

HRT AND VIABLE ALTERNATIVES Dr. Kevin Passero, N.D.

Background:

Hormone replacement has been a growing topic among middle aged women and doctors in recent years. It is estimated that in the next decade, more women than ever before, as many as 52 million, will be age 50 or older. Further, by the year 2030 there will be some 1.2 billion women age 50 and above. Finding valuable, safe and effective treatments for the symptoms of menopause and for the management of illness related to this change in life will be of the utmost importance for managing the health of our world.

Until recently, little criticism or speculation was given to conventional estrogen and progesterin therapy considered the standard of care for more than two decades. Many questions have been raised since the release of the Women's Health Initiative study which brought to the forefront concerns about efficacy and safety of this once thought miracle treatment. This landmark study launched in 1991 consists of a set of clinical trials and observational studies that included over 161,000 women. Its primary objective was to address the most common causes of death, disability and poor quality of life in postmenopausal women. Several arms of the study were discontinued in 2003 and 2004 when research analysis started to reveal several associated risks arising from this type of hormone replacement.

Several complications arose from the arm of women receiving CCE (conjugated equine estroge at 0.625 mg/d plus medroxyprogesterone acetate, 2.5 mg/d, in 1 tablet. The primary adverse outcome reported in a 2002 JAMA article entitled *Risks and Benefits of Estrogen Plus Progesterin in Healthy Postmenopausal Women* was an increase in the incidence of invasive breast cancer in women taking HRT vs. placebo. Coronary Heart Disease (CHD), once thought to be prevented by HRT, was also shown to be more pervasive in women taking CEE plus medroxyprogesterone. The article goes on to state "Overall health risks exceeded benefits from use of combined estrogen plus progesterin among healthy postmenopausal US women." It also continues to state in the conclusions that "The risk-benefit profile found in this trial [WHI] is not consistent with the requirements for a viable intervention for primary prevention of chronic diseases, and the results indicate that this regimen should not be initiated or continued for primary prevention of CHD."^[1]

In response to growing concerns of standard practice and clinical guidelines NAMS (The North American Menopause Society) has created a position paper compiled by a panel of experts from the medical and research community. The Panel utilized the 2002 and 2003 WHI reports combined with a comprehensive literature search conducted to identify all new papers published subsequent to the 2003 report. The positions compiled by the panel include the following information: 1) Estrogen Therapy (ET) and combined estrogen-progestogen therapy (EPT) did not reduce coronary heart disease incidence in the WHI study. Until further evaluation no ET or EPT regimen should be used for primary or secondary prevention of CHD. 2) ET/EPT may increase the risk of ischemic stroke in postmenopausal women. In women with a history of CHD or ischemic

cerebrovascular disease, ET does not significantly influence stroke risk. For this reason it is important to manage risk factors for stroke in these women regardless of HT use. 3) Breast cancer risk probably increases with EPT use beyond 5 years. The estrogen only (CEE) arm of the study showed no increase incidence of breast cancer rates. 4) Moderate to severe menopausal symptoms including vasomotor symptoms and sleep disruption from vasomotor symptoms remains the primary indication for systemic ET and EPT. 5) The evidence for ET/EPT showed a definitive reduction in risk for postmenopausal osteoporosis related fractures. However, the risks and benefits ET/EPT therapy need to be carefully weighed as a therapy for osteoporosis risk reduction. 6) EPT after the age of 65 for primary prevention of dementia is not recommended as it may increase the chances of this population developing the condition.

Although ET/EPT may still have some significant benefits for the women entering the peri and menopausal phases of their life there is reason to look elsewhere for viable treatment options in light of the emerging possibilities for risk. Bio-identical hormones, herbs, lifestyle habits and nutritional products are all rising to the forefront of possible alternatives to conventional HRT.

A recent poll of over 1,000 Americans revealed that 6 in 10 people take dietary supplements on a regular basis. However, only 49% of these people report discussing their use of supplements with their doctors. The Village Green has a well educated staff backed by a licensed Naturopathic Doctor, a Master Herbalist and compounding pharmacist who specialize in blending natural therapies with conventional modalities. If you or your patients are interested in exploring these options, The Village Green offers unparalleled knowledge and expertise to help implement complementary and alternative therapies in the safest and most effective manner.

The following information is a brief review of current and past literature relating to the most pertinent CAM therapies for addressing menopausal symptoms. Please review it at your leisure and feel free to call Village Green anytime if you have further questions or want to obtain more information. Our Naturopathic Doctor, Master Herbalist or compounding Pharmacists would be happy to assist you in making the appropriate decisions for your patients.

Natural Therapies:

Exercise:

Several clinical trials have showed the beneficial effects of an exercise program for the reduction of hot flashes^{1,2}. A 2004 study from the Journal of Physiological Anthropology and Applied Human Science put 35 women with climacteric symptoms through a 12 week trial to assess the effects of exercise on hot flashes. 20 women were enrolled in a 12 week program that included physical exercise at least 3 times per week plus education about menopause. The remaining 15 women were not enrolled and instructed to refrain from exercising during the study period. Other outcomes measured in the study were quality of life and attitude towards exercise. The 12 week program demonstrated

significant improvement on climacteric symptoms in the exercising women. Beneficial changes were also seen for psychosomatic symptoms, especially paresthesia and nervousness.¹

In the prospective, randomized study conducted by Lindh-Astrand et al 75 postmenopausal, sedentary women with vasomotor symptoms were randomized to: exercise three-times weekly over 12 weeks (15 women), oral oestradiol therapy for 12 weeks (15 women) and 45 women to three other treatment arms. Exercise criteria included a 60 min aerobic class with moderate intensity that activated major muscle groups such as the thighs, abdominal and back muscles combined with passages into high intensity to increase heart rate and fitness. The women in the exercise group were required to attend this class 2x weekly and spend one additional hour per week engaging in exercise of such intensity that she had to take a shower afterward. Symptoms were assessed by a log book, Kupperman's Index, self administered MOOD Scale and the symptom check list-90 (SCL-90). Questionnaires were completed at baseline, after 4, 8 and 12 weeks of treatment and 12 and 24 weeks after end of therapy at their visits to the clinic. Of the 10 women who completed the exercise arm of the study a one third decrease in the number of hot flashes was observed. Further, in 5 women who continued exercise over the entire 36 week period there was a 50% reduction in the mean number of hot flashes. The exercise group also showed statistical improvement comparable to the estrogen group in general psychological wellbeing according the SCL. Kupperman's index decreased more rapidly but not more pronouncedly in the estrogen group than in the exercise group.²

Although not all the literature supports the use of exercise as an effective tool for the treatment of climacteric symptoms there is enough evidence to try this cost effective modality. The best results from the literature seem to come at 60 minutes of moderate to intense exercise 3 times per week. Further, the National Cancer Institute recommends exercise as a preventative method for reducing risk of breast cancer. It is also known that a sedentary lifestyle, a major factor for obesity, is tied to several other forms of cancer including colon cancer.

Diet:

Some aspects of menopausal symptoms, particularly hot flashes have been shown to respond to certain patterns in dietary habits. The strongest correlation is associated with phytoestrogen containing food products like soy, flax and red clover. However, it is important to consider the benefits of a well rounded diet high in whole foods and balanced nutrition. Low fat vegetable based diets have been shown to have a positive impact on preventing certain types of cancer. According to the American Cancer Society somewhere between 30%-40% of cancer cases can be linked to a poor diet.

Further, a diet rich in whole foods can have a positive effect on blood sugar regulation and the insulin response. An experimental study was conducted to explore the association between blood glucose levels and incidence of hot flashes. Results of the study demonstrated a significant reduction in the incidence of hot flashes during periods of elevated blood glucose vs. states that mimicked starvation.³ The researches concluded that conditions of fasting may trigger the unknown mechanism for menopausal hot

flashes. This is reason to consider avoiding sharp inclines and declines in blood sugar that often result from diets high in sugar and refined carbohydrates.

Nutritional Supplements:

Several nutritional supplements have demonstrated beneficial effects in relation to the treatment of menopausal symptoms.

Vitamin E:

Although somewhat dated, several clinical studies done in the 1940's showed Vitamin E to be effective in relieving hot flashes when compared to placebo.^{[4][5][6]} The results of one of these trials not only showed improvements in hot flashes, but a beneficial change in vaginal tissue was also noted.^[4] It is of importance to note that beneficial changes were observed with Vitamin E only when supplementation lasted at least 4 weeks in duration.

The first placebo-controlled, randomized, crossover trial on Vitamin E investigated its benefits for relieving hot flashes in 105 breast cancer survivors. Results demonstrated that 400 IU of Vitamin E given twice daily significantly improved symptoms of hot flashes^[7]. Although statistical significance was small, the study further emphasis the role of Vitamin E for support with menopausal symptoms.

Recent news has brought some attention to the potential dangers of taking Vitamin E in amounts previously thought to be safe. However, the study that was cited in the news story has some significant flaws that warrant further investigation into its validity. The results of the study alluded to the fact that taking 400IU of Vitamin E daily can increase chances of overall mortality. What the authors failed to mention was that the research reviewed was conducted with older subjects who had chronic illness and were therefore likely to have higher mortality rates anyway. This type of review, a meta-analysis, reviewed other studies, some of which were more than 10 years old and of varying quality. The statistical significance was very small and because it was not an actual clinical trial with controls or blinding it is only as valid as the studies it reviewed. Meta-analyses are notorious for being very easy to manipulate because studies to be reviewed can be preferentially selected for based on their outcome. Decades of well designed clinical trials and studies have repeatedly shown not only the safety of Vitamin E in doses ranging from 400IU-800IU but also their beneficial role in protecting the cardiovascular system and blunting the negative effects of reactive oxygen species.

Gamma-oryzanol

Gamma-oryzanol, isolated from rice bran oil, is a naturally occurring mixture of plant chemicals called sterols and ferulic acid esters. Several clinical trials have shown it's effectiveness in managing menopausal symptoms including hot flashes.^{[8][9][10][11]}

In one study eight menopausal women and thirteen women post bi-lateral oophorectomy were administered 300mg/day of gamma-oryzanol. Over 67% of women in both categories had a 50% or greater reduction in menopausal symptoms at the close of the 38 day trial.^[8] In another study using the same dose of gamma-oryzanol (300mg/day), 85% of the 40 women involved reported improvements in their climacteric symptoms. Further results also showed decreases in total cholesterol and triglycerides with increases in HDL-cholesterol in hyperlipidemic subjects.^[9] Other human studies have supported the ability of gamma-oryzanol to be effective in lowering blood cholesterol and triglyceride levels.^[10]

Bio-Identical Hormones:

Bio-Identical hormones refer to estrogen and progesterone analogs that exactly mimic the chemical structure of estrogens and progesterone produced by human ovaries during reproductive years. The term Hormone Replacement Therapy does not differentiate whether replacement was carried out using bio-identical structures or synthetic analogues. Current and past research points to significant differences in how our body responds to these two classes of hormones and the differences may contribute to many of the negative effects that were discovered through the WHI research project and the Heart and Estrogen/Progestin Replacement Study (HERS).

Exogenous steroids are enzymatically degraded and eliminated. When this happens, metabolites are produced as a by-product of the degradation process, some of which can be metabolically active. Based on this, it must be taken into account that *the net effect of the administration of a single hormone is the sum of the metabolic effect of that hormone and the cascade of its metabolites.*^[12] In theory, this cascade of enzymatic degradation and metabolic by-products could be significantly amplified if several estrogens, especially estrogens foreign to the human system, are administered simultaneously like in the case of conjugated equine estrogen. It makes sound logical sense to use bio-identical hormones vs. synthetic hormones when administering HRT.

Bio-identical hormones including estriol, estrone, estradiol, and progesterone were not used in the WHI study. However, these bio-identical hormones do show much of the protective effects desired for HRT without the negative effects that arose from the HRT in the WHI.

Progesterone:

Progesterone is a term that is incorrectly used interchangeably to describe both natural, bio-identical progesterone and synthetic substitutes. As research continues to progress it is becoming clear that some of the potential negative outcomes from the WHI and HERS were due to the synthetic progestins contained in the HRT. Numerous studies have shown the ability of micronized natural progesterone administered orally to produce safe, therapeutic blood levels without unwanted side effects commonly experienced with synthetic analogues.^{[12][13][14][15][16]}

The most significant research surrounding bio-identical vs. synthetic progesterone is the large role synthetic progestins may have played in the increased instance of CHD seen in the HERS and WHI studies. While estrogens, both synthetic and bio-identical, appear to increase endothelium-dependant vasodilation in postmenopausal women synthetic progesterones appear to have the opposite effect. Several studies demonstrate that synthetic progestins, including both medroxyprogesterone and 19-nortestosterone derivatives, negate the protective vasodilatory effects of estrogen.^{[17][18][19][20][32]}

Faludi et al set out to assess the vasodilatory effects of estrogen alone and in combination with norethisterone on post-menopausal women with mild to moderate hypertension using a double-blind, randomized, 20 week clinical trial. The authors speculated that progesterone derivatives with higher androgenic activity oppose the beneficial effects of estrogen on vascular response and lipid profiles.

Effects on vasodilation were assessed after each treatment period using brachial artery ultrasound done according to the Guidelines for the ultrasound assessment of endothelial-dependant flow-mediated vasodilation of the brachial artery. Women receiving estrogen (2mg estradiol/day) showed statistically significant ($P < 0.05$) increase in flow-mediated dilation (+53%+64.1%). The addition of a progesterone derivative (norethisterone acetate 1 mg/day) to other women receiving the same doses of estrogen, blunted these benefits to +22.4%- (-)9.8%. These results led researchers to conclude that the improvement in endothelial function observed in the group treated with estradiol was abolished by the addition of norethisterone acetate. They continue to state that the improved endothelial function observed with estrogen therapy can represent an important mechanism of protection against CAD. However, in women with an intact uterus the addition of synthetic progestins with high androgenic activity should be avoided.^[18]

Other significant findings of the study relate to the negative effects that norethisterone had on the positive changes seen in lipid profiles with the administration of estradiol and atorvastatin. The administration of estradiol combined with atorvastatin resulted in an increase of HDL-c levels similar to those seen with estradiol alone. However, these benefits were reverted by the addition of norethisterone acetate.^[18]

The results of the study emphasize the negative effects that synthetic progestins can have on the protective role of estrogen in the body. In this particular case it is assumed that the negative effects are due to higher androgenic activity of the type of progesterone used and eludes that other forms of progesterone with less androgenic activity like medroxyprogesterone acetate (MPA) are safe. It is important to consider that one of the major reasons for discontinuing the CEE + MPA arm of the WHI was due to the increase incidence of CAD in healthy women taking this HRT combination. These findings mirror the findings of the Heart and Estrogen/Progestin Replacement Study (HERS) which demonstrated that estrogen and progestin (MPA) therapy did not reduce the overall rate of coronary events in postmenopausal women with established coronary disease^[38] and warrants a further look into the influence of MPA on vasodilation.

Akihiko and colleagues investigated whether MPA impairs favorable effects of estrogen on endothelial function by measuring endothelium-dependent vascular reactivity in 48

naturally postmenopausal women.^[17] Vasodilatory responses of the brachial artery were evaluated by measuring flow-mediated vasodilation (FMD) by use of high-resolution ultrasonography. Conjugated equine estrogen (CEE) significantly increased FMD from 4.5% to 8.5% ($P < 0.001$), whereas no significant changes were observed in either the CEE+ 2.5 mg MPA group (5.0% to 6.2%) or the CEE+ 5.0 mg MPA group (4.9% to 3.6%). Through ANOVA statistical analysis it was observed that FMD was decreased in parallel with increasing MPA dosage. The authors conclude that the addition of MPA at 2.5mg, the standard dosage level used for continuous combined therapy, attenuates estrogen-induced enhancement of endothelium-dependant vasodilation.^[17]

The results of these studies show that both classes of synthetic progestins have the potential to exacerbate coronary artery disease and negate beneficial effects of estrogen on vasodilation. Conversely, bio-identical progesterone, usually administered as micronized progesterone, has been shown not to interfere with the beneficial effects of estrogen and poses a much safer alternative when considering estrogen and progestin administration.

Rosano et al compared the influence of natural progesterone and medroxyprogesterone acetate on the beneficial effects of estrogen on exercise-induced myocardial ischemia in postmenopausal women. 17-beta estradiol was administered to 18 postmenopausal women with coronary artery disease or previous myocardial infarction for 4 weeks (3 weeks of 1mg/day and 1 week of 2mg/day) in a single blind manner. Estradiol (2mg/day) was continued and the subjects were randomized in double blind fashion to either transvaginal progesterone gel (90 mg on alternate days) and oral MPA (10mg/day) or vice versa for 12 days. After an additional 2 weeks on estradiol alone patients were crossed over into the opposite progestin treatment group. Treadmill exercise testing was administered after each estradiol phase and at day 10 of each progestin phase. Time to 1-mm ST segment depression increased with estradiol, as compared with baseline ($P < 0.001$). There was a significant increase in exercise time to the onset of 1-mm ST segment depression by combination estradiol/progesterone as compared with combination estradiol/MPA by an average of 92 seconds ($P < 0.001$). The authors state that “the results of the present study indicate a synergistic effect of estrogen and progesterone, but not estrogen and MPA, on exercise time to myocardial ischemia”.^[32]

The results not only demonstrate the need to consider choice of progestin for women at high cardiovascular risk, but for all women receiving progestin therapy. If bio-identical progesterone poses no negative effects on the beneficial properties of estrogen while both classes of synthetic progestin's do, all women should utilize bio-identicals when considering progestin therapy in combination with estrogen replacement.

Further studies have also demonstrated the negative effects of MPA on estrogens beneficial cardiovascular properties. Miyagawa et al treated ovariectomized rhesus monkeys with physiological levels of 17-beta estradiol in combination with medroxyprogesterone or progesterone for four weeks. The researchers demonstrated that 17-beta estradiol combined with progesterone had protective effects on coronary vasospasm while 17-beta estradiol combined with medroxyprogesterone failed to protect, allowing vasospasm.^[19]

Synthetic progestins also demonstrate antagonistic effects on the lipid lowering effects of estrogens.^[18] The results obtained from the study conducted by Faludi and colleagues clearly showed the negative effects that norethisterone had on the positive changes seen in lipid profiles with the administration of estradiol by itself and in combination with atorvastatin. While norethisterone did not offset the beneficial effect of estrogen and atorvastatin in relation to total cholesterol numbers it did (in a non-statistically significant manner) reduce the ability of estrogen to decrease LDL-c (estrogen alone decreased LDL-c by 20.3% vs. estrogen + norethisterone decreased LDL-c by only 12.1%). However, elevation of HDL-c levels was significant with the administration of estradiol alone or estradiol combined with atorvastatin (Estradiol = +15.5; P<0.001) and (E+A= +13.07; P= 0.032) while (E+P = -9.1%). The researchers concluded that the addition of norethisterone acetate reverted the benefits of estrogen on HDL-c levels.^[18]

Jensen et al set out to determine the effects of long term use of percutaneous estrogens in combination with oral micronized progesterone on serum lipoproteins in postmenopausal women. Forty-five postmenopausal women were followed for a total of 2 years in this placebo controlled study. Twenty women were assigned to receive 5mg percutaneous estradiol daily from days 1 to 24 of tablet cycle and 25 were assigned to a placebo group in a double blind fashion. After one year, 200 mg of oral micronized progesterone was added to the estradiol group for 12 days each cycle (days 13-24). During the first year of cutaneous estradiol therapy total serum levels of cholesterol and LDL cholesterol were significantly reduced compared to placebo. The researchers observed no significant differences in the serum levels of triglycerides and HDL cholesterol. Addition of oral progesterone during the second year did not significantly alter the total serum cholesterol and LDL cholesterol, both of which remained significantly reduced in the hormone group. During the last 6 months of combined hormone therapy, HDL levels increased resulting in an overall statistically significant rise in HDL cholesterol by the end of the study period (P<0.05).^[21]

Add to this information the fact that bio-identical progesterone also demonstrates protective effects on the endometrium when administered with estrogen^[22] and there seems to be little reason for the utilization of synthetic progestins in the role of HRT.

Estrogens:

Bio-identical estrogens including estriol and estradiol have proved to be beneficial in addressing several aspects of menopausal care. These range from cardiovascular benefits, relief from vasomotor symptoms, reduction of bone resorption, reduction of urinary tract infections, reduction of skin aging, benefit hypertensive states and improve blood sugar and insulin sensitivity in diabetics.

The literature strongly supports the use of bio-identical estrogen (estradiol) as an effective treatment for climacteric symptoms.^{[23][24][25][26]}

One randomized double blind study investigated the use of 25, 50, 100 and 200 micrograms/per 24hrs of transdermal estradiol on 50 postmenopausal women experiencing more than 10 hot flashes daily. Transdermal estradiol administration reduced the number of hot flashes in a dose dependant manner. Compared to placebo, the 50 microgram/per 24hrs group and higher reached statistical significance in regards to the reduction of hot flashes measured by a calculated rate of occurrence per hour.^[24]

A more recent randomized, double blind placebo controlled study investigated the effectiveness of 17-beta estradiol on hot flashes in 99 postmenopausal women. Buccal administration was utilized for delivery of a 0.05, 0.1, 0.2, or 0.4 mg dose of estradiol. Hot flashes were measured objectively using digital thermography and subjectively through diary recordings. The frequency of hot flushes was significantly reduced from baseline in all estradiol groups by day 28. However, only the 0.4mg dose of estradiol produced statistically significant reductions in hot flashes when compared to placebo. If 3 participants in the placebo group with elevated estradiol levels are removed from the analyses all doses of estrogen showed statistically significant reductions in hot flashes when compared to placebo. The authors speculate that intermittent estrogen production after 1 year of amenorrhea may account for some of the so-called placebo response found in this and other studies. Also of interesting note was that all doses of estrogen produced maturation indices of vaginal tissue equal to that of premenopausal subjects at the end of the 4 weeks.^[25]

Another recent study compared the effectiveness of acupuncture and oral estradiol for the treatment of vasomotor symptoms in 45 postmenopausal women. The study used 2 mg/day of 17 beta-estradiol administered orally for 12 weeks. Hot flash frequency decreased from 8.4 flushes/24 hours to 0.8 flushes/24 hours in the estradiol group during treatment. During the 24 week follow up period, the decrease in the number of hot flushes per 24 hours remained unchanged in all treatment groups.^[26]

Estrogen and Bone Density:

Positive effects of estradiol on bone density is another important factor to consider when contemplating the use of bio-identical hormones. A review of the recent literature shows strong evidence for the use of estradiol to improve and maintain bone densities.^{[27][28][29][30][31]} Also of an interesting note is that several of these trials found very favorable effects of estradiol on bone density when used in a low dose.^{[27][28][30]}

Prestwood and colleuges set out to explore if low dose estrogen could be effective at preventing bone loss in postmenopausal women in an effort to find viable treatments that minimize the adverse events correlated with conventional doses of HRT. They conducted a randomized, double-blind, placebo-controlled study among 167 healthy women over the age of 65 for a period of 4 years. Women allocated to the treatment group received 0.25mg/day of 17 beta-estradiol. All women who had not had a hysterectomy also received 100 mg/day of micronized progesterone for 2 weeks every 6 months. All participants in the study received 1300 mg/day of elemental calcium and 1000 IU/day of vitamin D. Dual-energy x-ray absorptiometry showed that low-dose

estrogen significantly increased bone density at the hip, spine, wrist and total body BMD. Serum and urine markers of bone turnover were also significantly lower in women receiving low dose estrogen compared to the placebo group. There were no significant differences between treatment group and control group in areas of breast tenderness, fluid retention, bloating, and headaches. At year 2 the treatment group showed a significant increase in endometrial thickness. However, after proper follow-up and treatment, all biopsies revealed atrophic endometrium. There were no significant differences in abnormal mammograms between treatment and placebo group or in the number of abnormal follow-up mammogram results. No cases of breast cancer were reported during the study.^[30]

Another clinical trial compared the effects of low and conventional dose transdermal estradiol on bone loss in the spine and femur. In this open clinical trial women were divided into 2 groups, those above age 67 and those below age 67. Within each group women were assigned either a dose of 25 micrograms of transdermal oestrogen or 50 micrograms of transdermal oestrogen. All women in the above 67 age group were also instructed to take 1,000mg of calcium daily by diet or supplement. The changes observed in the 80 women who finished the trial between 0-3 years were similar whether patients were divided by age or dosage. Results showed that both low and conventional dose estradiol increased bone mineral density in the lumbar spine. The higher dose estradiol was not associated with a greater response of bone mass at either the spine or femoral neck and there was no evidence of an increasing BMD response as estradiol dosage/kg body weight increased. The average change in BMD over 3 years was significantly lower at the femoral neck than in the lumbar spine for both dosage groups.^[27]

Benefits of low dose estrogen is confirmed by another double blind, randomized dose ranging study. Micronized estradiol was administered in either 0.5mg, 1mg and 2mg oral doses to 41 postmenopausal women over an 18 month period. Subjects were also instructed to take 1500mg of calcium carbonate daily. The researches concluded that micronized 17 beta-estradiol has a continuous skeletal dose-response effect in the range of 0.5-2.0 mg and that calcium intake positively modifies the skeletal response to 1.0 mg micronized 17 beta-estradiol.^[28]

The positive effect of estradiol on bone density at low doses is very promising as a viable method for preventing and treating osteoporosis while minimizing any potential adverse effects from exogenous estrogen exposure. In light of these studies, it is important to consider the use of calcium supplementation in the range of 1000-1500 mg/day when attempting to achieve positive outcomes on bone density with low dose estradiol therapy.

Estrogen and Cardiovascular Function:

Although CEE alone and combined with synthetic progesterone did not show beneficial effects for women with CHD in the WHI or HERS study, the literature strongly suggests the ability of estradiol to exert a positive effect on the cardiovascular system of

postmenopausal women with or without already withstanding CHD. Much of the literature reviewed in the progesterone portion of this paper exemplifies the beneficial role estradiol plays on vascular dilatation and cardiovascular health.^{[18][32]}

Rosano and colleagues observed the beneficial effects of sublingual estradiol in eleven women with coronary artery disease. In this study, treadmill exercise tests were used to evaluate the effect of 1 mg sublingual estradiol on myocardial ischemia when compared to placebo. Administration of estradiol increased time to 1mm ST segment depression ($p < 0.004$) and overall exercise time ($p < 0.01$).^[33] It was unknown exactly how estrogen mediates improved cardiovascular function but Rosano's group postulated that the benefits were a result of reduced myocardial oxygen consumption through a decrease in peripheral vascular resistance or by lowering preload. It was also speculated that estrogens beneficial effects are a result of a direct vasodilatory action on coronary arteries.

Other researchers have confirmed the vasodilatory effects of 17 beta-estradiol on coronary and systemic arteries.^{[35][36][37]} The studies reviewed in this paper make a strong argument for the continued use of estradiol for the prevention and treatment of CAD. It is of interest to note that all of these research findings were thought to be the reason why estrogen therapy was beneficial in the management of cardiovascular disease for post menopausal women. However, information from the WHI and HERS revealed this might not be the case. A very possible explanation may be that protective cardiovascular properties resulting from estrogen therapy were offset by the negative cardiovascular influences that seem to arise from synthetic progesterone use.

Conclusion:

It is clear that doctors and patients are in need of viable alternatives to standard hormone replacement therapy. The information in this paper is designed to help bring some of the most well researched complementary and alternative therapies to the forefront. Weighing these treatment options with patient history and risk factors is vitally important to designing the best treatment plan.

The results of the WHI informed us that hormone replacement can come with very serious risks. It is therefore very important to weigh these risks with potential benefits of therapy. Bio-identical hormones seem to offer a much more logical approach to hormone replacement therapy because their use allows doctors to create the same hormone footprints present in a women's body prior to menopause. The literature suggests that some of the negative findings associated with the WHI and HERS are a direct result of using synthetic analogues of our natural hormone structures. However, the use of exogenous hormones does come with potential risks whether they are bio-identical or synthetic. For this reason, any hormone replacement should be reserved for cases that do not respond to less invasive therapies. This paper is designed to introduce the practitioner to the spectrum of least invasive, exercise and diet, to a more moderate approach, botanicals and supplements, to the therapies with the highest potential risk of adverse effects, bio-identical hormones.

These complementary and alternative therapies offer more choices for health care providers who want safer and less invasive therapies for their patients. Due to the lack of primary research on many of these substances it is not always clear which one will work most effectively for each individual. However, with proper evaluation of risk factors and assessment of individual symptomology many of these therapies can be implemented successfully.

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