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Volume 20, Issue No. 1 **January-February, 2003**

BIOIDENTICAL HORMONE REPLACEMENT THERAPY: Theory and Evidence

Recently released data indicate the risks of using conventional hormone replacement therapy (HRT) are higher than originally anticipated.[1,2,3] It has been suggested that bioidentical hormone replacement therapy (BHRT) is an effective, safer alternative to HRT[4,5,6]. The purpose of this paper is to present the theory of BHRT and examine the available evidence on its risks and benefits.

Definitions:
Bioidentical Hormones: Synthetic or nonsynthetic chemicals identical in structure to hormones produced in the body. In theory, these hormones should produce the same physiological effects as endogenously produced hormones.[4,6] BHRT estrogens and progesterone are synthesized from soy and yams.[6]
Natural Hormones: Non-synthesized substances with hormonal activity, e.g., plant phytoestrogens. These agents do not have the same chemical structure as endogenous hormones.[4,6]
Hormone Replacement Therapy (HRT): Postmenopausal supplementation with an estrogen and progestagen (if patient has an intact uterus). The most widely used HRT regimen consists of conjugated equine estrogen and medroxyprogesterone acetate.[6] These drugs are not chemically identical to human hormones.

Estrogens:
The body produces three main forms of estrogen: estrone, estradiol and estriol. Estradiol is the primary estrogen secreted by the ovaries before menopause. In the liver, estradiol is converted to estrone and subsequently to estriol. Estrone can also be produced from androstenedione in fat tissue and after menopause estrone becomes the predominant estrogen. Estradiol is the most potent estrogen with an activity 12 times greater than estrone and 80 times greater than estriol.[7] BHRT oral estrogen supplements typically consist of estriol alone or estriol in combination with smaller percentages of the stronger estrogens (tri-estrogen: 80-90 % estriol, 7-10% estradiol, 3-10% estrone; bi-estrogen: 80-90% estriol, 10-20% estradiol).[4,8] Estriol is reported to have both estrogenic agonist and antagonist effects.[9] In theory, estriol could blunt the adverse effects of estradiol and estrone and potentiate their beneficial effects.[5]

No published studies evaluating the effectiveness of double and triple estrogen formulations were found but there is data that indicate estriol can relieve menopausal symptoms when taken orally[10,11] and significantly improve urogenital symptoms when administered vaginally.[12,13] Vaginal estriol preparations have been widely used in Europe for several years.[12,13]

Studies investigating the effect of estriol on bone density have produced conflicting results.[4,5] Only Japanese studies have demonstrated a positive effect suggesting that diet and / or genetics may have been confounding factors.[5,14] The higher potency estrogens are known to reduce postmenopausal loss of bone mass. It is possible that bi- and tri-estrogen formulations have a more favourable effect on bone than estriol alone but this premise has not been tested.[4]

There is no reliable data at this time on cardiovascular outcomes of estriol, bi-estrogen or tri-estrogen therapy. Studies on the effects of oral estriol on lipid profiles, an intermediate marker for cardiovascular disease, have produced mixed results.[5]

According to BHRT theory, estriol does not cause proliferation of endometrial and breast tissue and, when given in combination, antagonizes the proliferative effect of the stronger estrogens.[4,5] While earlier studies suggest that estriol has no effect on the uterus[10,15], more recent studies report significant growth of the endometrium during estriol therapy[16,17]. Careful monitoring of patients using oral or vaginal estriol formulations is recommended and prophylactic therapy with a progestagen should be considered.[5,7,16]

Similarly, in regards to breast cancer, animal and epidemiological studies support a protective effect for estriol[4] but there are *in vitro* studies that indicate estriol has stimulatory effect on human breast cancer cells[18.19]. Until further research clarifies this issue, estriol formulations should not be recommended as an alternative to HRT in women with breast cancer or at risk of breast cancer.[5]

Progesterone:
The primary purpose of the progestagen component of HRT is to counteract the proliferative effect of estrogen on the endometrium and reduce the risk of uterine cancer. The bioidentical progestagen is progesterone.[20] Micronized progesterone is marketed in a 100 mg capsule (Prometrium®) approved by Health Canada. It can also be compounded in different strengths and/or delivery forms.[6]

Oral and vaginal formulations of micronized progesterone are well absorbed and have been shown to provide endometrial protection.[21] However, bioavailability studies on transdermal progesterone preparations report variable results[22-26]; therefore topical progesterone formulations are not recommended for this purpose[8,26]. Oral progesterone appears to be better tolerated than the synthetic progestin, medroxyprogesterone acetate (MPA), according to a recently published Canadian study.[27] Patients taking estrogen + progesterone reported improved scores on menstrual problems (vaginal bleeding, breast tenderness, abdominal cramps and bloating) and cognitive difficulties (clumsiness, concentration and memory) compared to those taking estrogen + MPA.[27]

It has been suggested that bioidentical progesterone has effects independent of estrogen on menopausal symptoms and postmenopausal bone density loss. In one study, monotherapy with oral progesterone had no effect on symptoms.[28] A study evaluating the effect of transdermal progesterone reported an 83 % reduction in hot flashes.[29] This study also looked at bone density and found no benefit after one year of treatment.[29] Progesterone appears to reduce the beneficial lipid effects of estrogen to a lesser degree than medroxyprogesterone.[30] Whether or not this translates to a significant difference in cardiovascular outcomes of HRT has not yet been determined.

Indirect evidence suggests that there may be an increased risk of breast cancer when progestagens are added to estrogen therapy.[31] Among women enrolled in the Postmenopausal Estrogen/Progestin Interventions (PEPI) trial, breast tissue density was higher in those treated with the estrogen/progestin combinations than with estrogen alone regardless of whether the progestogen used was MPA or progesterone.[32] The 2002 Canadian clinical practice guidelines for the care and treatment of breast cancer recommend that the same cautions apply to progestagen as to estrogen use in patients with breast cancer.[31]

Key Points:
1. There is insufficient evidence to conclude that BHRT is safer than conventional HRT. The same precautions and limitations regarding HRT should also be applied to BHRT: short-term (maximum use 4 years); indicated only for the relief of menopausal symptoms; not recommended for the prevention of chronic diseases.[33]

2. When considering the use of BHRT, patients need to be informed of the potential risks of hormone replacement, e.g. increased incidence of CVD events, breast cancer.[33] "Bioidentical" may be confused with "natural" and many people believe that natural products are safer.[34]

3. There are concerns about variations in bioavailability that might compromise the safety and efficacy of compounded BHRT products. Patients should be carefully monitored to determine if they are receiving the appropriate dose. This may involve serum testing especially in circumstances when inadequate or excess levels could put the patient at risk of serious adverse effects.[6] Saliva testing has also been used to monitor hormone levels but recently published studies have demonstrated a poor correlation between saliva progesterone levels and plasma progesterone levels[24,26,35] and question the value of saliva tests in monitoring hormone therapy[26,35].

4. BHRT may be effective in alleviating menopausal symptoms and it offers the advantage of a wide variety of dose and delivery systems allowing therapy to be tailored to the individual needs and preferences of patients.[4,5,6]

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References available by request

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