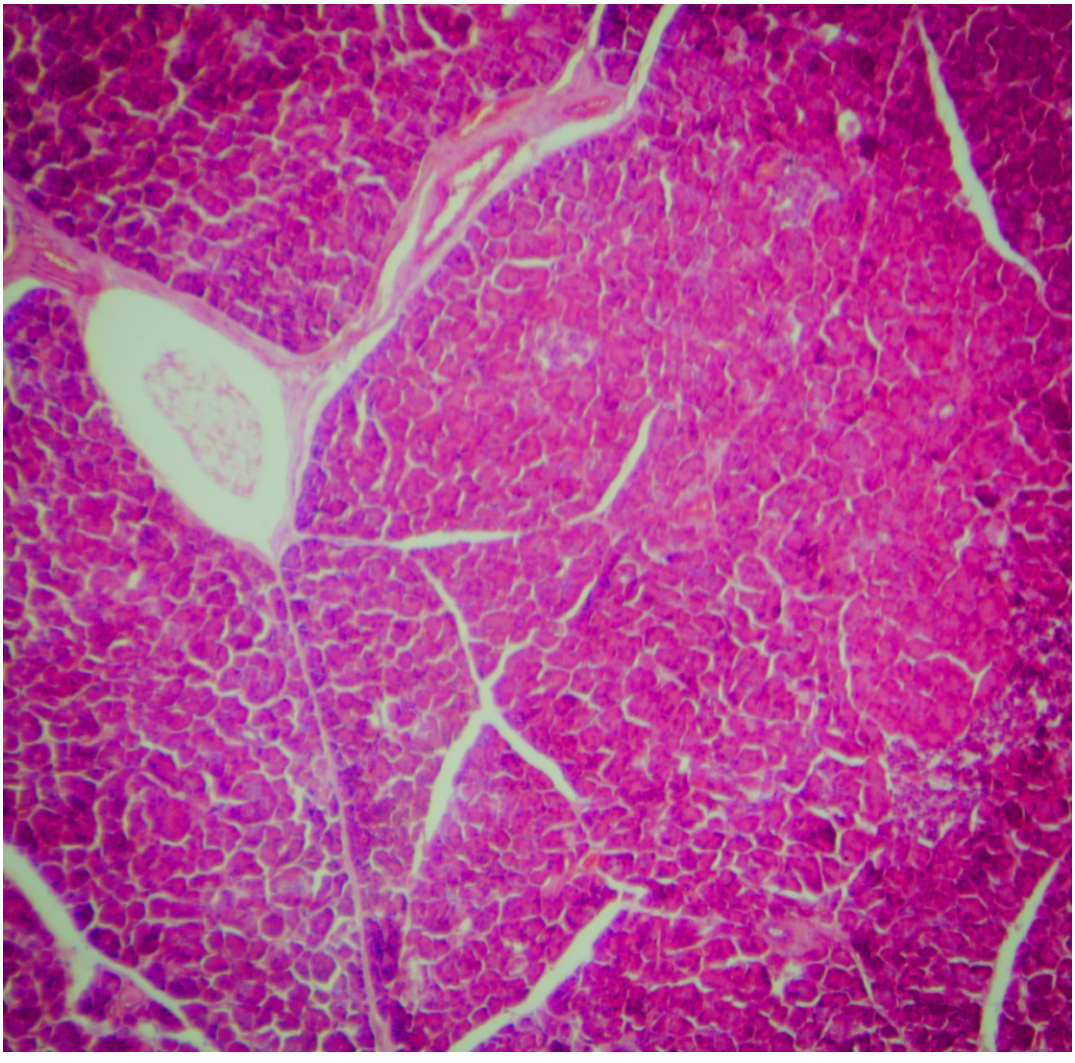
NATURAL MEDICINE JOURNAL

AUGUST 2014 SUPPLEMENT

SPECIAL ISSUE

Endocrinology



LITERATURE REVIEW

Bioidentical Hormone Replacement Therapy

ABSTRACT & COMMENTARY

Polycystic Ovarian Spectrum

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NATURAL MEDICINE JOURNAL

SPECIAL ISSUE **ENDOCRINOLOGY**
AUGUST 2014 VOL 6, NO. 8 (SUPPL)

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This Issue's Contributors


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TINA BEAUDOIN, ND, received her doctorate of naturopathic medicine from Bastyr University. Beaudoin has a private practice in Bedford, New Hampshire, and serves as the current President of the New Hampshire Association of Naturopathic Doctors. She also enjoys giving conference and corporate lectures and being a medical educator at Emerson Ecologics.


Jaclyn Chasse, ND

JACLYN CHASSE, ND, is a naturopathic physician in New Hampshire with a clinical practice focused on fertility, women's health, and pediatrics. She works as the medical director for Emerson Ecologics and also holds an adjunct faculty position at Bastyr University, where she earned her naturopathic degree. She has coauthored several scientific journal articles in the field of medical biophysics and integrative medicine. Chasse serves is dedicated to advancing naturopathic medicine through local and federal legislative advocacy, public awareness efforts and physician education. She is past-president of the New Hampshire Association of Naturopathic Doctors and serves on several committees and boards including the Editorial Board of NMJ, the American Herbal Products Association (AHPA) Board of Trustees and the AANP Board of Directors, where she was recently elected by the membership to take office as President in January of 2016.


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SARAH BEDELL COOK, ND, completed her Naturopathic Doctorate and residency at the Southwest College of Naturopathic Medicine. She has an undergraduate degree from Washington University in St. Louis, MO. She has worked in clinical practice and dietary supplement sales. She is currently a faculty member at the Nutrition Therapy Institute in Denver. She is also completing a Certificate in Biomedical Writing through the University of the Sciences in Philadelphia and works as a freelance medical writer. She is a member of the American Medical Writers Association and the American Association of Naturopathic Physicians.


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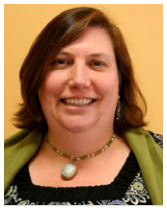

Lorinda Sorensen, ND, MSAC

LORINDA SORENSEN, ND, MSAC, is an assistant professor at National University of Health Sciences, Lombard, Illinois, where she teaches classes in naturopathic philosophy, endocrinology, women's' health, and botanical medicine. Sorensen attended Bastyr University, Kenmore, Washington, where she received both her doctorate of naturopathic medicine (ND) and a master's of science in acupuncture (MSA). She has practiced in Washington State, Nebraska, Iowa, Illinois, and New Zealand, where she was a consultant for the health products industry and in naturopathic education. In the past, she was a committee member of the Nebraska's Acupuncture Licensing Act Task Force for Rules and Regulations for legislative bill 270. She currently serves on the board and several committees of the Illinois Association of Naturopathic Physicians, is a member of the American Herbalists Guild and the American Botanical Council, and actively mentors students.


Setareh Tais, ND

SETAREH TAIS, ND, is a naturopathic doctor practicing general family medicine with a focus on women's health, pediatrics, and reproductive health in Fresno, California. She received her doctorate of naturopathic medicine from Bastyr University, Kenmore, Washington, and completed a naturopathic family medicine residency program with additional training in reproductive endocrinology and infertility. She is the president of the California Naturopathic Doctors Association, a founding board member of the Endocrinology Association of Naturopathic Physicians, a member of the American Association of Naturopathic Physicians, and a member of the Pediatric Association of Naturopathic Physicians. For more information about her practice, please visit www.fresnoholisticmedicine.com and for more information on naturopathic reproductive endocrinology, please visit www.endoanp.com.

NATURAL MEDICINE JOURNAL

PUBLISHED BY
CHAT Inc.
P.O. Box 17232
Boulder, CO 80308

Natural Medicine Journal (ISSN 2157-6769) is published 12 times per year by CHAT Inc.

MESSAGE FROM THE PUBLISHER

Endocrinology and Integrative Medicine: The Perfect Pairing

One of my favorite metaphors is the one that endocrinologist Deepak Chopra, MD, uses to describe the delicate nature of the endocrine system, comparing it to a spider's web: "Touch one strand and the whole web trembles." Yes, the web is delicate, but spider silk is deceptively strong—in 2013 researchers at Arizona State University discovered that this biological polymer material is at least 5 times as strong as piano wire. And yet we've all had the experience (or misfortune) of walking into a delicate web and having it tremble and collapse around us.

Similar to a spider's web, the endocrine system illustrates its strengths while at the same time magnifying its vulnerabilities. Endocrine glands and the hormones they secrete are complexly interrelated and interdependent. These glands work synergistically to control metabolism, growth, and development. Yet because of this interconnectivity, the entire system is susceptible to imbalance. The effects of dysfunction within the endocrine system can cause ripples throughout the entire body system.

It's challenging to quantify the magnitude of the physical, emotional, and financial toll that endocrine disorders cause. Here's one example: About 5 million women in the United States have polycystic ovarian syndrome, an endocrine disorder that remains one of the leading causes of female infertility, as well as other unpleasant and disruptive symptoms. Another 20 million Americans have some form of thyroid disorder. And in 2012, more than 29 million Americans had diabetes—with more than 8 million of those people going undiagnosed. An additional 86 million suffer with prediabetes.

Using an integrative approach to restoring endocrine balance and function has become paramount, as little progress is being made to halt or even slow the present trend. The endocrine system is complex and so too are the root causes of disorders associated with endocrine dysfunction. Looking well beyond symptom management and delving into underlying factors is where naturopathic physicians and integrative practitioners shine.

For all these reasons, we at *Natural Medicine Journal* chose to focus on the complicated and essential topic of endocrinology in this special digital issue.

So, with immense gratitude to our guest editor, Jaclyn Chasse, ND, and on behalf of the entire *Natural Medicine Journal* team, we hope you enjoy this special issue.

In good health,

Karolyn A. Gazella
Publisher

Connecting Endocrinology and Naturopathic Medicine

An interview with Alan Christianson, ND

By Jaclyn Chasse, ND

In this interview with the president of the Endocrine Association of Naturopathic Physicians, we discuss the organization's focus as a collaborative forum for practitioners meeting the challenges of treating endocrine disorders with naturopathic medicine. Alan Christianson, ND, also offers insight into the future of naturopathic endocrinology as more patients turn to natural medicine for solutions to a wide range of hormonal dysfunction, from infertility to thyroid disease to metabolic syndrome.

ABOUT THE EXPERT

Alan Christianson, ND, is a naturopathic physician in Phoenix, Arizona, who helps people overcome adrenal and thyroid disorders and achieve lasting fat loss and vibrant energy. He is the author of the bestselling *Complete Idiot's Guide to Thyroid Disease* (ALPHA, 2011) and *Healing Hashimoto's: A Savvy Patient's Guide* (CreateSpace Independent Publishing Platform, 2012). Christianson is the founding physician of Integrative Health Care in Scottsdale, Arizona, and the founding president of the Endocrine Association of Naturopathic Physicians. He trains doctors internationally on the treatment of obesity, thyroid disease, and hormone replacement therapy.

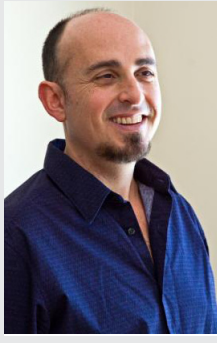
Treat the Patient, Not the Lab Test

An interview with Michael Friedman, ND

By Tina Kaczor, ND, FABNO

In this interview, Michael Friedman, ND, founder and executive director of the Association for the Advancement of Restorative Medicine (AARM) discusses the challenges of treating patients with thyroid and adrenal dysfunction and why he believes a collaborative response to these endocrinological issues—using naturopathic, herbal, and conventional medicine together—provides patients with the best care. Learn more about AARM at www.restorativemedicine.org.

ABOUT THE EXPERT



A licensed naturopathic physician and medical herbalist, Michael Friedman, ND, is the executive director of the nonprofit professional society Association for the Advancement of Restorative Medicine. He is the editor in chief of the affiliated *Journal of Restorative Medicine*. Among Friedman's publications are accounts of some of his more unusual and difficult cases that include remission of stage 4 metastatic ocular melanoma, treatment of lymphoma with poke root and Pacific yew, and the use of botanical and mineral supplementation to treat non–insulin dependent diabetes.

Vitamin D Status and In Vitro Fertilization Outcomes

Elucidating the Effects of Vitamin D on Fecundity

By Setareh Tais, ND

REFERENCE

Rudick BJ, Ingles SA, Chung K, Stanczyk FZ, Paulson RJ, Bendikson KA. Influence of vitamin D levels on in vitro fertilization outcomes in donor-recipient cycles. *Fertil Steril.* 2014;101 (2):447-452.

DESIGN

Retrospective cohort study

PARTICIPANTS

A diverse population of 99 recipients of egg donation at the University of Southern California Fertility Center, Los Angeles (53% Caucasian, 20% Asian, 16% Hispanic, and 7% African American). Each recipient was matched to a unique egg donor. Consideration and statistical adjustments were made for potential confounders such as donor and recipient age, recipient body mass index, race, number of embryos transferred, and embryo quality.

STUDY INTERVENTION

Serum vitamin D levels [25(OH)D] were assessed at baseline and categorized based on conventionally accepted reference ranges for vitamin deficiency (<20 ng/mL), insufficiency (20-30 ng/mL), and normal or replete (>30 ng/mL).

PRIMARY OUTCOME MEASURES

The primary measure was clinical pregnancy, which was defined by sonographic presence of cardiac activity at 7 to 8 weeks of gestation. A secondary outcome measure was the live-birth rate.

KEY FINDINGS

Of the 99 study participants, 35% were replete, 38% were insufficient, and 26% were deficient in vitamin D. Adjusted clinical pregnancy rates were 78% in vitamin D–replete recipients and 37% in vitamin D–deficient recipients (P=0.004). Live-birth rates were 31% among vitamin D–deficient recipients compared with 59% among vitamin D–replete recipients. There were no statistically significant differences in adjusted clinical pregnancy and live-birth rates among recipients who were deficient in vitamin D compared to those who were sufficient in vitamin D.

PRACTICE IMPLICATIONS

In this study, vitamin D deficiency was associated with a 50% reduction in pregnancy and live-birth rates in recipients of donor eggs compared to patients who had adequate vitamin D levels. Vitamin D is a precursor to a fat-soluble secosteroid hormone, 1,25(OH_2) vitamin D, with pleiotropic effects on a wide variety of intracellular regulatory reactions, including those of the reproductive system.[1] Vitamin D has been shown to have immune-modulating and antiinflammatory effects. Previous studies have shown that vitamin D deficiency is associated with insulin resistance, hyperandrogenism, polycystic ovarian syndrome, and pregnancy complications such as preeclampsia, infertility, and recurrent miscarriages.[2-4] Numerous studies on the association of serum and follicular vitamin D status on in vitro fertilization outcomes have been conducted and demonstrate that women with replete vitamin D levels have higher pregnancy rates than women who are deficient in vitamin D.[5,6]

Because previous studies have not shown a correlation between vitamin D status and embryo or oocyte quality, the authors used oocyte donor recipients to test their hypothesis that the effects of vitamin D are mediated through the endometrium via intracellular signaling between the embryo and the endometrium. The results of the study demonstrate that vitamin D status is more closely implicated in endometrial function related to implantation, and not oocyte quality. This is supported by evidence that the active form of vitamin D, calcitriol, binds to the vitamin D receptor in the endometrium to target genes (eg, Hox gene 10A) that are necessary for embryo implantation and placentation.[7,8] Furthermore, calcitriol has been shown to decrease inflammatory cytokines like colony stimulating factor 2, interleukin (IL)-1, IL-6, and tumor-necrosis factor that are implicated in early pregnancy loss.[9] More research is warranted to expand on what we know about vitamin D and endometrial function.

While this study adds to the growing data that vitamin D may play a role in fertility, further studies are warranted to demonstrate the effects of vitamin D therapy and repletion on pregnancy rates. Clinicians who are providing preconception counseling and treating infertile women should assess vitamin D levels and treat deficiencies with vitamin D supplementation, not just for overall health benefits and chronic disease risk reduction, but for improving fertility, pregnancy health, and live-birth rates.

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Polycystic Ovarian Spectrum

The new "PCOS"?

By Jaclyn Chasse, ND

REFERENCE

Sjaarda LA, Mumford SL, Kissell K, et al. Increased androgen, anti-Müllerian hormone, and sporadic anovulation in healthy, eumenorrheic women: a mild PCOS-like phenotype? *J Clin Endocrinol Metab.* 2014;99(6):2208-2216.

DESIGN

Prospective cohort study

PARTICIPANTS

Between 2005 and 2007, 259 eumenorrheic women without a self-reported history of infertility, polycystic ovarian syndrome (PCOS), or other endocrine disorders (including diabetes, Cushing's syndrome, or conditions affecting the thyroid, adrenals, or hypothalamus) were tracked over 1 to 2 menstrual cycles. Researchers required that participants discontinue all hormonal medications (including Depo-Provera, Norplant, and intrauterine devices) for 12 months before the study. Participants were also required to discontinue oral contraceptives or other hormone supplements 3 months before enrollment.

The participants provided health and lifestyle information, including assessment of hair growth and history of acne as well as physical assessment including weight, height, and body composition.

In all, 509 total cycles were monitored, with timing of menstrual cycle phase assisted by fertility monitors. The women provided blood samples up to 8 times per menstrual cycle, and all of them provided at least 5 samples per cycle. These samples corresponded to early menstruation; midfollicular phase; 3 samples periovulation; and samples in early, mid-, and late luteal phases. All samples were collected in the morning after fasting.

Serum levels of estradiol, progesterone, insulin, sex hormone–binding globulin, leuteinizing hormone (LH), follicle-stimulating hormone (FSH), albumin, glucose, blood lipids, antimüllerian hormone (AMH), and total testosterone (T) were measured. Sporadic anovulatory cycles were defined as having an observed progesterone peak less than or equal to 5 ng/mL and having no detectable serum LH peak on the later cycle measurements.

KEY FINDINGS

Overall, participants were healthy young women (ages 18-44 y). T concentration and age were inversely related. The lowest T quartile had a mean age of 32.7±8.0 years, compared with 23.6±6.1 years in the highest quartile (P<0.001). A history of acne treated by a physician or with the use of medication was significantly lower in the lowest T concentration quartile compared with the 3 higher quartiles, but incidence of hirsutism was not different across quartiles among these healthy women.

Total T concentrations throughout the cycle ranged from 3.0 ng/dL to 135.6 ng/dL overall, and from 6.8 ng/dL to 79.2 ng/dL at baseline during menses. T concentrations increased to their highest levels around ovulation.

Compared with ovulatory cycles (n=467), sporadic anovulatory cycles (n=42) had marginally higher total T and significantly higher free T (mean 23.7 ng/dL [95% confidence interval (CI): 21.4-26.3] vs 21.6 ng/dL [95% CI: 20.9-22.3], P=0.08, and 0.36 ng/dL [95% CI: 0.33-0.40] vs 0.32 ng/dL [95% CI: 0.31-0.33], P= 0.02, respectively) during menses and throughout the luteal phase (P<0.01 for all participants). Women with higher T had elevated AMH concentrations and increased reporting of history of acne requiring medical treatment, but not increased hirsutism. The percentage of anovulatory cycles was significantly higher across quartiles of increasing total T. Also, the LH-to-FSH ratio and AMH were higher across quartiles of increasing total T, independent of age. Notably, AMH in the highest T quartile was approximately double that observed in the lowest quartile.

PRACTICE IMPLICATIONS

Diagnostic criteria for PCOS as defined by the American College of Gynecologists and Obstetricians in 2003[1] include chronic anovulation and hyperandrogenism as defined by hormone measurements or clinical findings like acne and hirsutism. About 4% to 6% of women fit these diagnostic criteria, and these women are at a higher risk of pregnancy loss in the first trimester, pregnancy complications, insulin resistance, and obesity.

This study is significant for the naturopathic clinical approach to menstrual imbalance and PCOS as the results demonstrate that the pattern of hormone imbalance seen in PCOS can be observed in women who would not meet the criteria for diagnosis. This finding suggests that the functional changes that exist in PCOS exist not as a discrete, black-and-white imbalance but rather on a scale consisting of shades of gray, creating a need for a designation of "pre-PCOS" or "subclinical PCOS."

As expected, higher T levels were observed in younger study subjects. Additionally, it is nothing new to note that higher T levels correlate with a

higher incidence of acne in women. While hirsutism has also been associated with higher serum T, that was not seen in this study, suggesting that the level of T needed to impact hair growth exceeds the level observed to affect menstrual patterns in women, and eumenorrheic women may not have an imbalance severe enough to observe this clinical symptom of PCOS.

AMH is a hormone produced by primordial follicles as they develop within the ovary. It has previously been reported that higher AMH levels can be observed in women with PCOS, as there are more follicles in development (thus, the term *polycystic*) during the follicular phase.[2] Interestingly, the higher AMH level was observed in this study in healthy women without menstrual irregularity but with elevated T compared to other healthy cohorts. Sporadic anovulatory cycles and an increased LH-to-FSH ratio were also observed with greater frequency in the healthy subjects with higher T levels. Both of these findings suggest that the hyperandrogenicity seen in women with PCOS can exist, perhaps to a lesser extent, in healthy women with only occasional menstrual irregularity.

This finding has significant practice implications, as it may alter a practitioner's approach to treatment of women with occasional hormone imbalance who do not meet the traditional diagnostic criteria for PCOS. It appears from this study that *polycystic ovarian syndrome* is in fact a *polycystic ovarian spectrum*, wherein a pattern of hormonal balance exists across a scale of severity, with the most distal endpoint being anovulation, hirsutism, acne, insulin resistance, and other hallmark criteria of diagnosable PCOS. This could expand treatment options for eumenorrheic women whether for their acne, infertility, or menstrual imbalances to include nutrients traditionally recommended for women with PCOS, including N-acetyl cysteine and inositol.

Interestingly, the samples evaluated in 2012 for T and AMH for the sake of this study were previously analyzed in 2007 for other hormones, and several papers were published based on those findings. This previous analysis was referred to as the BioCycle study. Findings included a lack of difference in cholesterol levels among women with sporadic anovulatory cycles[3] and lower estradiol, progesterone, and LH peak levels in women with sporadic anovulation compared to healthy cohorts.[4] Additionally, metabolic markers have been studied. Leptin levels have been found to be moderately inversely associated with sporadic anovulation.[5] Studies continue to be published from the wealth of data collected in this study.

All in all, these findings suggest a possible underlying cause of occasional anovulation, such as a longer-term, even subclinical follicular, ovarian, hypothalamic, or pituitary dysfunction, even in otherwise healthy, menstruating women.

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Antidiabetic Effects of Ginseng Extract

Is Ginseng a Panacea for Impaired Glucose?

By Lorinda Sorensen, ND, MSAc

REFERENCE

Park SH, Oh MR, Choi EK, et al. An 8-week, randomized, double-blind, placebo-controlled clinical trial for the antidiabetic effects of hydrolyzed ginseng extract. *J Ginseng Res.* Epub 26 May 2014.

STUDY DESIGN

Randomized, double-blind, placebo-controlled clinical trial for patients with impaired fasting glucose

PARTICIPANTS

Adults with impaired fasting glucose measurements between 5.6 and 6.9 mmol/L (101-124 mg/dL) and without a diagnosis of another disease were selected to be included in the trial. One hundred patients were screened for inclusion, and 77 were excluded. Exclusion criteria included other abnormal laboratory tests; cardiovascular, gastrointestinal, or renal disease; a history of antipsychotic medication use; corticosteroid or lipid-lowering medication use; alcohol or substance abuse; acute or chronic inflammation; allergy or hypersensitivity to any of the ingredients in the test products; pregnancy or breastfeeding. Twenty-three remaining participants were randomized to either a hydrolyzed ginseng extract or placebo. Three participants dropped out for personal reasons, leaving 20 people to finish the trial.

INTERVENTION

Hydrolyzed ginseng extract (HGE; Ilhwa Co Ltd, Guri, South Korea) was used. The ginseng was hydrolyzed by pectinase and contained 7.54 mg/g of the ginsenoside Rg1; 1.87 mg/g of Re; 5.42 mg/g of Rb1; 0.29 mg/g of Rc; 0.36 mg/g of Rb2; and 0.70 mg/g of Rd. The compound K (another ginsenoside metabolite) content in the HGE was 6.3 mg/g. Both the placebo and the ginseng supplement contained pumpkin seed oil, refined palm oil, and a yellow wax. It was administered as a capsule (480 mg/cap 2x/d).

OUTCOME MEASURES

Assessment parameters included fasting plasma glucose (FPG), postprandial glucose (PPG; also known as the oral glucose tolerance test [OGTT]), fasting plasma insulin (FPI), and postprandial insulin (PPI). Using the homeostasis model, insulin resistance (homeostatic model assessment [HOMA]-IR) and beta-cell sensitivity (HOMA-β) were also tracked. Measurements for circulating endproducts of glycosylation included glycated albumin, fructosamine, and hemoglobin A1c (HbA1c). Lastly, kinetics of glucose and insulin changes were assessed using incremental area under the curve (iAUC) and maximum concentration (C_{max}) of each.

Assessed in this trial were FPG, plasma glucose during PPG/OGTT, glucose iAUC, and glucose C_{max}, insulin [fasting plasma insulin (FPI), plasma insulin during OGTT (PPI), insulin iAUC, and insulin C_{max}], HOMA-IR, HOMA-β, glycated albumin, fructosamine, HbA1c, and safety evaluation tests including such as complete blood count, comprehensive metabolic pane, and electrocardiogram.

KEY FINDINGS

After the 8-week intervention of 480 mg twice daily, statistically significant differences were found in FPG (P=0.017) and PPG60min (P=0.01). PPG30min (P=0.059), FPI (P=0.063), and PPI60min (P=0.077) showed a tendency to improve slightly more than placebo group, although the results did not reach statistical significance.

PRACTICE IMPLICATIONS

The health impact associated with poor glucose control has grown, especially the incidence of non–insulin dependent diabetes and cardiovascular disease. The World Health Organization has estimated that 347 million people worldwide have diabetes, and by 2030 diabetes will be the 7th leading cause of death.[1] While it is essential to address the many determining factors that are implicated in this insidious illness, researchers are also continuing to seek out different types of medications, including more botanical extracts.

Panax ginseng is possibly one of the most familiar and researched botanical medicines in the world. It has long been used for *qi* tonification and respiratory and digestive support in China, and it has increased in popularity in North America as an adaptogen. Recent preclinical investigations have supported the use of ginseng in abnormal metabolic parameters such as glucose intolerance, metabolic syndrome, and non–insulin dependent diabetes mellitus (NIDDM). However, human intervention trials are still in the early stages and have mixed results. While this recent study has shown some modest improvement in FPG and PPG, the researchers did not provide detail on randomization or blinding, which means this study cannot be included in a systematic analysis. Neither did they give specific outcomes at 8 weeks regarding fasting lab results. Instead, the study relies on a graphic representation of standard deviation of the iAUC, and while that is becoming standard, it is the opinion of these authors that more detail should be included to truly assess the validity of this study.

A 2011 systematic review of red ginseng and NIDDM analyzed 4 randomized clinical trials and revealed that bias was most likely present in at least 3 of the studies.[2] One type of bias is location bias; many of the smaller studies, such as this one, are from Korea, where the majority of red ginseng is grown and most likely subsidized by the government. Another problem discussed in the 2011 review, also present in our example, is the small number of participants.

A particular factor that may be important when evaluating the literature and considering whether to use ginseng in patients is the type of ginseng product. Korean red ginseng has specific parameters for processing: It must be harvested when the root is 6 years old and steamed or heated properly to increase the saponin content. According to Chen and Chen in their book *Chinese Medical Herbology and Pharmacology*, red ginseng is warmer when unprocessed and is best used for *qi* and *yang* deficiencies. Wild-crafted red ginseng is the most expensive resource, reserved for severe cases of *qi* deficiency.[3]

In this particular study, the ginseng was hydrolyzed using pectinase. Hydrolyzation alters the composition of the ginsenosides to produce more active metabolites. Ginsenosides have been the subject of a significant amount of preclinical research. *In vivo* studies with ginsenosides RB2, Rg1, Rh2, and Re showed activation of adenosine monophosphate kinase (AMPK), which has been shown to improve insulin sensitivity, reduce hepatic glucose production, and have an antiobesity effect.[4,5]

Another way to process ginseng is fermentation using β glucosidase–producing microorganisms[6] or the gypenoside pathway in the human gut.[7] The types and amounts of ginsenosides vary by processing technique. For example, the ginsenoside protopanaxadiols Rb1, Rb2, and Rc, are converted via deglycosylation reactions by intestinal bacteria into compound K,[7,8] which has been shown to suppress NF-κB activation[9] and induce autophagy and apoptosis.[10] (Rb1 is also found in *Panax quinquefolius*, American ginseng, in significant amounts.[11])

Other secondary factors may support a clinician's use of *Panax ginseng*. One example is in patients who need support to correct a hypothalamic–pituitary-adrenal axis that has been imbalanced by stress. Another may be to lessen inflammation. Yet another reason is to improve energy so the patient can start or increase an exercise plan. *Panax ginseng* may be used to tonify a system, and yet it can be used safely for very specific purposes, like the stimulation of the AMPK and NF-KB pathways.

The evidence in this study adds to a large body of research on Panax ginseng. While research continues on the nuances of which ginsenosides are best and at which dosages, clinicians can feel comfortable recommending ginseng as an adaptogen and to improve physical stamina, a use in keeping with its traditional role for millennia.

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Thyroxine and Triiodothyronine in Commercially Available Thyroid Supplements?

Hidden hormones could have unintended health consequences

By Tina Beaudoin, ND

OVERVIEW

A study recently published in the journal *Thyroid* found potentially dangerous adulteration in many popular thyroid supplements that should be of concern to all integrative practitioners.[1]

The study looked at 10 commercially available thyroid health supplements sold via local retail stores or the Internet. Using the keywords "thyroid health," "thyroid supplements," and "thyroid support," they found 5 herb-based and 5 desiccated thyroid tissue–based supplements to study. The 5 herb-based products also contained varying amounts of tyrosine and iodine and did not list or indicate that any animal tissue was used in the manufacturing of the products. The 5 products containing thyroid tissue were from bovine sources and described as including "raw thyroid" tissue, concentrate, or powder.

The authors tested 3 samples from each product for thyroid hormones T3 and T4 using high-performance liquid chromatography. Each product was given a unique product identification number to blind laboratory investigators during product testing. Levothyroxine and liothyronine obtained from a local pharmacy served as controls and standards.

The results? Nine out of 10 products tested positive for containing T3, with 4 out of 9 of those products exceeding a total daily dose of 10 µg per day. Five products contained detectable amounts of both T3 and T4. At the daily recommended dose of 4 capsules, one product contained thyroid hormone levels that reached doses restricted to availability by prescription only for both T3 (at >5 µg/d) and T4 (at 25 µg/d). All of the herb-based supplements tested positive for T3, and 2 of these 5 products also tested positive for T4 at levels of 17 µg and 91 µg per day based on daily dose recommendations. The herb-based products contained iodine ranging from 100 mg to 225 mg and L-tyrosine ranging from 150 mg to 1000 mg. The authors noted that guggul *(Commiphora mukul)*, kelp, ashwagandha *(Withania somnifera)*, bladderwrack *(Fucus vesiculosis), Coleus forskohlii*, and *Schisandra chinensis* were the herbs commonly found in the botanical formulas.

PRACTICE IMPLICATIONS

In the integrative community, it is commonplace to utilize dietary and botanical supplements to help support optimal health and vitality. Thyroid dysfunction is common, with nearly 5% of the US population above the age of 12 years having hypothyroidism.[2] The occurrence of hypothyroidism is even greater among older people, affecting 5%-20% of women and 3%-8% of men.[3] The implications of this study are significant, as many patients seek integrative care for thyroid health, and according to this study's results, a practitioner could unknowingly be medicating a patient with active thyroid hormone when recommending a thyroid support supplement.

This study suggests intentional adulteration of thyroid support supplements with T3 and T4 hormones in 9 out of 10 products sampled. It was alarming to note that the greatest levels of T3 were found not in thyroid glandular extracts but rather in the botanical supplements sampled. Every one of the botanical products sampled tested positive for T3, with the total daily dose ranging from 2.73 µg to 32.13 µg. Four of the products fall within range of or exceed prescription dosing treatment recommendations. The occurrence of only T3 in 4 of the products leads to speculation of selective adulteration of the hormone in these products.

The authors also cited cases of adulteration in dietary supplements for weight loss; while not surprising, it is no less concerning. There are also well-documented instances of adulteration among popular botanicals, including *ginkgo biloba*, saw palmetto, and black cohosh, as well as other product categories such as sexual health and bodybuilding supplements.[4-6]

This study presents several issues of clinical importance. First is the potential danger of thyrotoxicosis secondary to adulterated thyroid support supplements. Second, this study demonstrates the need for clinicians to ask their patients for a complete list of dietary supplements and recognize the potential dangers that some of these products can pose. Third, clinicians need to discern whether or not the supplements recommended in clinical practice are exactly what they purport to be. Becoming familiar with and confident of the quality practices of preferred supplement manufacturers is of utmost importance.

STUDY LIMITATIONS

The study design would have been stronger if it had included a third category of products that contained only tyrosine and iodine. As thyroid hormones are built upon iodine and tyrosine, the authors should ensure that the methods used to evaluate hormone content adequately differentiate between iodine, tyrosine, and true T3/T4 content. This was not discussed in the study but could indicate a potential study flaw.

ENSURING QUALITY AND PURITY

In 1994, the Dietary Supplement Health and Education Act (DSHEA) passed historical legislation that granted the US Food and Drug Administration the authority to prohibit unsafe and mislabeled dietary supplements. As of June 2010, all manufacturers are required to be compliant with DSHEA guidelines set for safety, consistency, quality, purity, and potency. However, there is clearly a need for manufacturers to exceed requirements set forth by DSHEA as the 800 plus–page document of guidelines does not guarantee all aspects of quality. Utilizing third-party certifications to verify current Good Manufacturing Practices compliance is one opportunity that manufacturers can employ to raise the bar on quality practices.

There is also latitude in the DSHEA guidelines on frequency of batch testing of raw materials and finished products for purity and potency. Asking manufacturers how often they are testing their materials is another way to help discern quality practices. Does the manufacturer rely on the validity of the certificate of analysis provided by a supplier when purchasing raw materials, or does it utilize in-house or third-party testing laboratories to verify and guarantee quality?

These are just a few of the questions one might consider when trying to determine their level of investment and commitment to quality practices. If you use thyroid support dietary supplements in your practice, ask the manufacturer if the product or its component ingredients have been tested for T3 and T4 adulteration. While there are many very high-quality dietary supplement manufacturers, this article serves as a reminder and opportunity to hold steadfast to quality practices in the dietary supplement industry as we strive to offer our patients the very best care.

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Bioidentical Hormone Replacement Therapy in Postmenopausal Osteoporosis

By Sarah Bedell Cook, ND

ABSTRACT

Osteoporosis is estimated to affect more than 10 million Americans, with postmenopausal women at particular risk. Osteoporotic fractures can lead to postural changes, emotional distress, and chronic pain. Currently all medications approved by the US Food and Drug Administration for the treatment of osteoporosis carry slight to modest risks depending on the individual, the duration, the dosage, and the drug being used. Estrogen replacement therapy is not currently indicated for the treatment of osteoporosis, but it is approved for osteoporosis prevention. Interest in bioidentical hormone replacement as an alternative to conventional hormone replacement has increased in the last 12 years, although not always for logical or scientific reasons. The purpose of this review is to bring clinicians up to date on current information on the efficacy and safety of bioidentical hormones for the prevention of postmenopausal osteoporosis.

INTRODUCTION

Osteoporosis—characterized by low bone mineral density (BMD), compromised bone strength, and increased fracture risk—is the most common bone disease in humans.[1] The National Osteoporosis Foundation estimates that more than 10 million Americans have osteoporosis and an additional 33.6 million have osteopenia.[1] Together, osteoporosis and osteopenia affect the majority of postmenopausal women in the United States,[2] and 1 in 2 white women can expect to experience an osteoporotic fracture at some time in her life.[3] Osteoporosis and its related fractures increase with age, and annual hip fractures are expected to rise to 289,000 by the year 2030 in the United States.[4] Osteoporotic fractures can have a profound effect on quality of life, leading to postural changes, anxiety, depression, and chronic pain.[1] In addition, hip fractures are associated with increased risk of death within 1 year.[5] The economic impact of osteoporotic fractures was estimated at $17 billion in 2005 and is expected to double or triple by 2040.[1,6]

TABLE 1
Treatment Guidelines for Osteoporosis

First-line agents	Alendronate (Fosamax) Zoledronic acid (Reclast) Risedronate (Actonel) Denosumab (Prolia)
Second- and third-line agents	Ibandronate (Boniva) Raloxifene (Evista)
Teriparatide (Forteo) in most severe cases or failure of past therapies	
Calcitonin as last line of therapy or not at all	
No combination therapy	

Source: The American Association of Clinical Endocrinologists.[7]

TABLE 2
Recommended Lifestyle Changes for Osteoporosis Prevention

1. Eating a diet rich in fruits and vegetables
2. Ensuring adequate intake of calcium and vitamin D
3. Engaging in regular weight-bearing exercise
4. Stopping smoking
5. Avoiding excessive alcohol consumption
6. Avoiding high intake of vitamin A

Source: The National Osteoporosis Foundation.[1]

The most recent guidelines from the American Association of Clinical Endocrinologists for the treatment of osteoporosis were published in 2010 (Table 1)[7]. Bisphosphonate medications are first-line agents for osteoporosis, but prescriptions of bisphosphonates decreased by more than 50% between 2008 and 2012 as awareness of rare but serious adverse effects emerged.[8] These rare adverse effects include osteonecrosis of the jaw, atrial fibrillation, esophageal cancer, and atypical femur fractures.[9] More common side effects that lead women

(continued on page 18)

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to discontinue bisphosphonate medications include heartburn, headache, constipation, diarrhea, and joint pain. Raloxifene, a selective estrogen receptor modulator, is a second-line agent. Raloxifene is less effective than bisphosphonates, may increase hot flashes or night sweats, and is associated with a small increase in thromboembolism and stroke.[10]

Because there is no ideal treatment for osteoporosis, prevention is extremely important. Lifestyle changes are foundational to the prevention of osteoporosis (Table 2), but some women, despite a healthy diet and lifestyle, continue to experience a decline in BMD after menopause. Several medications approved for the treatment of osteoporosis are also indicated for prevention (eg, alendronate, risedronate, zoledronic acid, ibandronate, raloxifene). In addition, estrogen therapy is approved for the prevention of osteoporosis. Estrogen therapy's protective effect against bone loss was one of the findings of the Women's Health Initiative (WHI) first reported in 2002.[11] The WHI, a randomized placebo-controlled trial of more than 27,000 postmenopausal women across the United States, established that treatment with conjugated equine estrogens (CEE) with or without medroxyprogesterone (MPA) decreased hip fracture risk by 33%. This benefit, however, was accompanied by a slight but statistically significant increased risk of thromboembolic disease and an even more slight but still statistically significant risk of invasive breast cancer.[12]

Since publication of data from the WHI, patients and providers have sought alternatives to conventional hormone replacement therapy (HRT). Among these alternatives is bioidentical hormone replacement therapy (BHRT). Although the US Food and Drug Administration (FDA) does not recognize a definition for "bioidentical hormone," professional organizations have established that the term refers to a compound that structurally mimics an endogenous hormone.[13] Bioidentical hormones include estrone, 17β-estradiol, estriol, progesterone, testosterone, and dehydroepiandrosterone (DHEA). Although compounded bioidentical formulations are not FDA-approved, it is important to note that there are many FDA-approved bioidentical hormone products on the market (Table 3). Comprehensive reviews of BHRT have been published elsewhere.[14-17] The purpose of this review is to summarize recent data on the efficacy and safety of different formulations, delivery systems, and dosages of bioidentical hormones for the prevention of postmenopausal osteoporosis.

EFFECTS OF BIOIDENTICAL HORMONES ON BONE

ESTRADIOL

Estradiol (17β-estradiol) is the most physiologically active form of estrogen and is endogenously produced at the highest level before menopause. Estradiol is available in a variety of FDA-approved formulations and in compounded formulas, including estradiol alone or in combination with other hormones. A PubMed search of human female clinical trials within the last 10 years with search terms of "estradiol" or "17β-estradiol" and "osteoporosis" or "bone" combined with a literature search of references from review articles produced 13 relevant studies on the effect of 17β-estradiol on BMD (Table 4).

TABLE 3. US Food and Drug Administration Approved Bioidentical Hormone Products

Composition and Application	Product Name
Oral 17β-estradiol	Estrace Various generics
17β-estradiol patch	Alora Climara Estraderm Menostar Minivelle Vivelle Vivelle-dot Various generics
17β-estradiol gel	Divigel EstroGel Elestrin
17β-estradiol topical emulsion	Estrasorb
17β-estradiol transdermal spray	Evamist
17β-estradiol vaginal cream	Estrace vaginal cream
17β-estradiol vaginal ring	Estring
Estradiol acetate vaginal ring	Femring
Estradiol vaginal tablet	Vagifem
Oral 17β-estradiol + synthetic progestin	Activella Angeliq Prefest
Transdermal 17β-estradiol + synthetic progestin	CombiPatch Climara Pro
Oral micronized progesterone	Prometrium

Source: The North American Menopause Society.[73]

TABLE 4. Trials of 17β-estradiol and Bone Mineral Density

			Type, Dose, and Regimen			
Source	Design	No. of Patients	Estrogen	Progestogen	Length of Trial	Results
Al-Azzawi et al,[37] 2005	RCT	174	TV estradiol: 7.5 µg/d, 50 µg/d, 1000 µg/d	None	96 wk	Lumbar BMD increase of 0.3%, 2.7%,[a] and 3.3%[a]
Ettinger et al,[28] 2004	Placebo-controlled RCT	417	TD patch estradiol: 14 µg/d	None	2 y	Lumbar BMD increase of 2.6%[a]; hip BMD increase of 0.4%[a]
Farr et al,[24] 2013	Placebo-controlled RCT	76	Oral CEE: 0.45 mg/d	None	4 y	Change in BMD did not differ between CEE-treated group and TD estradiol group
			TD estradiol: (50 µg/d)	MP		
Gambacciani et al,[21] 2008	Open trial	Data not available	Oral estradiol: 1 mg/d, 0.5 mg/d	Norethisterone acetate: 0.5 mg/d, 0.25 mg/d	2 y	BMD increase ranged from +1.8%[a] in the femoral neck of the ultra low–dose group to +5.2%[a] in spine of low-dose group
Greenwald et al,[22] 2005	Placebo-controlled RCT	189	Oral estradiol: 0.25 mg/d, 0.5 mg/d, 1 mg/d, 2 mg/d	Norethindrone acetate: 0 mg/d, 0.25 mg/d, 1 mg/d	2 y	All doses of oral estradiol prevented bone loss[b]
Mizunuma et al,[20] 2010	Placebo-controlled RCT	309	Oral estradiol: 0.5 mg/d, 1 mg/d	None or levonorgestrel	2 y	BMD of 10%[b] in 1 mg/d group; BMD increase of 8%[b] in 0.5 mg/d group
Prestwood et al,[19] 2003	Placebo-controlled RCT	167	Oral estradiol: 0.25 mg/d	None or MP	3 y	BMD increased by 2.6%[b] in the femoral neck, 3.6%[b] in the hip, 2.8%[b] in the spine, and 1.2%[b] total body
Salminen et al,[36] 2007	RCT	115	TV estradiol: 7.5 µg/d	None	2 y	Small but nonsignificant increase in hip and lumbar BMD in treatment group
Schaefers et al,[29] 2009	RCT	500	TD patch estradiol: 14 µg/d; raloxifene: 60 mg/d	None	2 y	TD estradiol increased BMD by 2.4% (95% CI:1.9-2.9), comparable to raloxifene
Stanosz et al,[25] 2009	Placebo-controlled RCT	75	Oral estradiol and estriol: varying doses; TD patch estradiol: varying doses	Levonorgestrel	1 y	Greatest increase in BMD in TD group (+3.8%)[b]
Tuppurainen et al,[18] 2010	Placebo-controlled RCT	167	Oral estradiol: 2 mg/d	Norethisterone: 1 mg/d	5 y	Treatment increased BMD by 4.2%[b] in lumbar spine and 1.3%[b] in femoral neck
Warming et al,[26] 2005	Placebo-controlled RCT	212	TD patch estradiol: 45 µg/d	Levonorgestrel	2 y	TD estradiol increased BMD by 8%[b] in the spine, 6%[b] in the hip, and 3%[b] total body
Yang et al,[33] 2007	RCT	120	TD gel estradiol: 0.75 mg, 1.5 mg, 3 mg/d; oral estriol: 2 mg/d	None	1 y	Significant increaseb in BMD in all groups except the lowest dose (0.75 mg). All doses of TD estradiol prevented loss of BMD

Abbreviations: BMD, bone mineral density; CI, confidence interval; MP, micronized progesterone; RCT, randomized clinical trial; TD, transdermal; TV, transvaginal.

[a]Results reached statistical significance ($P<.05$) in comparison to baseline

[b]Results reached statistical significance ($P<.05$) in comparison to controls

In this section, we summarize the data on different delivery systems of estradiol, clarify which are FDA-approved for osteoporosis prevention, address the efficacy of compounded formulations, and discuss duration of effect.

Although the studies on oral 17β-estradiol do not rival the WHI in size or duration, substantial data exist on its ability to maintain and increase BMD. Prevention of osteoporosis is an FDA-approved indication for its use, and the FDA asserts that the effects of oral estradiol are equivalent to the effects of CEE when given in equivalent doses. Oral estradiol from a conventional pharmacy comes in 3 standard dosages: 2 mg, 1 mg, and 0.5 mg. All of these have demonstrated efficacy at increasing BMD with 3 to 5 years of follow-up in placebo-controlled trials.[18,19] Even studies that show a dose-dependent effect of estradiol on BMD demonstrate that the lowest oral dose (0.25 mg/d) is effective at preventing BMD loss in postmenopausal women.[20-22]

It has been suggested that transdermal application of 17β-estradiol might offer effective bone-sparing benefit with less risk than oral estrogens, especially when it comes to deep vein thromboses, ischemic strokes, triglyceride levels, and inflammatory markers.[23] Like oral estradiol, transdermal estradiol patches are FDA-approved for osteoporosis prevention. The Kronos Early Estrogen Prevention Study (KEEPS), a randomized placebo-controlled study published in 2013, demonstrated comparable changes in BMD between women treated with oral CEE (Premarin, 0.45 mg/d) and those treated with transdermal 17β-estradiol patch (Climara, 50 µg/d) plus pulsed micronized progesterone with 4 years of follow-up.[24] These results were consistent with earlier studies demonstrating bone-building efficacy of standard-dose (45 µg/d or more) transdermal 17β-estradiol patches.[25-27] Evidence suggests that even an ultra low–dose (14 µg/d) transdermal 17β-estradiol patch can increase BMD[28] and that this dosage has similar efficacy as raloxifene.[29]

Other forms of transdermal estradiol (eg, gel, emulsion, or spray) do not carry an FDA-approved indication for osteoporosis prevention, so their prescription for this purpose is considered an off-label use. Studies do suggest, however, that these delivery systems are effective ways to achieve therapeutic levels of estrogen that can positively affect BMD. Studies have shown that 17β-estradiol transdermal gel (Divigel, 1.0 mg/d) is comparable to oral estradiol for the maintenance of BMD and reduction of bone turnover and is equally effective as

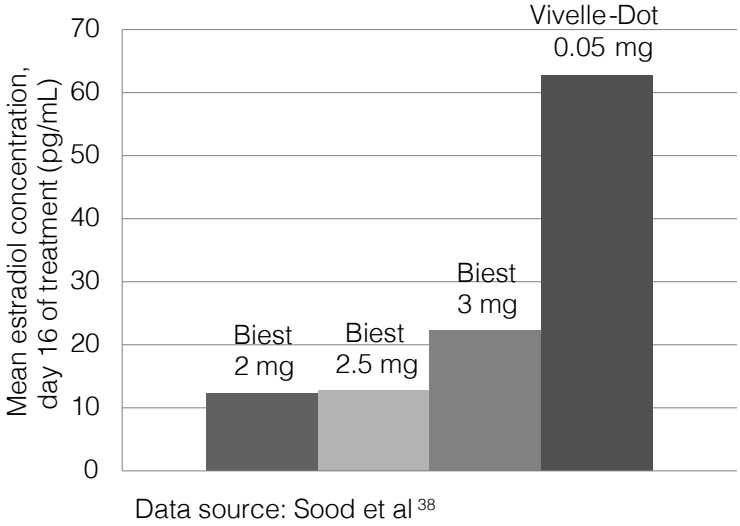
> “Because there is no ideal treatment for osteoporosis, prevention is extremely important.”

the estradiol patch (Estraderm TTS, 50 µg/d) at preserving BMD.[30,31] It has also been shown that estradiol transdermal gel (1.0 mg/d) is effective at increasing BMD equally well in smokers and nonsmokers.[32] A study to compare the efficacy of different doses of estradiol transdermal gel (delivering 0.75 g, 1.5 mg, or 3.0 mg 17β-estradiol/d) demonstrated significant increase in bone mass in the groups receiving 1.5 mg/d and 3.0 mg/d and that even the lowest dose prevented bone loss in postmenopausal women after 12 months of treatment.[33] Newer delivery systems for transdermal estradiol include estradiol topical emulsion (Estrasorb) and estradiol transdermal spray (Evamist). Although no specific studies on osteoporosis were identified for these products, pharmacokinetic studies demonstrate that they also deliver therapeutic levels of estradiol.[34,35]

A variation on transdermal application of estradiol is transvaginal application. Like the gels, emulsion, and spray, transvaginal estradiol is also not indicated for the prevention of osteoporosis, so its prescription for this purpose would be considered an off-label use. There is minimal data to suggest that this delivery method might have a systemic effect on BMD. Two small studies demonstrated that transvaginal had a dose-dependent effect on BMD, with even the lowest dose (7.5 µg/d) preventing bone loss.[36,37]

Despite the body of evidence demonstrating a bone-sparing effect of most commercial preparations of estradiol, questions remain about the reliability of compounded formulas to deliver an effective dose. There were no pharmacokinetic studies on compounded BHRT until a 2013 study published by Sood et al.[38] This study compared serum hormone levels in women prescribed compounded estrogen cream (Biest 2.0 mg, 2.5 g, or 3.0 mg) plus compounded oral progesterone (100 mg) to those in women prescribed a conventional estradiol patch (Vivelle-Dot, 0.05 mg) plus oral micronized progesterone (Prometrium, 100 mg). The dosages were chosen because of their assumed bioequiva-

Figure. Steady-state estradiol concentration with Biest cream vs Vivelle-Dot



Data source: Sood et al [38]

lence in practice: Most pharmacists consider Biest 2.5 g to be approximately equivalent to a standard 0.05-mg transdermal patch. Results showed, however, that Biest 2.5 mg yielded significantly lower steady-state levels of estradiol than the FDA-approved patch (area under the curve for estradiol=286 vs 917 $P<0.001$). Even the higher dose of Biest (3.0 mg) yielded lower steady-state levels than Vivelle-Dot (Figure). The authors of this study raised the question of whether transdermal compounded creams, at commonly prescribed doses, are sufficient to provide bone-protective effects.

Another consideration in regard to the efficacy of 17β-estradiol for the prevention of osteoporosis is its duration of effect. It is generally accepted that the bone-sparing effect of any estrogen therapy persists while taking the medication and then quickly dissipates within 3 to 4 years after discontinuing use. Data from the cumulative follow-up period of the WHI showed that the risk reduction in hip fractures observed during intervention did persist over the cumulative 13 years of follow-up in the CEE plus MPA group only (hazard ratio [HR]: 0.81 [95% confidence interval [CI]: 0.68-0.97),[12] but the risk reduction attenuated in the CEE-only group, resulting in a cumulative incidence of hip fracture that was the same as placebo at 10.7 years of follow-up.[39] This finding was consistent with other studies that have shown the incidence rate of fracture returns to that of women who have never taken HRT within 1 to 5 years of discontinuing use.[40,41] Further studies are needed to determine whether the bone-sparing effect of 17β-estradiol persists or declines after discontinuing treatment.

ESTRIOL

Estriol is the weakest of the estrogens, with approximately one-tenth the potency of estradiol. Estriol is not FDA-approved and therefore is only available as compounded BHRT. It is the primary estrogen in both Biest and Triest, popular compounded formulas, because of the perceived safety of estriol. Unfortunately, studies assessing the bone-sparing effect of estriol have included small sample sizes and yielded contradictory results. Several small Japanese studies, with sample sizes ranging from 24 to 151, have demonstrated that oral estriol (2 mg/d) increases BMD from 1.79% to 3.3% within 1 to 2 years of treatment.[42-45] Two of these studies demonstrated comparable efficacy between CEE (0.625 mg/d) and oral estriol.[42,43] Other studies, however, demonstrated no increase in BMD in postmenopausal women receiving oral estriol for 2 years.[46-48] The contradictory results of these small studies provide insufficient data to draw any conclusions about the efficacy of estriol for the maintenance of BMD or reduction in fracture risk in postmenopausal women.

ESTRONE

Estrone increases endogenously after menopause when the adrenal glands play more of a role in hormone synthesis. Estrone and estradiol can interconvert reversibly, which suggests that these 2 hormones might have similar effects. Estrone is available in FDA-approved formulations, such as piperizine estrone sulfate (PES), or compounded formulations. The studies of estrone's effect on BMD are minimal, with small-scale studies suggesting that PES can increase BMD in postmenopausal women with 2 years of follow-up.[49,50] Because the available data on the bone-sparing effects of estrone are limited, however, it is impossible to conclude whether a prescription of estrone offers any benefit beyond that of estradiol.

PROGESTERONE

Bioidentical United States Pharmacopeia–approved progesterone is available in over-the-counter creams, compounded hormone formulations, and 3 FDA-approved formulations. Progesterone is most commonly prescribed in combination with estrogen therapy—for women with intact uteri—to

prevent the uterine hyperplasia that can result from unopposed estrogen. Only 100 mg daily or 200 mg for 12 days per month has been researched and shown to prevent estrogen-induced endometrial hyperplasia.[51]

It has been suggested that progesterone might play a direct role in bone health.[52] Evidence to support this claim includes the following observations: progesterone appears to have a stimulating effect on osteoblasts in vitro, bone loss can occur during perimenopause when estrogen levels remain high and progesterone declines, and higher endogenous progesterone levels associated with ovulation correlate with improvement in markers of bone turnover.[52] Clinical trials to support any beneficial effect of progesterone on BMD or fracture risk, however, are lacking. The minimal studies conducted to evaluate the effect of progesterone on BMD have yielded negative results.[51,53,54] Evidence does not, therefore, support the use of progesterone alone to maintain BMD.

TESTOSTERONE

Testosterone is produced in small quantities by the ovaries and adrenal glands in women. Testosterone is not FDA-approved for the prevention of osteoporosis. There is some evidence, however, to suggest that testosterone plays a direct role in bone health: in vitro studies demonstrate that testosterone stimulates osteoblast differentiation and inhibits osteoblast apoptosis; in addition, orchiectomy in men produces rapid bone loss.[55] In women, because testosterone can metabolize to estradiol, it is unclear which of these hormones has the most influence on bone density. Clinical trials on the effect of testosterone on BMD in women are limited. A recent study comparing the effect of implanted 17β-estradiol (50 mg) plus testosterone (40 mg) to no treatment showed an increase in BMD at 1 year in the treatment group that was not statistically significant.[56] In a prospective trial of 34 postmenopausal women randomized to receive either estradiol implants (50 mg) or estradiol (50 mg) plus testosterone (50 mg) implants for 3 years, BMD increased more rapidly in the combined treatment group.[57]

DHEA

Dehydroepiandrosterone-sulfate (DHEA-S) and DHEA, precursor hormones that convert into testosterone and estrogens, decline with age. DHEA is not FDA-approved for the prevention of osteoporosis but is available as an over-the-counter supplement. DHEA can inhibit osteoclastic bone resorption,[58] and low levels correlate with bone loss. A study of more than 1,000 postmenopausal women demonstrated that high DHEA-S levels at baseline were associated with less bone loss, but the effect diminished over time.[59] In a study of 208 healthy men and women (age range, 60-79 y), 12 months of supplementation with DHEA (50 mg/d) improved bone turnover specifically in women >70 years old.[60] A smaller study, in contrast, demonstrated that 6 months of supplementation with DHEA (100 mg/d) produced no change in BMD.[61] The DHEA and Well-Ness (DAWN) Study demonstrated that 12 months of supplementation with DHEA (100 mg/d) had a beneficial effect on BMD in women but not in men.[62] Evidence suggests, though inconclusively, that DHEA supplementation may have some skeletal benefit in women.

> “Research suggests that the addition of bioidentical progesterone to estrogen therapy incurs less risk than the addition of a synthetic progestin.”

SAFETY OF BIOIDENTICAL HORMONES

Risk assessment for any form of HRT is complex and depends on numerous factors, including age of the patient initiating treatment, duration of treatment, and biochemical individuality. Studies on the use of testosterone in women are limited, range from 1 month to 2 years, and raise safety concerns that include endometrial cancer, breast cancer, and cardiovascular disease.[63] Safety data on the use of DHEA in women are even scarcer, providing insufficient evidence on its effect on the breast or the uterus and mixed evidence on its effect on the cardiovascular system.[64] There is minimal research to distinguish the safety of bioidentical progesterone from synthetic progestins and even less to distinguish the safety of bioidentical estradiol from nonbioidentical estrogens. In the absence of comparable data, the FDA has asserted that the risks and benefits of all hormones at equivalent dosages should be assumed to be the same. According to the results of the WHI, this means that some of the most

serious risks of any estrogen replacement (with or without progestin or progesterone) include thromboembolic events or invasive breast cancer.[12]

It has been suggested that thromboembolic risk associated with estrogen therapy might vary depending on the route of administration.[23] First-pass hepatic metabolism of oral estrogens stimulates hepatic protein synthesis of inflammatory compounds, including c-reactive protein, insulin-like growth factor, and clotting factors—factors associated with increased thromboembolic risk. Data from a recent 3-year study in 75 women given transdermal compounded BHRT (Biest, progesterone, testosterone, and/or DHEA) support this assertion.[65] Compounded transdermal BHRT produced no net thrombotic potential and favorable changes in inflammatory and immune markers. The Million Women Study, in which more than 1 million women were followed for a mean of 3.1 years, demonstrated that current use of oral but not transdermal estrogen therapy increased the risk of venous thromboembolism (relative risk: 1.42 [95% CI: 1.22-1.66] vs 0.82 [95% CI: 0.64-1.06]).[66] These results supported previous findings of the Estrogen and Thromboembolism Risk (ESTHER) Study, a multicenter case-control study that demonstrated an increased risk of venous thromboembolism with oral but not transdermal use of estrogen and a 4-fold increased risk of myocardial infarction (MI) associated with oral estrogen compared to transdermal estradiol therapy.[67] The ESTHER study also demonstrated that micronized progesterone had no thrombogenic effect, whereas norpregnane derivatives resulted in an almost 4-fold increase in thrombogenic events. In contrast to these data, a large population-based study conducted in the United Kingdom demonstrated comparable risk of MI for users of both oral and transdermal estrogens.[68] In the United States, the KEEPS Trial compared the effect of oral CEE (Premarin, 0.45 mg/d), transdermal 17β-estradiol (Climara patch, 50 µg/d), or placebo on the progression of atherosclerosis in recently postmenopausal women.[69] Participants in the 2 active treatment groups were also given micronized progesterone (Prometrium 200 mg 12 d/mo). The KEEPS Trial demonstrated equal rates of atherosclerotic progression at 4 years of follow-up in all groups and no statistically significant differences in the rates of MI, transient ischemic attack, stroke, or venous thromboembolic disease; those receiving 17β-estradiol also experienced improved glucose and insulin sensitivity with neutral effects on other biomarkers such as cholesterol and triglyceride levels.

The most compelling research comparing breast cancer risk of BHRT to that of conventional HRT suggests that the addition of bioidentical progesterone to estrogen therapy incurs less risk than the addition of a synthetic progestin. A recent case-control study conducted in France in 1,555 menopausal women demonstrated a significant increase in breast cancer risk in groups receiving estrogen plus a synthetic progestin but no increased risk in those receiving estrogen plus micronized progesterone (odds ratio: 0.69-0.80, depending on duration of use).[70] Similar results were reported in the French E3N cohort study (N=80,377), which was conducted for a mean follow-up of 8.1 years in postmenopausal women.[71] Compared to no HRT, estrogen alone and estrogen plus a synthetic progestin (dydrogesterone or progestogen) yielded significantly increased risk for breast cancer, whereas the relative risk for estrogen plus natural progesterone was 1.00 (95% CI: 0.82-1.22). Consistent with these findings, a prospective, randomized trial of 77 women demonstrated that women in the group assigned CEE plus MPA experienced a marked increase in breast cell proliferation, whereas the group assigned to transdermal estradiol (1.5 mg/d) plus oral micronized progesterone (200 mg/d) did not.[72] Results of the KEEPS Trial showed no statistically significant differences in the rates of breast cancer after 4 years of CEE, transdermal 17β-estradiol, or placebo.[69] Although the KEEPS Trial was not designed to assess breast cancer risk and was too short to conclusively assess cancer risk, these findings punctuate those of the French studies that suggest bioidentical progesterone incurs less breast cancer risk than synthetic progestins when combined with estrogen therapy.

CONCLUSION

Randomized, double-blind, placebo-controlled trials on BHRT are lacking, but observational and case-control studies suggest that bioidentical estradiol (particularly oral or patch forms) is comparable to CEE for slowing bone loss, slightly increasing BMD, and reducing fracture risk. Minimal data suggest that DHEA and testosterone also have a beneficial effect on bone health in women. Transdermal administration of 17β-estradiol appears to carry less risk of thromboembolic events than orally administered CEE, and bioidentical progesterone might carry less risk of thromboembolism and breast cancer than synthetic progestins. Otherwise, it is most prudent to assume that BHRT carries the same risk profile as conventional HRT.

There is no ideal medication for either the treatment or prevention of postmenopausal osteoporosis. The choice of a prescription medication requires an astute understanding of the benefits and risks of each drug, while also understanding the risks of having osteoporosis as a woman ages. For postmenopausal women who experience bone loss despite a healthy lifestyle, BHRT might offer a viable alternative to other medications for the prevention of osteoporosis.

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