (n = 379) were eligible for inclusion in the analysis. A further 36 lacked complete data, leaving a final sample of 343. Participants' average age was 58.3 (± 12.5). About half were male and 37% were African American, Hispanic, or of another non-Caucasian race or ethnicity. Sixty-eight percent described religion as very important to them, and 43% were classified as having high religious community support. Thirty-seven percent had had an EoL discussion with a physician and 25% expressed a preference at baseline for aggressive treatment measures. Sixty-one percent of those with low religious community support and 46% of those with high religious community support reported having advance care planning (for example, a living will or a "DNR" order).

Participants reporting high levels of spiritual support from medical personnel (including chaplains) had a greater chance of receiving hospice care (odds ratio [OR], 2.62; $P = 0.001$), a lower chance of receiving aggressive interventions at EoL (OR, 0.41; $P = 0.02$), and lower chance of dying in an ICU (OR, 0.25; $P = 0.003$), all as compared with those reporting high levels of spiritual support from a religious community. These findings were even more pronounced when the analysis was restricted to those with high scores for religious coping or to racial and ethnic minority participants. The analysis was not broken out by race/ethnicity, but the actual proportions in the minority category were 55% African American, 44% Hispanic, and 1% "other." Those with high religious community support also had significantly less hospice care ($P = 0.02$), received significantly more aggressive interventions at EoL ($P = 0.03$), and were more likely to die in an ICU ($P = 0.01$), as compared to those with low religious community support.

COMMENTARY

This study raises a number of interesting questions about the way decisions at EoL are framed, how the physician-patient relationship is affected by current patterns of medical practice, and the role and limits of social support. To evaluate how the study answers these questions, it is instructive to consider the assumptions that the investigators seem to make, but which are left largely unspoken.

The first and most important of these deals with how value is assigned to outcomes. The characterizations of hospice care as appropriate and of ICU care as inappropriate in the context of EoL represent an assignment of value. Contained in it are arguments from cost (hospice care is less expensive than ICU care), allocation (sophisticated ICU resources should be expended on those most likely to benefit from them), and preference (lower intensity care is more comfortable and better preserves patient dignity). These arguments are valid, but not exclusively so. They represent choices and values that could — indeed would — be seen differently by people with different experiences, preferences, and goals.

Current trends in policy and research support the idea of recognizing and respecting patients' wishes. There is even evidence that clinical outcomes are better when decision-making is shared.[1,2,3] However, tension is created when patients' goals do not align with what research evidence suggests is most efficient, economical, or equitable. This is especially true with EoL, when decisions have added emotional weight. There is no reason to suppose that a preference for hospice care and an avoidance of aggressive interventions is less ethically valid than any other choice, but if "patient-centeredness" is to be respected, it also must not be seen as superior to all other choices. From this perspective, the present study might be re-evaluated on

Summary Points

- Those with high levels of religious involvement and support were less likely to receive hospice care and more likely to receive aggressive treatment measures at end of life.
- Those who received high levels of spiritual support from those in the medical system were more likely to receive hospice care rather than ICU care and other aggressive measures.
- Those with high levels of religious involvement and support were more likely to recognize that they were dying and had higher self-reported quality of life.

the basis of the number of patients who participated in appropriate decision-making and whose wishes were complied with. From an ethical point of view, all such cases are successes.

A second assumption relates to the consequences of the "medicalization" of EoL decisions. It is increasingly common for hospitalized patients to be treated by hospitalists regardless of whether they have a pre-existing relationship with a primary care physician. This means that important care choices are made or informed by clinicians who likely do not have experience with their patients' pre-illness lives and attitudes. In the absence of such knowledge, clinicians must be guided by prevailing norms supplemented by what they can glean from the patient. The net effect of this is to narrow what options are discussed to the most uncontroversial.

By comparison, patients' clergy, friends from church, and family members are much more likely to know their habits and preferences, and to know how to contextualize EoL discussions, even if they may not be able to present specific options. The present study plainly judges such relationships (as measured by high religious coping and high religious community support) as having a negative effect on the choices made by exerting influence in favor of aggressive interventions. Yet there is more to the picture. Those with high religious community support were also significantly more likely to be aware that they were dying, and they had significantly higher self-reported QoL, both as compared with those who had low religious community support. This suggests a more realistic outlook and better psychological integration, important factors in clear and independent decision making. The input of physicians in EoL decisions is clearly very important, but it is also the case that the current structure of medical care limits the participation of physicians who might be best placed to know and respond to the patient.

A third assumption deals with the distinctness of EoL as a life phase. It is certainly true that death and dying are events without (personal) precedent in each person's life. As such, they oblige us to make new and unfamiliar choices. However, it seems implausible to think that these choices are not colored by earlier experience (both personal and social). The extent to which these influences are common to the patients, physicians, hospital culture, and community weighs heavily in how well EoL is integrated into the life that precedes it. In the present study, minority patients were found to be less likely to opt for hospice care and decline aggressive measures. This must be seen in the context of minority patients' prior access to medical care and experience of medical decision making. A history of poor access to care might make hospice look like a lower-quality, less technologically advanced option. To have the chance to choose what one feels has been denied in the past is a powerful motivator. This is only the most obvious example. Other more subtle factors in patients' experiences, and the ways in which they differed from those of their physicians and the dominant culture of the hospital, also played a part.

This study is a welcome reminder of the role that physicians and others can and must play in helping patients make decisions in areas that are more than simply "medical." Patients must rely on those with expertise that they lack to navigate unfamiliar situations. However, it is also important to remember the diversity of experiences and expectations that all parties bring to these interactions. Patients' preferences may not always align with the dictates of "evidence," and those whose professional lives are driven by what is or is not evidence-based must be careful to keep the patient and his/her wishes in the center of the picture. ■

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ABSTRACT & COMMENTARY

Herbal Authenticity as per DNA Barcoding in Canada

By David Kiefer, MD, Editor

SYNOPSIS: A DNA identification technique led this research group to postulate that many herbal products and herbal leaf samples were incorrectly identified and/or adulterated.

SOURCE: Newmaster SG, et al. DNA barcoding detects contamination and substitution in North American herbal products. *BMC Med* 2013;11:222.

The researchers of this study used a biotechnology technique, DNA barcoding, to analyze natural product samples, looking for short, standardized gene sequences specific to a given species. Multiple DNA extracts were taken from 100 mg of the herbal products and analyzed using standard polymerase chain reaction techniques for two gene sequences, as per references mentioned in this article. The two sequences used were *rbcL* (imperfect for separating the identity of closely related species) and *ITS2* (high species resolution based on nuclear, rather than plastid, genome). The reference for these samples was called a standard reference material herbal barcode library (currently at 100 species, but being expanded by the researchers), which contains known gene sequences to which the samples can be compared. Of note, as per a critique that appeared soon after the publication of this article, this study's reference genetic library was not the same as that used as an herbal industry standard.[1]

The researchers blindly chose 44 single-ingredient herbal products from 12 companies. These were 41 capsules, one tablet, and two powders, representing 30 different species of plants. These were submitted for analysis using only a product label; brand names were excluded. The herbal products chosen were brands commonly available in North American retail outlets and were purchased from stores in Toronto, as well as through mail order from the United States.

Additionally, 50 leaf samples, representing 42 plant species, were collected from taxonomically identified (the "gold standard") plants in horticulture greenhouses, accounting for all 30 of the herbal product plant species as well as related species. These were also blindly submitted for analysis as an independent test of validity of the DNA barcoding technique.

The samples were then categorized as authentic (DNA matched the species listed on the label), contamination (DNA found for a species other than what was listed on the label), substitution (DNA found for a species other than what was listed on the label, ***and*** the label species DNA was not found), and filler (DNA from known fillers, such as wheat, soybean, and rice, was detected).

Summary Points

- Approximately half (48%) of 44 herbal products tested had the correct plant DNA present, but more than half of the products (59%) contained at least some plants not listed on the label.
- Fillers and plant adulterants were also found.
- There are some concerns about the methodology and clinical relevance of these results.

The results were as follows. First, the DNA from the 100 reference plants showed 100% species resolution, in that there were DNA regions specific to each of those plants as analyzed by this technique. Of the herbal products, 40/44 (91%) were successfully DNA barcoded using the two combined gene regions. The more accurate gene region, *ITS2*, only missed three herbal products, which the researchers posit was due to substitution by plants not in their reference library. For the herbal leaf samples, 57% were matched correctly to the reference library using *rbcL* and 100% using *ITS2*.

The categorical breakdown of the herbal products is shown in Table 1. The researchers combined these results by pointing out that 59% of the products contained plant species not on the labels, while 33% also contained plant fillers or contaminants not listed on the labels. Approximately 8% of the products contained unidentifiable sequences not yet

Table

For the 44 herbal products, the percentage that were authentic, substitution, contamination, and fillers.

Category	Percentage
Authentic	48%
Substitution	32%
Contamination	21%
Filler	21%

in the reference library; some of these were sequences represented plants in completely different plant families from the plants on the labels.

The researchers provided company-by-company data as well. Only two of the 12 companies had only authentic products (10/12 with product substitution), whereas three companies had no authentic products. However, for 90% of the plant species analyzed, the researchers found at least one company that "got it right," that is, had an authentic product.

A full table was provided for the product labels as compared to the DNA barcoding findings, with some interesting, if not concerning, results. For example, one *Ginkgo biloba* product was actually black walnut (*Juglans nigra*), while only rice was found in one *Ginkgo biloba* product and one St. John's wort (*Hypericum perforatum*) product.

COMMENTARY

The headlines were striking: Almost every major newspaper had some version of the *New York Times* warning "Herbal Supplements Are Often Not What They Seem."[2] Dear to the heart of dietary supplement users, these results fanned the fire of anxiety and fear about supplement quality. Additionally, if this author (DK) is a litmus test of reality, this study may have been the first time that many people heard of the use of DNA barcoding, presumed the "gold standard," for everything from forensics to "personalized medicine," and now, apparently, for herbal product identification. The story, however, is not so simple and clear-cut, primarily because of some methodological problems and a technology that is still in its infancy.

On this note, the paper brought the ire of herbal industry experts, pointing out numerous inconsistencies and flaws. Most notably, and probably a fatal oversight, is that DNA may not be present in herbal extracts, even though the physiologically active phytochemicals will be. Without a product list, it is difficult to know how many of the 44 products tested were standardized extracts and therefore not expected to "light up" on a DNA barcoding test. Along the same vein, the heat treatment that most plants undergo in processing for consumer sale will damage, if not destroy, DNA, hopefully leaving the phytochemicals intact. Again, no DNA would expected to be present. Finally, the polymerase chain reaction technique, part of this DNA barcoding analysis, is very sensitive for even the faintest trace amounts of DNA; contamination in the testing laboratory, not the herbal products, can't be ruled out as a cause of the "contamination" category of these findings. Proper controls, lacking in this study, could have theoretically mitigated these false negatives.

The authors of this study mention some of the prior work on DNA barcoding, and marketplace analyses of adulteration and substitution, which are in the ballpark for the percentages presented here. They aptly put their results into clinical context, with some of the dangerous substitutions at the top of their discussion, including the presence of wheat as a filler, possibly of concern to our patients with celiac disease. Fillers by definition aren't "bad," and actually are necessary (and legally approved) to help formulate products. Consumers have the right to know what's in each product, and such compounds should be on the label. Alternatively, they mention some of the pitfalls of their work including the incomplete herbal DNA reference library.

Strict attention to herbal quality is of paramount importance, but it remains to be seen whether this DNA barcoding technique is the best way to assess authenticity. It needs to be corroborated and cross-checked with other laboratories and gene banks. The study mentions several papers and sources for other herbal reference libraries.[1] Insomuch as the researchers themselves state that "There are currently no best practices in place for identifying the species of the various ingredients used in herbal products," a combination of adherence to the legally mandated current good manufacturing processes and refinement of the DNA barcoding techniques might be just the perfect combination to foster product quality. ■

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ABSTRACT & COMMENTARY

Vitamin D Supplementation and Parkinson's Disease

By Traci Pantuso, ND, MS

Adjunct Faculty, Bastyr University, Seattle, WA

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

SYNOPSIS: Supplementing patients with Parkinson's disease with 1200 IU of vitamin D3 may stabilize Parkinson's disease symptoms in patients with vitamin D receptor CT and TT genotypes but not the *Fok*I CC genotype.

SOURCE: Suzuki M, et al. Randomized, double-blind, placebo-controlled trial of vitamin D supplementation in Parkinson's disease. *Am J Clin Nutr* 2013;97:1004-1013.

Serum vitamin D (25(OH)D) has been demonstrated to be associated with the severity of Parkinson's disease (PD) by a number of researchers. In a previous study conducted by the same authors, it was found that higher 25(OH) D serum levels were significantly associated with decreased severity of PD measured by the Hoehn and Yahr stage (HY) and the Unified Parkinson's Disease Rating Stage (UPDRS) scores in PD patients. The authors also found that the VDR *Fok*I CC genotype was also associated with a milder form of Parkinson's disease. Single nucleotide polymorphisms (SNPs) in the VDR gene may alter the function of the receptor and how the VDR receptor interacts with 25(OH)D. To further examine the role of 25(OH)D and VDR genotypes in PD, the authors conducted a double-blind, placebo-controlled trial at Katsushika Medical center in Tokyo, Japan.

The authors enrolled a total of 114 PD patients aged 45-85 years and randomly assigned them to either the placebo or 1200 IU/day of vitamin D3 group for 1 year. UK Parkinson's Disease Society Brain Bank inclusion criteria were used. The patients needed to be diagnosed with PD by two or more neurologists, and not have first- or second-degree relatives with PD. Fifty-eight patients were randomly assigned to the placebo and 56 patients were randomly assigned to the 1200 IU/day vitamin D3 group. The vitamin D3 was purchased from Zenyaku Co Ltd. Blood pressure, body mass index, levodopa equivalency dose (LED), serum calcium, parathyroid hormone, liver and renal function tests, and serum concentrations of 25(OH)D and 1,25(OH) D were measured at enrollment and 12 months. To measure PD severity, the modified HY stage, UPDRS, Mini-Mental State Examination (MMSE), EuroQol 5 Dimension (EQ-5D), and Parkinson's disease Questionnaire-39 (PDQ39) were also measured at baseline and 12 months. Patients were followed up every 0.5-3 months to monitor disease progression and to adjust drug doses. To evaluate VDR genotypes and vitamin D binding, protein polymerase chain reaction and direct sequencing techniques were used.

Summary Points

- Daily supplementation of 1200 IU of vitamin D3 for 12 months significantly prevented the deterioration of Parkinson's disease (PD) without adverse events.
- The number needed to treat was six patients for no deterioration in Hoehn and Yahr stages in PD patients.
- VDR *Fok*I genotypes may play a key role in vitamin D supplementation and require further research.

Intention-to-treat analyses were conducted based on 55 patients in the vitamin D3 group and 57 patients in the placebo group. A total of 10 patients withdrew from the study and this was not significant between the two groups. Compliance was 96.5% in the placebo group and 89.1% in the vitamin D3 group. The mean age of the study population was 72 years old. Tables provided by the authors demonstrated that both groups were similar in regards to patient characteristics. No significant differences between the vitamin D3 and placebo groups were noted with 25(OH)D and 1,25(OH) D serum levels at baseline. There were also no significant differences demonstrated with respect to VDR or GC genotypes between the groups. Twenty-two percent of the total participants had vitamin D levels at ≥ 30 ng/mL and were considered vitamin D sufficient, while 48% of the total participants had vitamin D levels < 20 ng/mL and determined to be deficient.

The levels of 25(OH)D increased in the vitamin D3 group from a mean ± SD of 22.5 ± 9.7 ng/mL to 41.7 ± 12.6 ng/mL after 12 months ($P < 0.0001$). The vitamin D3 concentrations remained relatively the same from baseline to 12 months as expected in the placebo group. In the vitamin D3 group, 1,25 OH D levels were significantly increased from a mean ± SD of 61.3 ± 17.1 ng/mL at baseline to 69.9 ± 18 after 12 months ($P < 0.0001$) and no significant changes were found in the placebo group.

Five patients in the vitamin D3 group and three patients in the placebo group had reductions in their anti-parkinsonian medications expressed as the LED, and this difference between groups was not significant. The LED of a given drug is the amount of the drug that is required to produce the same anti-parkinsonian effect as 100 mg of immediate release levodopa.

Modified HY stages significantly worsened in the placebo group between baseline and 12 months ($P = 0.0006$), while remaining stable in the vitamin D3 group. There was a significant difference between the vitamin D3 group and the placebo group modified HY stages ($P = 0.0005$).

Sixteen of 55 patients receiving vitamin D3 had HY stages that were neither improved nor worsened compared to 7/57 patients in the placebo group ($P = 0.028$). The risk difference was 17% (95% confidence interval [CI], 2-32%) and the number needed to treat was six patients (95% CI, 48, 3 patients).

UPDRS part II scores were worsened from baseline to 12 months in the placebo group ($P = 0.004$) and remained stable in the vitamin D3 group. There was also a statistical significance between the groups' UPDRS part II scores ($P = 0.004$). There were no differences found with UPDRS total or parts I, III, or IV between groups. No differences were found on MMSE scores between or within groups. The vitamin D3 group had significantly improved scores on the PDQ39 compared to the placebo group ($P = 0.04$).

VDR *Fok*I genotypes were found to significantly interact with the effects of vitamin D3 on the HY stage (P-interaction = 0.045) and the UPDRS total (P-interaction = 0.039) and part II (P-interaction = 0.035). No interactions were found between the other VDR genotypes and GC genotypes that were tested.

The authors did not comment on any vitamin D3 intra-group differences (i.e., deficient, insufficient, or sufficient 25(OH)D levels at baseline) on any of the study results between baseline and 12 months.

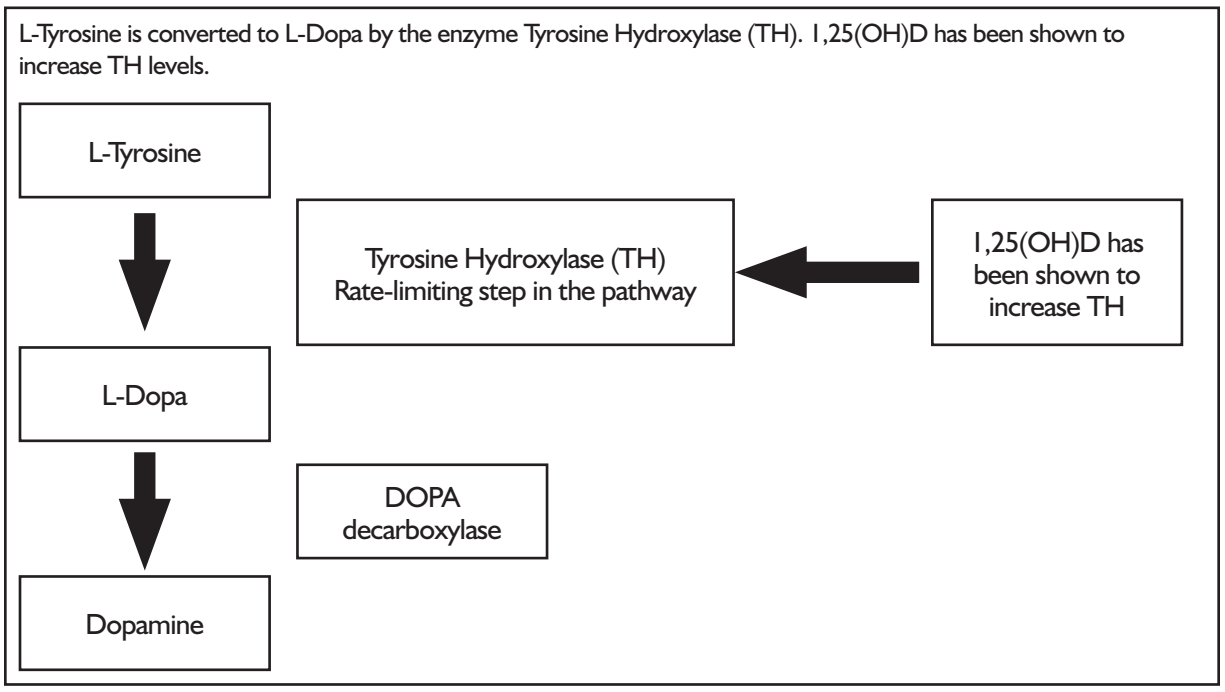
- Vitamin D (25(OH)D) serum levels increased from 22.5 to 41.7 ng/mL with 1200 IU/day for 12 months in the vitamin D3 group, with no increases in the placebo group.
- The placebo group's modified HY stages were significantly worsened compared to the vitamin D3 group.
- The VDR *Fok*I TT ($P = 0.0006$) and CT ($P = 0.030$) but not CC genotypes were found to play a role in the effects of vitamin D3 on the HY stage and the UPDRS total and UPDRS part II.

COMMENTARY

This study is an important addition to the growing body of evidence suggesting that low vitamin D status may be a factor in PD symptomatology, and that daily vitamin D3 supplementation may stabilize PD severity without side effects. This research study offers compelling evidence that the vitamin D pathway requires further elucidation to understand how the different *Fok*I VDR genotypes effect the function of the pathway in PD. VDR is expressed in the dopamine-rich substantia nigra of the brain, and the active form of vitamin D (1,25(OH)D) has been shown to increase the expression of the rate-limiting enzyme tyrosine hydroxylase in the production of dopamine, further pointing to the role of vitamin D in PD (*see Figure 1*). The optimum vitamin D (25(OH)D) levels for brain health have yet to be determined and require more research. In this study, 22% of the total participants had vitamin D levels ≥ 30 ng/mL and were considered vitamin D-sufficient while 48% of the total participants had vitamin D levels < 20 ng/mL and were determined to be deficient. The authors neglected to comment on the 30% of the patients who had insufficient vitamin D levels between 20-29 ng/mL.

There were a number of limitations in this study. The study population was modest in size (n = 114) and some patients had early PD and others had more advanced PD. The study population appears to be mostly Japanese as the study took place in Tokyo, Japan, and the authors did not comment on the ethnicity of the study participants. VDR *Fok*I polymorphisms show ethnic variation. The VDR *Fok*I polymorphisms investigated by the authors in this study were CC:CT:TT and the ratios for these polymorphisms in the study population were 34:52:14, respectively. The ethnic variation ratios of the CC:CT:TT VDR *Fok*I polymorphisms are as follows: African, 42:48:10; Hispanic, 46:46:8; Pacific, 29:58:13; and white, 40:47:13, respectively. Because of the ethnic variation in the VDR *Fok*I polymorphisms, it may be an important variable for further studies to include ethnicity as to increase the clinical utility of the results. This randomized,

Figure 1. Dopamine Synthesis Pathway



controlled study investigating the relationships between vitamin D3, PD, and VDR genotypes provides quite compelling evidence that vitamin D3 supplementation as an adjunctive treatment in PD may be efficacious.[1] As vitamin D is relatively inexpensive, commonly available, and did not demonstrate adverse side effects when dosed at 1200 IU/day, it is a reasonable approach to supporting brain health in PD patients. ■

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WOMEN'S HEALTH

ABSTRACT AND COMMENTARY

Acupuncture and Moxibustion May Increase Pregnancy Rates in IVF after Embryo Implantation Failure

By Natawadee Young, MD

Associate Professor of Family Medicine, AnMed Health Family Medicine Residency Program, Anderson, South Carolina

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

SYNOPSIS: This prospective trial performed at an infertility clinic in Brazil randomized 84 women who had at least two prior failed in vitro fertilization (IVF) attempts to three groups. The first group had acupuncture plus moxibustion in addition to IVF, the second had sham acupuncture and IVF, and the third group only underwent IVF. Results showed a significant increase in clinical pregnancy rates in the true acupuncture plus moxibustion group compared to the sham acupuncture and the IVF only groups (35.7% vs 10.7% and 7.1%, respectively).

SOURCE: Villahermosa DI, et al. Influence of acupuncture on the outcomes of in vitro fertilization when embryo implantation has failed: A prospective randomized controlled clinical trial. *Acupunct Med* 2013;31:157-161 doi: 10.1136./acupmed-2012-010269.

This prospective, randomized trial was conducted at the Clinic for Human Reproduction, Faculty of Medicine of ABC, Santo Andre SP, Brazil. Women aged ≤ 38 years with infertility who had at least two prior unsuccessful IVF attempts (defined as embryo implantation failure) were asked to participate. The study excluded transfer of frozen or poor-quality embryos, prior use of acupuncture by participants, use of other adjunctive infertility treatments, severe oligospermia in the partner (< 2 million/mL), and age of male partner > 50 years.

Randomization was done with sealed envelopes using computer-generated numbers to create three groups: true acupuncture with moxibustion (n = 28), sham acupuncture (n = 28), and control (n = 28). Blinding of participants, treating providers, and investigators was not discussed. All participants underwent IVF treatment using the same clinic protocol. The women in the true acupuncture arm received moxibustion at nine acupuncture points (Bl18, Bl22, Bl23, Bl52, CV3, CV4, CV5, CV7, GV4) typically used for infertility for 5 minutes, followed by traditional acupuncture needling at 12 points (PC6, Ki3, Ki6, Ki7, Ki10, Lr3, Sp4, Sp6, Sp10, St10, St40, Lu7, unilaterally and Zigong bilaterally). All sessions were performed by the same acupuncturist with more than 5 years of practice. Needles were manually inserted and stimulated to obtain *de qi* sensation and left in place for 20 minutes. The *de qi* sensation is described as an aching discomfort at the site of the acupuncture needle felt by the patient when the acupuncture needle is gently twisted by the acupuncturist. The acupuncturist feels *de qi* as a "grasping" sensation by the patient's tissues as the needle is gently twisted and manipulated. Traditional Chinese medicine (TCM) methods of acupuncture advocate that the *de qi* sensation is a sign that qi is being moved by the acupuncture treatment — the goal of acupuncture in restoring balance.[1]

Women in the sham acupuncture group had eight needles inserted in non-acupuncture point locations bilaterally in the arm and thigh. Needles were inserted superficially, in points unrelated to the meridian, and without eliciting *de qi*. Needles were left in for 20 minutes. No moxibustion was performed on the sham acupuncture group. Women in the control group underwent IVF only per clinic protocol.

Investigators measured demographic data, number of oocytes retrieved, endometrial thickness, and number of transferred embryos from all groups. Primary outcomes measured were chemical pregnancy rates (defined as fraction of βhCG on 12th day after embryo transfer) and clinical pregnancy rates (defined as presence of an intrauterine gestational sac seen on transvaginal ultrasound after the fourth or fifth week of gestation).

Summary Points

- A small randomized, controlled trial showed that acupuncture and moxibustion in addition to in vitro fertilization significantly improved clinical pregnancy rates in women who had embryo implantation failure. However, there should be larger and more robust trials to see if this result can be replicated.
- Future research on acupuncture would benefit from adhering to more fidelity in reporting according to STRICTA and CONSORT protocols.

All three groups of women had no baseline differences in demographic data including age, duration of infertility, fraction with primary infertility, and number of previous IVF cycles. There were no dropouts or incomplete data. All three groups had the same number of embryos transferred (mean = 2.2, $P = 0.5238$). There was a trend toward higher number of oocytes retrieved (8.4 ± 3.1 [true] vs 6.5 ± 3.1 [sham] vs 6.5 ± 3.5 [control], $P = 0.0427$) but no statistical significance. However, women in the true acupuncture and moxibustion group had thicker endometrial measurements (10.3 ± 1.6 mm vs 8.5 ± 1.6 mm [sham] vs 8.7 ± 1.6 mm [control], $P = 0.0002$).

For the primary outcome of biochemical pregnancy rates, there was a statistically significant trend toward higher rates in the true acupuncture group (39.3% vs 10.7% [sham] vs 10.7% [control], $P = 0.0327$; 95% confidence interval [CI], 1.08-9.91). There was a statistically significant increase in clinical pregnancy rate in the true acupuncture group compared to the other two groups (35.7% [true acupuncture] vs. 10.7% [sham] vs. 7.1% [control], $P = 0.0169$; 95% CI, 1.25-14.09).

COMMENTARY

Up to 17% of couples will experience difficulty in conceiving at some period in their lives. Despite many gains, current pregnancy rates with IVF range around 30%. These authors are studying a subset of women undergoing IVF who have failed two or more IVF cycles, defined as embryo implantation failure (EIF). They state that in women with EIF,

pregnancy rates in subsequent IVF cycles fall to less than 10%.[2] The treatment arm compared using acupuncture and moxibustion to a sham acupuncture group vs IVF alone.

Moxibustion is a TCM method of heating acupuncture points on the skin, traditionally by placing moxa, a dried plant mugwort (*Artemisia vulgaris*) on skin points and burning it or heating the skin with it. According to TCM concepts, this heating of skin along acupuncture points facilitates normal movement and flow of Qi. TCM concepts of infertility often ascribe the imbalance to a deficiency of heat in the lower warmer.[3] As such, moxibustion is often an essential component in TCM treatments for infertility.

Although this was a small study (n = 84), the authors did plan to enroll at least 66 patients to have enough power to detect a statistical difference, accounting for an estimated clinical pregnancy rate of 10%. Demographics did not show any significant differences between the women in the three groups. Results showed a slightly lower than normal clinical pregnancy rate in the IVF only group of 7.1%, as well as an expected rate of pregnancy in the sham acupuncture group of 10%. However the true acupuncture + moxibustion arm showed a statistically significant increase in clinical pregnancy rate of 35.7%. This would mean an absolute risk reduction of 28.6% between the IVF only and the true acupuncture and moxibustion group and a number needed to treat (NNT) of 3.5.

It would have been difficult to blind the acupuncturist, since only one acupuncturist performed all treatments: moxibustion, true, and sham acupuncture. There was also no discussion about concealing allocation or blinding of either patients or IVF providers/ researchers. All research was conducted at one site in Brazil over a 2-year time period. All these factors would contribute to a bias that would favor the treatment outcome. It is unclear how study authors chose the specific moxibustion and acupuncture points used for the study arm of this trial, although many of these acupoints are commonly used in the TCM treatment of infertility. This standardization of points makes the study more replicable; however, according to TCM precepts, different acupuncturists may have chosen different points or tailored them to the individual patient.

In this particular study, given the lack of allocation concealment and the lack of blinding of acupuncturist and study, can the increase in clinical pregnancy rate be truly attributed to acupuncture and moxibustion itself? There are other potential confounders that were not accounted for in study design. Since there was no sham moxibustion in the sham acupuncture arm, did the longer treatment time in the true acupuncture and moxibustion group make the difference? In addition, the sham acupuncture protocol of inserting needles superficially in non-acupuncture points may not have been an inert treatment and may have contributed to some treatment effect.

There was no mention of adverse effects or harms. There were apparently no dropouts. However, inclusion criteria were very stringent, and generalization of this acupuncture and moxibustion protocol to other groups would be difficult without a clearer reporting of the actual methods.

There has been considerable research into how acupuncture may improve assisted reproductive techniques, especially IVF. Several studies have measured biochemical responses to acupuncture.[4] Others have looked at pregnancy rates if acupuncture is performed on different days of IVF treatment, in particular, around days before and after embryo transfer.[5] Yet other studies have looked at acupuncture's influence on perceived stress in the women undergoing infertility treatment and whether that corresponds to IVF success rates.[6] Recent systematic reviews and meta-analyses of RCTs of acupuncture's effects on infertility and IVF have commented on the heterogeneity of studies along with methodological flaws in study design.[7]

Nevertheless, many acupuncture studies do suggest the plausibility of acupuncture influencing fertility. Studies have shown that acupuncture can affect stress levels in couples going through infertility treatments.[5] Acupuncture can influence reproductive hormones levels and increase ovarian blood flow.[3,8]

However, little has been studied about combining moxibustion and acupuncture as an adjunct to IVF.

The revised STRICTA (STandards in Reporting Interventions in Clinical Trials of Acupuncture) protocol, developed by expert consensus in 2010, calls for fidelity in reporting acupuncture trials methodology according to a six-item checklist. The checklist asks authors to clearly state: 1) acupuncture rationale, 2) details of needling, 3) treatment regimen, 4) other components of treatment, 5) practitioner background, and 6) control or comparator interventions. STRICTA protocol was designed to be used in conjunction with the 25-item checklist developed by the CONSORT working group that provides an evidence-based reporting protocol for reporting all parallel, randomized, control trials.[9] The aim of both STRICTA and CONSORT protocols is to ensure that all trials have clear and transparent reporting standards so that replication, generalization, and critical appraisal of studies are possible. Future acupuncture studies would greatly benefit from conforming to these reporting protocols.

In conclusion, this small, randomized, controlled trial on a specific subset of women with infertility who have failed earlier IVF treatments suggests that combining acupuncture with moxibustion significantly increased clinical pregnancy rate compared with sham acupuncture and IVF alone. Further research is needed to reproduce these findings and stricter reporting of methods is needed to further the study of acupuncture's influence on infertility. ■

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SHORT REPORT

Vitamin D and Pain

By David Kiefer, MD

SOURCE: Sanghi D, et al. Does vitamin D improve osteoarthritis of the knee: A randomized controlled pilot trial. *Clin Orthop Relat* Res 2013;471:3556-3562.

Vitamin D should probably be the *Time Magazine* nutrient of the year (decade?), given the variety of body systems with some physiological connection to the effects of vitamin D. Add to the list pain — in this case pain from osteoarthritis (OA) of the knee. In 107 people with documented knee OA and vitamin D insufficiency (serum 25-hydroxyvitamin D (25(OH)D) ≤ 50 nmol/L), the half allocated to receiving oral vitamin D3 (or cholecalciferol, dosed at 60,000 IU daily for 10 days and then 60,000 IU once monthly for the remainder of the 1-year study) had less pain as per the visual analog scale (VAS) and WOMAC scores (effect sizes 0.37 and 0.78, respectively) and improved knee function at 12 months when compared to the placebo group. There were no differences between the groups with respect to knee stiffness. The serum 25(OH)D increased in the vitamin D group by 45.7 nmol/L, whereas the placebo group only increased 2.1 nmol/L after the year. A major limiting factor of these findings was the low effect sizes, equating with only about 1 mm on the VAS score and 2 points on the WOMAC, making the authors question the clinical relevance. The authors consider these results important for the planning of future clinical trials that would have sufficient power to detect clinically significant differences.

Summary Points

- Statistically significant, but clinically minimal, improvements in knee pain and function were observed with 1 year of treatment with oral vitamin D3.

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- describe and critique the objectives, methods, results and conclusions of useful, current, peer-reviewed clinical studies in alternative medicine as published in the scientific literature.

CME QUESTIONS

1. According to the study on spiritual care at end of life, which population was most likely to receive hospice care?
a. Minority patients with low levels of religious support
b. Patients in non-religiously affiliated hospitals
c. Patients receiving spiritual support from physicians, nurses, and chaplains
d. Patients receiving spiritual support from community-based religious organizations

2. Which of the following is *true* about herbal products?
a. All of the herbal products tested had DNA evidence that matched the label.
b. DNA might not be present in an herbal extract.
c. Common fillers identified in this study include whey and slippery elm root.
d. In this study, "substitution" was defined as an herbal product with less than 70% of the quantity expected for the plant on the label.

3. Vitamin D3 supplementation in PD patients has demonstrated:
a. improvement in the HY stage score.
b. stabilization in the HY stage score.
c. no interaction with VDR genotypes.
d. worsening in the HY stage score.

4. What is the goal of the STRICTA protocol in acupuncture research?
a. To ensure that all trials have clear and transparent reporting standards to improve replication and generalizability
b. To ensure adequate funding for acupuncture research
c. To ensure that acupuncture trials can be critically appraised and findings can be generalized
d. Both a and c
e. All of the above

5. Which of the following is true regarding the randomized, controlled clinical trial for vitamin D and knee osteoarthritis (OA)?
a. The effective dose was 600 IU daily.
b. The patients enrolled were vitamin D sufficient.
c. The vitamin D group displayed an increase in serum 25(OH)D after 1 year.
d. Oral vitamin D was statistically effective for hip OA but not for knee OA.

[IN FUTURE ISSUES]

Exercise and mortality | Yoga and menopause | Walnuts and chronic diseases | Resveratrol

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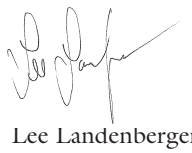

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Continuing Education Director
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