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FOR CLINICIANS WHO PROVIDE CARE FOR WOMEN

Hormone Therapy and Osteoporosis



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The biological effects of estrogen deficiency and replacement are well known, and the recent results from the hormone therapy arm of the Women's Health Initiative confirm antifracture efficacy of a hormone regimen often styled as standard. In that study of some 16,000 women conjugated estrogen (0.625mg/day) with medroxyprogesterone acetate (MPA) (2.5mg/day) produced significant reductions in hip, spine and all other non-spine fractures in women who likely did not have osteoporosis by bone density criteria. The robust outcome confirms the prior smaller studies of vertebral fractures and the many bone density studies demonstrating the bone conserving effects of estrogen given to postmenopausal women. The demonstration that lower doses of estrogen plus progestin have very similar effects on bone density outcomes, suggests that similar beneficial effects on fracture might be seen with these doses and their use may result in a more beneficial risk benefit profile for hormone therapy among postmenopausal women.

More than 60 years ago Fuller Albright demonstrated that women who had had ovariectomy performed at an age prior to the natural age of menopause were more likely to present with vertebral fractures.¹

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He also showed negative calcium balance in these women; that is calcium losses from the body were greater than calcium intake, and presumably therefore these women were continuing to lose bone tissue, the only available source of the excess calcium loss. For many years after, the role of estrogen on skeletal homeostasis was debated, since estrogen's role was considered by many to be limited to the reproductive organs. Thirty-five years ago our group, in Scotland, began the first controlled clinical trial of estrogen intervention designed to test the hypothesis that estrogen would prevent loss of bone in ovariectomized women.^{2,3} A parallel study of estrogen intervention in women who had had a hysterectomy, but had ovarian conservation was also initiated. In those studies we demonstrated that bone density could be preserved by estrogen, and that the effects were evident even if therapy was delayed until six years after ovariectomy.

Long-term data from those studies demonstrated a reduction in the risk of vertebral fracture (called vertebral deformity in the publication) but essentially the same deformities that are the end points of phase 3 studies for registration of medicines for osteoporosis today. Similar data have been published for hormone therapy by Nachtigall et al,⁴ and Lufkin et al⁵ showed vertebral fracture reductions in patients with osteoporosis treated with transdermal estrogens. Despite these data, there has been some concern that the data

FROM THE EDITOR

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Preventive Health Strategies: Hormone Therapy and Behavior Modification

As clinicians are provided with more results from the Women's Health Initiative, (WHI) the role of hormone therapy (HT) in the management of postmenopausal women continues to change.¹ The utilization of hormone therapy in postmenopausal women was once perceived as a preventive health strategy to reduce the risk of heart disease, prevent bone loss, and to reduce the incidence of Alzheimer's disease.

Robert Lindsay, M.D., provides important information on hormone therapy and prevention of bone loss and fracture. The results of the WHI had only two very positive findings, and prevention of fracture was one of these.² Secondly, it is important to underscore the fact that for many women, osteoporosis or bone loss is a significant issue. The risk factors for bone loss are menopause, a family history of osteoporosis, and prior fractures in the patient. As pointed out in the National Osteoporosis Risk Assessment (NORA) study, fractures can occur even with low, but not osteoporotic bone mineral density.³ Therefore, the important information from the Women's Health Initiative is that the use of hormone therapy in this population not at risk for osteoporosis results in a significant reduction of fractures.² These findings would argue that an effective treatment strategy for the prevention of bone loss is hormone therapy. When hormone therapy is discontinued, there is a significant loss of bone density over the succeeding 12 months.^{4,5}

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Menopausal Medicine

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for fracture prevention by hormone therapy were not as robust as those obtained for recently developed osteoporosis specific drugs. The issue was highlighted by the large, high-quality phase 3 studies demonstrating fracture efficacy for alendronate and risedronate in patients with osteoporosis.⁶⁻⁸ Reductions in fracture risk for vertebral fractures, hip fractures as well as other non-vertebral fractures have been clearly demonstrated in those studies, and the inference was drawn that those data implied superior efficacy for bisphosphonates when compared to hormone or estrogen therapy, despite the lack of head-to-head trials.

The recently published data from the Women's Health Initiative hormone therapy placebo controlled clinical trial is a much needed addition to the osteoporosis literature.⁹ In that study, despite its early termination after an observation period of 5.2 years, on the recommendation of the data safety monitoring board, a standard regimen of hormonal therapy (conjugated equine estrogen 0.625mg/day + medroxyprogesterone acetate 2.5mg/day) reduced the risk of vertebral, hip, and other non-vertebral fractures. Risk reductions were 34% for clinical vertebral fractures and for hip fractures and 23% for other non-vertebral fractures (Table 1). Fracture numbers in this clinical trial matched any of the major pivotal studies for other anti-osteoporosis agents. In all, 1,487 fractures were reported in the original publication with 159 fewer fractures occurring in the hormone arm of the study. Overall, in 10,000 women years of observation that translated into 44 fewer fractures per 10,000 women years of observation, the highest numerical change in risk for any outcome, and only one of two statistically significant outcomes when corrections were applied in the statistical analysis for examination of multiple outcomes (the other was venous thromboembolic disease). These fractures included 106 hip fractures, with a reduction in risk of 34%. This compares with 46 hip fractures in the Alendronate fracture intervention trials (33 in FIT 1 and 43 in FIT 2), and 232 fractures in the two arms of the risedronate HIP study (101 in individuals with osteoporosis and 131 in women > 80 years of age whose osteoporosis status was mostly unknown).⁶⁻⁸

Since these studies were presented as four trials, it is fair to note that the number of hip fractures in WHI is well into

the range achieved in these regulatory studies. Only FIT 1 and HIP 1 were able to show a drug effect on hip fracture risk, without further analytical processing, demonstrating the difficulty even with effective agents in demonstrating fracture risk reductions at the hip. A simple assessment suggests that it is the complex pathophysiology of hip fracture that leads to this outcome. Hip fractures usually occur following a fall directly onto the hip, and as age increases the risk of falls increases until there comes a point when the frequency of falls is so high that addressing the presence of osteoporosis in the hip with an osteoporosis drug will likely prove futile. This could explain HIP 2, but explaining FIT 2 is more difficult. One might consider the small number of fractures, and although there were fewer fractures in FIT 1 (with a positive significant outcome), the level of risk was also higher in that population. Is the outcome of FIT 2 then merely a numbers game? Recruitment into that study was based upon a diagnosis of osteoporosis by bone mineral density (BMD) at the hip defined by the manufacturer's database. Re-evaluation of recruits using the NHANES 3 database reclassified many of the participants from osteoporosis to low bone mass or osteopenia.¹⁰ Re-analysis of hip fracture in those with true BMD osteoporosis (n=1631) revealed 18 in the control group and eight in the alendronate group, a statistically significant effect. In the larger group, those with low bone mass, risk was sufficiently low that only 17 hip fractures occurred, making it unlikely that a drug effect could be seen. Care in study design is clearly an important aspect of drug development that can easily result in questions and concerns about the data.

Unfortunately, in the WHI hormone study, bone density evaluation was done at only a minority of sites and thus we do not know the distribution of BMD in this population, nor as yet do we know the BMD response to therapy in this subgroup. However, we do know that the women in the study ranged from 50 to 79 years of age and that their average age was close to 63 years. From NHANES 3 data we can assume that the majority of these women, if representative of the general population, would not have osteoporosis by BMD.¹⁰ Therefore, we have in WHI the most robust demonstration of a fracture benefit, that appears to be skeletal wide, in women whose osteoporosis status

is unknown. However, we have a number of studies in which similar hormone therapy regimens have been used in which the primary outcomes were the intermediary markers of BMD or bone remodeling. BMD increases over two to three years (the usual period of BMD clinical trials) are about 4% to 6% in the spine and 3% to 4% in the hip. Reductions in bone turnover using biochemical indicators of bone remodeling average approximately 50% and thus the effects of HT on bone remodeling are similar in magnitude to those seen with the bisphosphonates. Thus, although these agents affect different target sites in bone the net results on BMD, turnover, and fractures are very similar.

The outcomes of the hormone study of WHI have stirred considerable discussion, especially related to the use of hormone therapy for chronic disease prevention. Like any good study, the data generate at least as many questions as they provide answers, some relating to the regimen studied and route of administration. One important question from the point of view of osteoporosis prevention relates to dose. For many years following publication of two fairly small studies in which bone density evaluation was performed by techniques perhaps less sensitive than those used in clinical trials today, we have assumed that 0.625mg of conjugated estrogen or its equivalent was the necessary daily dose to prevent bone loss in postmenopausal women.^{11,12} Recent data have led us to re-evaluate that conclusion.

First, in early postmenopausal women, lower serum levels of estradiol have been associated with more rapid rates of bone loss, and in women over 65 years of age those producing least estrogen may have highest fracture rates.^{13,14} Data suggest that in older women doses lower than 0.625 are effective in stabilizing bone turnover and increasing bone mass. Within the past year data from a formal dose response study have been published in early postmenopausal women.¹⁵ These data suggest that lower doses of estrogen than previously thought reduce bone remodeling and prevent bone loss in the early years

after menopause. Previous thinking had argued that it would be during this period, if any, that higher doses of estrogen would be required to prevent bone loss. In the so-called women's HOPE study bone loss in both hip and spine was prevented by 0.3, 0.45, and 0.625mg/day with or without the addition of medroxyprogesterone acetate daily (2.5mg/day with 0.625 and 0.45mg CEE; 1.5mg/day with 0.45 and 0.3mg CEE). While mean changes in BMD was positive in all groups, there a slight but not significant smaller effect at lower doses. However,

| | Placebo | PremPro |
|------------------------------|---------|---------|
| Hip Fractures | 62 | 44 |
| Vertebral Fractures* | 60 | 41 |
| Other Osteoporotic Fractures | 701 | 579 |
| *Clinical Fractures | | |

examining the proportion of individuals who did not lose bone confirmed the same response rate at each dose, with response rates roughly equivalent to those seen in the Progestin Estrogen Prevention Intervention study (PEPI).¹⁶ Furthermore, the reductions in bone remodeling were

| | Relative risk* (95%CI) |
|------------------------------|------------------------|
| Hip Fractures | 0.66 (0.45-0.98) |
| Vertebral Fractures* | 0.66 (0.44-0.98) |
| Other Osteoporotic Fractures | 0.77 (0.69-0.86) |
| *Unadjusted | |

similar in all groups (slightly less in the 0.3mg CEE alone group). Reduction in remodeling rate is likely an important mechanism in the antifracture effect of antiresorptive agents, while mean BMD response accounts for only a fraction of the fracture efficacy. Thus, although we do not have fracture data with these lower doses of hormone therapy we would anticipate that should such a study be performed, it would also be positive.

Women who require hormone therapy for menopausal symptoms will also benefit

from protection of bone loss. This will persist as long as the patient takes the treatment. We know from several studies, dating back to the 1970s that when hormones are discontinued, bone loss begins.^{17,18} Termination of treatment with estrogen can be described as a medical menopause.

Whether bone loss is sufficiently accelerated to completely eliminate the estrogen effect on BMD, within a time frame of several years, can still be debated. Indeed whether there is a lingering fracture effect is also questionable, and some data clearly support a loss of fracture efficacy within

five to seven years after estrogens are discontinued, although some observational studies do indicate a fracture benefit from "ever use."^{19,20} Patients who discontinue hormone therapy will confront the question of what now, and will likely broach this with their health care providers. Some will neither want nor require other interventions. For others the judicious use of raloxifene

will afford skeletal protection and reduction in vertebral fracture risk, with other potential health care benefits and risks. For others the use of bone specific agents such as the bisphosphonates may be an option. However, before prescribing these, it is important for clinicians to evaluate fracture

risk in women discontinuing hormone therapy. Determination of bone density by dual x-ray absorptiometry (DXA) is the most common tool for this purpose. But treatment decisions using such bone specific agents, must not be based solely on BMD, since BMD is only one of several risk factors for fracture. As yet we have no generally accepted algorithm for determination of absolute

fracture risk for individual patients, and the outcome of the WHI hormone study perhaps increases the urgency for such a tool for the primary care physician.

Since our original observations, the scientific underpinnings of the estrogen effect on the skeleton have become significantly better understood.²¹ We now know that bone cells express estrogen receptors, that these receptors appear functional, and that biological responses can be observed in osteoblasts and probably also osteoclasts with estrogen exposure. In addition

other cells in marrow express estrogen receptors and may mediate local effects of estrogen (Figure 1). The discovery of the key regulatory mechanism for osteoclast development, RANK-ligand (receptor activation of NF- κ B) secreted primarily by osteoblasts, with its functional receptor RANK expressed on the surface of osteoclasts and their precursors, established a mechanism for the known interrelationship between bone formation and resorption. That RANK-ligand secretion and perhaps also the secretion of its decoy receptor osteoprotegerin may be controlled by estrogens, further supports the biology behind the skeletal effects of estrogen from both endogenous and exogenous sources.

One important remaining clinical question related to the other outcomes of this arm of WHI is whether we can improve the risk benefit equation for hormone therapy, and thereby continue to utilize hormonal therapy for prevention of osteoporosis. Several options for this can be hypothesized. Since, in WHI, the estrogen only study is continuing it is possible that the benefits and risks are different than those seen with combination therapy using MPA. However, that study has enrolled only about 10,000 individuals and is thus only about 60% of the size of the terminated HT study. Consequently, the benefits and risks may be similar, but the study size precludes achievement of significant outcomes at this stage. Time will answer that question. An alternative strategy might be to examine the effects of other estrogens and progestins or simply to lower the dose of estrogen and progestin used. Biological plausibility exists for this latter approach since it has been demonstrated that low levels of endogenous estradiol are biologically active, in postmenopausal women. Recent studies, that suggest we can reduce the

dose of estrogen given as intervention and effectively prevent bone loss, support the need for further investigation of these doses, and perhaps also other regimens and routes of administration to elicit

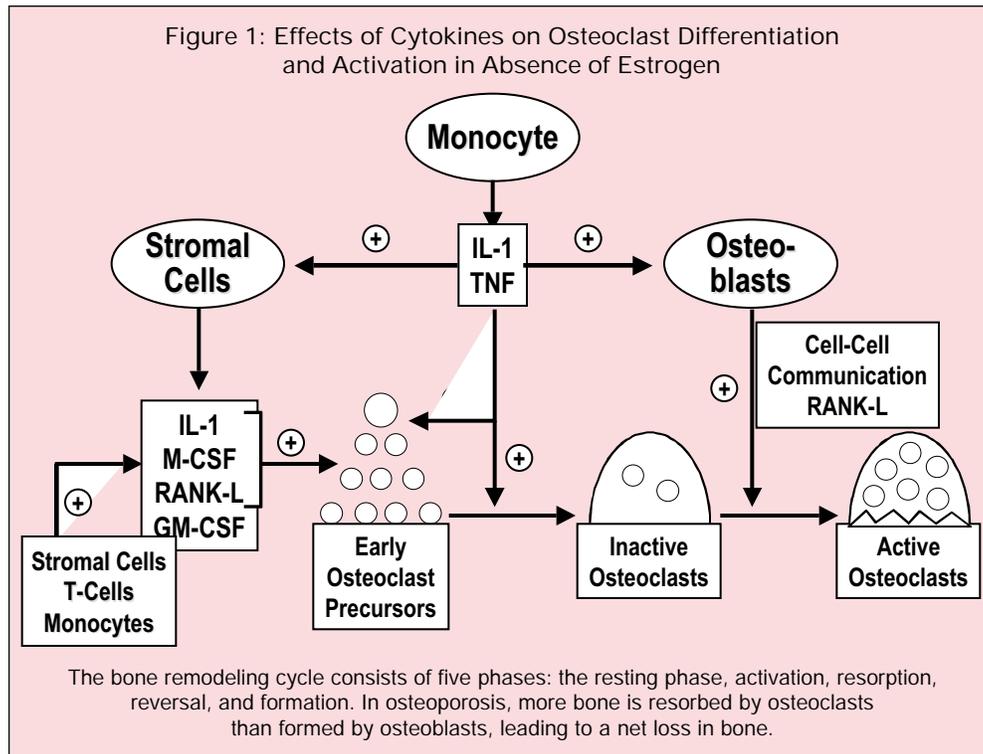
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whether or not there is an overall beneficial regimen of hormone therapy that can be used for disease prevention in the postmenopausal population. Regrettably, even if feasible, such studies are unlikely to be performed in the current environment.

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Prevention of Heart Disease – Beyond Hormone Replacement Therapy



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Obstetrician-gynecologists are among the most prevention-minded physicians. Our specialty incorporates cervical cancer screening, breast cancer screening, and contraception advice into our daily practices. We embraced the notion that hormone replacement therapy would not only treat symptoms of the menopause, but also prevent cardiovascular diseases so common in aging women. However, the early termination of the Women's Health Initiative (WHI) study has contradicted the numerous observational studies suggesting that hormone replacement therapy (HRT) could prevent cardiovascular disease. Numerous professional organizations including the American Society of Reproductive Medicine, the American Heart Association and the American College of Obstetricians and Gynecologists have recommended against HRT use solely for protection against cardiovascular diseases. We are now faced with patients who often started or continued HRT to prevent cardiac disease. Developing a clear and consistent message for these women and others who are currently perimenopausal about the prevention of cardiovascular diseases is the focus of this article.

Coronary heart disease (CHD) and stroke constitute the number one cause of mortality for women over the age of 50, accounting for more deaths, annually than combined cancer deaths. Over 50% of women can expect to die of cardiovascular disease (CHD or stroke) at current rates. Given the aging of the population, this problem is likely to grow. Data from a Mayo Clinic study suggest that incidence of myocardial infarction in men has gradually declined since 1979, but the incidence has increased by 35% in women.¹ The authors attribute the decline among men to effective CHD prevention programs. Moreover, these programs and the large-scale studies on which they are based have historically been geared primarily or exclusively toward men.

This has resulted in a lack of public awareness about the importance of heart disease in women. Women continue to be far more aware of the problem of breast cancer than that of heart disease. A recent survey of 73 popular general interest and women's magazines over the past decade found 286 articles about breast cancer and only 109 about heart disease.² Studies suggest that physicians have not done enough to help raise awareness of heart disease. The National Ambulatory Medical Care Survey of almost 550 million physician office visits in 1995, showed that obstetrician-gynecologists were 25% less likely than internists to provide cardiovascular disease prevention services such as blood pressure measurement, lipid screening and counseling about smoking cessation and weight loss, where appropriate.³ Obstetrician-gynecologists are frequently the only physicians women see. Thus, it behooves us to understand the basis for current recommendations for prevention of cardiovascular disease and stroke and to incorporate risk assessment for these diseases into our practices as an important contribution to disease prevention.

LIFESTYLE MODIFICATIONS

The behavioral changes listed in Table 1 can have a dramatic effect on the risk of CHD. Observational studies consistently show a strong association between healthy lifestyles and low risk of CHD and stroke. The women in the Nurses Health Study at lowest risk for CHD were those who maintained their body weight, exercised regularly, watched their diet, consumed moderate amounts of alcohol, and avoided tobacco. In fact, these five

behaviors accounted for a remarkable 84% reduction in risk. Unfortunately only 3% of the study population belonged to the group with all five healthy behaviors, but each of these behaviors can work independently to reduce CHD risk and should be encouraged as part of a prescription for preventing heart disease.⁴

Tobacco

Cigarette smoking has consistently been shown to increase risk of CHD in a dose-dependent, duration-dependent fashion. Risk of coronary events was two- to three-fold higher for current smokers of at least half-pack per day of cigarettes, in the Nurses Health Study. It is then no surprise that exposure to secondhand smoke also increases risk of CHD. According to the third National Health And Examination Survey (NHANES), some 37% of non-smokers are exposed to secondhand tobacco smoke.⁵ Of the 53,000 annual deaths caused by passive smoking, as many as 37,000 can be attributed to CHD. Counseling about tobacco intake should therefore include information about secondhand smoke. That such counseling would be effective is suggested by a meta-analysis of 16 trials comparing brief advice to usual care showed that smokers who were counseled to quit by their physicians were 70% more likely to quit than the control group.⁶

Exercise

Physical activity is important in the maintenance of body weight, normal glucose and fat metabolism, and overall cardiovascular health. Physical inactivity (< 1.0 hour per week) was associated with a 41% increase in risk of coronary events in the Nurses Health Study.⁴ Among some 73,000 women enrolled in the observational arm of the WHI, an increasing physical-activity score had a strong, graded, inverse association with the risk of both coronary events and total cardiovascular events, regardless of body mass index (BMI) or age.⁷

Studies of exercise training have shown a consistent impact on CHD and several of its major risk factors: obesity, hyperlipidemia, hypertension, and glucose intolerance. Although most data come from studies of men, studies of women with coronary disease also show increased survival and improved functioning in those who adhere to an exercise program.⁸ In a meta-analysis of 26 studies of randomized controlled trials of aerobic exer-

cise in over 1,500 subjects (normotensive and hypertensive), there was a mean reduction of systolic blood pressure (SBP) of 4.7 mm Hg and diastolic decrease of 3.1 mm Hg.⁹ Exercise was effective in lowering the risk of developing type 2 diabetes in randomized clinical trials¹⁰ of individuals with impaired glucose toler-

ance. Improvements in the lipoprotein profile have been demonstrated with even moderate to low intensity exercise, such as walking.^{11,12} In a study of overweight or mildly obese men and women, aged 50-65, these improvements (reduced low-density lipoproteins [LDL], increased high-density lipoproteins [HDL], reduced triglycerides)

occurred without weight loss.¹² The cardiovascular benefits of exercise are thus well recognized.

Diet

Women with a “healthy diet” are least likely to develop CHD. What constitutes a healthy diet? The third Report of the

Table 1: Guide to Lifestyle Intervention for Coronary Heart Disease Primary Prevention (CHD)

| Lifestyle Factors | Goals | Routine Screening | Recommendations |
|-------------------|--|--|--|
| Tobacco | <ol style="list-style-type: none"> 1. Complete cessation 2. Avoid second hand exposure | <ol style="list-style-type: none"> 1. Take a history of smoking status, duration of exposure 2. Assess willingness to stop | <ol style="list-style-type: none"> 1. Encourage cessation or reduction 2. Provide support: medication, counseling, referral to formal program |
| Physical activity | Minimum of 30 minutes of moderate intensity activity most days | <ol style="list-style-type: none"> 1. Ask about physical activity (leisure, occupational, home) 2. Consider stress test for >50 yrs old with >2 risk factors | <ol style="list-style-type: none"> 1. Encourage daily moderate intensity exercise (e.g. brisk walking) 2. Vigorous intensity exercise, resistance and flexibility training should complement #1 3. Incorporate more activity into daily routine (use stairs, etc) |
| Diet | Overall healthy eating habits | <ol style="list-style-type: none"> 1. Assess nutrition routinely 2. Consider referral for women with hyperlipidemia, diabetes, obesity or hypertension | <ol style="list-style-type: none"> 1. Balance caloric intake with energy needs to achieve desired weight 2. Fats: saturated <7% of total calories; <300 mg cholesterol, less trans-fatty acids, polyunsaturated fats <10% of calories, monounsaturated <20% calories 3. Salt < 6 gm/day 4. Alcohol <1 drink daily 5. Fruits and veggies >5/day |
| Weight management | <ol style="list-style-type: none"> 1. BMI: 18.5-24.9 2. Waist circumference < 35 inches | <ol style="list-style-type: none"> 1. Record height and weight, calculate BMI 2. Measure waist circumference | Encourage caloric restriction and increased activity to reduce weight by 10% in first year |

National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III, or ATP III) concluded that a diet rich in fruits, vegetables, whole grains, and unsaturated fatty acids confers a lower risk of CHD.¹³ While all specific nutrients necessary for protection against CHD are likely yet to be defined, those that appear likely to be important based on current data include: antioxidants, folate and other B vitamins and omega-3 fatty acids.¹⁴ A prospective study of over 69,000 nurses showed a 24% reduction in risk of CHD for those women with the greatest intake of fruits, vegetables, legumes, fish, poultry, and whole grains (corrected for other known risk factors for CHD).¹⁵ The Lyon Heart Trial was associated with a 60% reduction in CHD mortality through the so-called Mediterranean Diet.¹³ Consumption of this type of diet has also been linked to lower insulin levels, lower tissue plasminogen activator levels and decreased risk of stroke. Similar findings were noted in a study of over 34,000 postmenopausal women in Iowa, where there was an inverse relationship between whole grain consumption and death from ischemic heart disease.¹⁶

The type and amount of dietary fat consumed has received renewed

attention. In general, current American Heart Association guidelines call for limiting the proportion of calories obtained from fat to 25% to 35% with 7% or less of total calories from saturated fat.¹⁴ More stringent recommendations are made for those with known elevations in their LDL cholesterol or existing CHD. Diets rich in trans fatty acid can increase circulating LDL levels and reduce HDL levels. In contrast, the consumption of polyunsaturated or monounsaturated fat, can lower LDL and triglyceride levels and protect HDL levels.¹⁴ Eating fish and omega-3 fatty acids appears to protect against cardiac disease, with a relative risk of 0.45 for

CHD mortality among those who reported intake at least five days per week.¹⁷ Consumption of nuts, rich in monounsaturated fats, has also been linked to lower risk of cardiac disease in several large cohort stud-

Table 2: Summary of Diagnosis of Hypertension

| Blood pressure, mmHg | Classification |
|----------------------|----------------------|
| <120/<80 | Normal |
| 120-139/80-89 | Prehypertension |
| 140-159/90-99 | Stage 1 hypertension |
| >160/>100 | Stage 2 hypertension |

Adapted from Joint National Commission on Prevention Detection Evaluation and Treatment of High Blood Pressure report.²⁴

ies. The Iowa Women's Health Study showed a decrease in all-cause mortality among those who consumed at least two servings of nuts weekly.¹⁸ The American Heart Association and other professional organizations have called upon the food industry to provide more extensive labeling to help consumers make better choices.

Table 3: Criteria for Diagnosis of Diabetes or Impaired Glucose Tolerance (IGT)

| Normoglycemia | Impaired Glucose Tolerance | Diabetes |
|---|--|---|
| FPG <110 mg/dl 2hr PG _i ≤ 139 mg/dl * | FPG 110 mg/dl-125 mg/dl 2 hr PG* >139 and < 200 mg/dl | FPG>125 mg/dl 1. 2- hr PG ≥ 200 mg/dl 2. Symptoms of diabetes and random glucose ≥200 mg/dl |

*75 gm OGTT

FPG= fasting plasma glucose

Adapted: American Diabetes Association³⁶

Weight control

Obesity has reached epidemic proportions in the United States, with an estimated 97 million overweight or obese adults.¹⁹ Obesity is associated with several comorbid conditions that can contribute to an increased risk of CHD: hypertension, dyslipidemia, diabetes, and thrombophilia.¹⁹ Patients who are able to incorporate more physical activity into their daily routine are more likely to maintain modest weight reduction, which is often accompanied by reduction in SBP and improved lipoprotein profile. In the Framingham Heart Study, even a weight loss of 5 lbs. was associated with a reduction in CHD risk.²⁰

In a prospective study of risk factors for cancer, obese women who intentionally lost weight had a 30% to 40% decrease in diabetes related mortality.²¹ While obesity is associated with several major risk factors for CHD: hypertension, dyslipidemia, diabetes, it is important to recognize that it is also an independent risk factor for CHD and stroke.²² As with other lifestyle factors, encouraging a healthy diet and physical exercise may help provide the impetus for weight loss.

BLOOD PRESSURE

Elevated blood pressure is a well-recognized risk factor for CHD and stroke.¹⁹ Fortunately, age specific prevalence rates of hypertension have declined among American women. However, it remains an undertreated disease for an estimated 70% of hypertensive adults.¹⁹ Considering that 95% of hypertensive adults have additional risk factors for CHD, this is critically important.²³ Insulin resistance is present in an estimated 50% of women with hypertension. Obesity and type 2 diabetes are also common. Treatment of hypertension reduces the risk of CHD by 14% to 25% and stroke by 35% to 40% in large randomized trials.¹⁹

The most recent Joint National Commission on Prevention Detection Evaluation and Treatment of High Blood Pressure report (JNC-7) issued guidelines for diagnosis and treatment of hypertension, which stratify the risks associated with elevated blood pressure for different populations of patients (Table 2).²⁴ The JNC-7 report defined optimal blood pressure parameters: up to 120 mm Hg for the SBP and up to 80 mm Hg for the diastolic blood pressure (DBP). A new classification was created, pre-hypertension, to describe those at increased risk of developing hypertension, who should be educated about their risk and the importance of lifestyle modification (weight reduction, limited alcohol and sodium consumption, and increased exercise). If a compelling disorder is present,

those with prehypertension should be treated.²⁴ Diabetes, CHD, renal disease, or stroke constitute compelling conditions that merit a lower threshold for pharmacotherapy. If the SBP and DBP fall into disparate categories, the higher category should be used to determine clinical management.

Various randomized clinical trials of lifestyle modifications in high-risk individuals have shown that diet, exercise, and weight loss can delay the onset of hypertension or lessen its severity.²⁴ People who are sedentary have a 20% to 50% increased chance of developing hypertension, compared to more active individuals.²⁴ The DASH studies have explored the use of diets rich in fruits and vegetables and low in saturated fats to reduce hypertension.²⁵ In a three-year, randomized clinical trial of 841 individuals with high normal blood pressure, counseling about caloric restriction, sodium restriction, increasing dietary potassium or any combination of these, reduced the incidence of hypertension.²⁶ A more recent 48-month trial of over 2,000 overweight men and women with high normal blood pressure also compared usual care to weight loss intervention, sodium restriction, or a combination of weight loss and sodium restriction. This trial showed an 18% to 22% reduction in the incidence of hypertension among the active intervention groups, despite the high rate of recidivism in the weight loss group.²⁷

LIPID PROFILE

The importance of lipoprotein subfractions has been well established as a risk factor for CHD. Early emphasis on total cholesterol content has largely shifted to lipoprotein composition. Low-density lipoproteins (LDL) have been identified as the most atherogenic lipoproteins through various observational studies, animal data and clinical trials. Low-density lipoproteins contribute to the development of fatty streaks early in atherogenesis, and later in life LDL plays a role in coronary plaque instability. Erosion or rupture of plaques can cause myocardial ischemia.¹³ Genetic studies in which families have marked elevations of LDL show that these individuals tend to develop early and accelerated CHD, in the absence of other risk factors.¹³ The Framingham Heart Study showed that

elevations in LDL increased the risk of development of CHD by 24% to 68%.²⁸ Clinical trials of lipid-lowering medications or lifestyle modifications to lower LDL have shown a concomitant lowering of CHD risk with lower LDL.^{13,19} Recommendations for primary prevention include stratification of risk according to LDL level and the presence of other risk factors: age, smoking, family history of early CHD, hypertension, and low HDL levels.^{29,30}

Elevated serum triglyceride levels are being examined as a second important risk

Table 4: Risk Factors for Type 2 Diabetes

- Smoking
- Hypertension (treated or untreated)
- Family History
- Low HDL
- Overweight or Obese
- Sedentary
- Racial Background (non-white)
- Gestational Diabetes or Macrosomic Infant
- Polycystic Ovary Syndrome

Adapted from the American Diabetes Association^{13,36}

factor for CHD in women. This has been a controversial subject because early epidemiological studies suggested that other factors, such as diabetes, obesity, and hypertension, could account for the observed increase in CHD risk.¹³ Further studies showed that adjustment for these risk factors reduced the association in men, but not in women. Overall, elevated serum triglycerides appear to be a more potent risk factor in women than in men.³¹ Experimental and clinical data suggest that triglyceride rich lipoprotein remnants are atherogenic, behaving like LDL.¹³ Meta-analyses of several prospective cohort studies have shown a relationship between triglycerides and CHD.³² Triglyceride lowering drugs can reduce the risk of CHD by a mean of 27% to 30%.^{13,32} Because of the strong association between obesity, sedentary lifestyle, smoking, and excessive alcohol intake, lifestyle modifications can frequently lower triglyceride levels and CHD risk. Unfortunately, no large clinical trials have been performed in women to evaluate the impact of triglyceride lowering on CHD risk. Nonetheless, the ATP III interpretation of the evidence supported the conclusion that greater importance be placed on triglycerides as a marker for CHD risk and that specific target levels of triglycerides be achieved.^{13, 29,30}

Low levels of HDL have consistently been recognized as a risk factor for CHD in both sexes. Some recent guidelines have emphasized the need for different target levels in men and women.^{29,30} The mechanism of its protective effect appears to be the promotion of reverse cholesterol transport in foam cells, and its anti-oxidant and anti-inflammatory action within atherosclerotic plaques.¹³ Epidemiological evidence suggests that it is the lipoprotein that correlates most highly with CHD risk in the elderly. However, these studies do not identify a threshold HDL level with respect to risk of CHD.^{13,28}

DIABETES – SCREENING AND CONTROL

More than 7 million people are known to have type 2 diabetes, about 6% of the population over age 45. Another 6% have the disorder, but it has not been detected. In addition, another 6% have impaired glucose tolerance. This common endocrinopathy increases the risk of CHD by a factor of two to four.³³ Diabetes appears to eliminate the advantage women have, relative to men, as to age of onset of CHD presentation. Indeed, women with diabetes have the same rates of CHD as non-diabetic men. A cross-sectional study of type 2 diabetics in Finland showed mortality rates from CHD among diabetics without known cardiac disease to be equivalent to the mortality rates in non-diabetics with a history of previous myocardial infarction.³³ Diabetic women in the Nurses Health Study, who had no evidence of CHD at baseline, had a relative risk of mortality from CHD of 3.12 during 20 years of follow-up, compared to non-diabetic women without CHD.³⁴ Diabetes can act through a variety of mechanisms to promote CHD. These include metabolic factors (greater fluxes of FFA, dyslipidemia), increased oxidation of lipids stimulating foam cells formation, endothelial dysfunction, greater production of growth factors and cytokines that promote arterial wall injury, and greater tendency toward prothrombotic state.¹³ As well, patients with type 2 diabetes frequently have other risk factors for CHD, such as hypertension and obesity. Aggressive management of hypertension and hyperlipidemia and probably hyperglycemia can reduce mortality in diabetics.¹³ Management of hypertension

Table 5: Guide to Risk Intervention for Primary Prevention of CHD
Adapted from American Heart Association 2002 guidelines²⁹

| Risk Factor | Goal | Screening at Routine Intervals | Recommendations |
|-----------------------------|--|--|--|
| Blood Pressure | <ol style="list-style-type: none"> 1. Identify and treat hypertension (>140/90 mm/Hg) 2. Prevent clinical hypertension in patients with high normal BP (130-139/85-89 mm/Hg) | <ol style="list-style-type: none"> 1. Patients should rest for five minutes and refrain from smoking or caffeine ingestion for 30 minutes before measurement 2. Use appropriate sized cuff | <ol style="list-style-type: none"> 1. Lifestyle changes (Table 1) 2. Adequate intake of potassium (90 mmol daily) and calcium 3. Limit alcohol < 0.5oz (15ml) daily 4. Medication initially for high risk group or as secondary therapy if lifestyle changes fail for lower risk patients (see above) |
| Lipoproteins ³⁹ | <ol style="list-style-type: none"> 1. LDL <100-160 mg/dl (depending on other risk factors) 2. *Triglycerides <150mg/dl 3. *HDL>50 mg/dl <p>*Desirable levels</p> | <ol style="list-style-type: none"> 1. Fasting lipoprotein profile every 5 yrs (minimum) starting age 20 2. R/O secondary causes of hyperlipidemia (TSH, liver function test, U/A) 3. Set target for lipoprotein levels based on risk assessment (see text)³⁹ | <ol style="list-style-type: none"> 1.If LDL is > goal, start lifestyle changes 2. Consider medication after 12 wks if: <ol style="list-style-type: none"> a. 10-yr risk is >20% and LDL is >130 mg/dl b. <1 risk factor and LDL is >190 mg/dl |
| Diabetes | <ol style="list-style-type: none"> 1.Normal fasting glucose 2. Near normal glycosylated hemoglobin (<7.0%) | <ol style="list-style-type: none"> 1. Every three years starting at age 45 if low risk 2. Every two years or as clinically indicated for higher risk groups (table 4) | <ol style="list-style-type: none"> 1. American Diabetes Association diet 2. Oral hypoglycemic agents or insulin as indicated 3. More aggressive treatment of other CHD risk factors (e.g. BP, lipids) |
| Chronic Atrial Fibrillation | Normal sinus rhythm (NSR) | Check pulse for irregularities | <ol style="list-style-type: none"> 1. ECG to verify pulse irregularities 2. Convert to NSR 3. Anticoagulation for chronic or intermittent fib |
| Aspirin Use | Low dose ASA, if 10 yr. CHD risk >10% | Calculate 10 yr risk of CHD if age >40 yrs | <ol style="list-style-type: none"> 1. 75-160mg ASA, if risk >10% 2. Contraindicated if history of GI bleeding or hemorrhagic stroke |

was associated with a 32% reduction in CHD and stroke mortality.³⁵ Control of blood glucose can prevent many of the serious vascular complications of diabetes, including retinopathy and nephropathy.

Thus, early identification of those with type 2 diabetes or impaired glucose tolerance can prevent many of the complications of the disease. Current criteria for the diagnosis of diabetes are shown in Table 2.³⁶ The American Diabetes Association recommends screening for type 2 diabetes at least every three years, starting at age 45 (Table 5). Women at increased risk for diabetes (Table 4) should be screened more frequently.³⁶ Of note, many of these patients are most likely to be seen by their obstetrician-gynecologist before their internist or family physician.

METABOLIC SYNDROME

One of the secondary targets for CHD prevention is identification and treatment of the metabolic syndrome. To diagnose the metabolic syndrome, a patient must meet a minimum of three criteria:

1. abdominal obesity (waist circumference >35 inches).
2. Triglycerides >150 mg/dl.
3. HDL cholesterol <50 mg/dl in women.
4. High normal or elevated blood pressure.
5. Fasting plasma glucose > 110 mg/dl.

The NHANES-III data estimate the prevalence of metabolic syndrome to be 25% in American adults, with even higher levels in African American and Hispanic women. Epidemiologic data suggest that clustering of symptoms suggestive of insulin resistance are strongly associated with an increased risk of CHD. Clustering of three or more risk factors for CHD, including obesity was present in 17% of men and women in the Framingham database and accounted for 48% of CHD. Although these individuals were not assessed for insulin resistance or abdominal obesity, per se, these data emphasize the importance of a total metabolic picture in causing CHD.²⁰ Several studies suggest that acquired factors such as obesity or physical inactivity can interact with a genetic predisposition to bring about insulin resistance in some individuals.¹³

Women with polycystic ovarian syndrome (PCOS) exhibit several of the features of the metabolic syndrome. Obesity, particularly centrally deposited, is common among women with PCOS. Cohort studies of women PCOS suggest that 20%

to 30 % develop impaired glucose tolerance or type 2 diabetes.³⁷ Even younger, reproductive aged women with PCOS commonly have elevations in their triglycerides and low levels of HDL.³⁸ Clearly, screening for CHD risk factors and counseling about primary prevention are indicated for this population.

CHD: RISK ASSESSMENT TOOLS

Current American Heart Association guidelines call for assessment of risk for CHD starting at 20 years of age. The purpose of risk assessment is to identify modifiable CHD risk factors and to determine intensity of treatment. Those individuals at greatest risk should receive the greatest intensity of intervention and monitoring. The Framingham database is widely advocated, but does not necessarily apply to a multiethnic population.^{28, 29} The Adult Treatment Panel (ATP) recommendations use a simple risk assessment system (Table 5).¹³ Use of this system can help guide clinicians in establishing targets for LDL lowering. For women with 0-1 risk factors, the LDL should be less than 160 mg/dl. If there are two or more risk factors present, the LDL should be less than 130 mg/dl, and if any atherosclerotic disease or diabetes is present, the LDL level should be <100 mg/dl.

Absolute risk of CHD can also be easily calculated. The American Heart Association Web site, www.americanheart.org, features an interactive tool for patients or physicians to determine CHD risk over 10 years. Use of this tool can help in recommendations for aspirin use (Table 6) or as an alternative to the ATP-III risk assessment system.^{13,29} Whichever tool is used, it is important to update it annually (including family history) at routine visits.

EMPOWER THE PATIENT

Clearly, much of the impetus to adopt lifestyle changes must come from the patient, who may or may not be ready to hear a message about change. For those in the pre-contemplative stage, especially the younger reproductive age patient, brief messages designed to plant the seed of awareness are most appropriate. For perimenopausal and menopausal women, a more focused message is likely to be effective, as these women are closer to the age where CHD is more prevalent. Fortunately, there are numerous patient education supplements available. The American Heart Association's Web site, [\[move.org\]\(http://move.org\) includes information on cardiovascular diseases, health and fitness, and diet \(including recipes\) for the family. The American College of Obstetrician Gynecologists publishes several pamphlets on heart disease, nutrition, and diabetes that are written at a basic level. The Endocrine Society Web page \(\[www.endo-society.org\]\(http://www.endo-society.org\)\) includes information about cholesterol levels, obesity, and type 2 diabetes.](http://www.chooseto-</p></div><div data-bbox=)

SUMMARY

Cardiovascular diseases constitute the major cause of mortality for postmenopausal women, but current evidence suggests many of these events are preventable. Reminders about smoking cessation, diet, exercise, and weight gain should be incorporated into the routine annual exam. Screening recommendations for dyslipidemia, diabetes, and hypertension should be followed. While they are clearly not preventable with hormone replacement therapy, cardiovascular diseases can often be prevented by adoption of a healthy lifestyle.

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Dr. Pearson as revealed the following potential conflicts of interest: Research Consultant AstraZeneca, Johnson & Johnson – Merck, Kos Pharmaceuticals, Bristol-Myers Squibb, and Lifeline Technologies.

Dr. Archers column continued from page 1

These data would argue for an indefinite utilization of hormone therapy to prevent bone loss in at-risk individuals. The improvement in bone density with lower doses of estrogen and progesterin is an important finding in our move to enhance positive outcomes and minimize adverse events in HT users.⁶

The issue of cardiovascular disease, and specifically coronary heart disease, continues to be contentious. I believe that it is important that all physicians and healthcare providers are aware of the fact that there are differences in the interpretation of the outcomes of all clinical trials. It should be pointed out that the recent publication from the WHI finds that there is no significant increase in the incidence of coronary heart disease in postmenopausal women on hormone therapy.¹ These data are now distinctly different from the interim publication in 2002, which was interpreted as finding an increase in the occurrence of coronary heart disease in hormone therapy users.^{2, 7} The WHI final report is similar to the Heart and Estrogen/Progesterin Replacement Study (HERS), demonstrating an increase in the incidence of coronary heart disease in the first year after initiation of hormone therapy in an older group of women.¹ This is followed by a subsequent reduction in the relative hazard of coronary heart disease over the next several years.

The HT arm of the WHI has not shown prevention of coronary heart disease, but it is obvious that, except for the first year, there is no evidence of increase in the incidence of coronary heart disease. It should be noted that the overall mortality from coronary heart disease is not different between the hormone therapy and placebo groups.¹

Because of the concerns raised in the WHI publications of 2002 and 2003, we are pleased to have Vivian Lewis, M.D., and Thomas A. Pearson, M.D., M.P.H., Ph.D., provide us with a comprehensive article on behavior modification and the prevention of heart disease. Drs. Lewis and Pearson identify for each modification a significant reduction in the incidence of coronary heart disease. Perhaps the most important information provided is that of the American Heart Association Web site, www.americanheart.org, which has an interactive tool that can be used to determine coronary heart disease risk over the subsequent 10 years. One could estimate, by using this evaluation tool, that a 50-to 55-year-old woman with a cholesterol level between 200-240 mg/100 ml, a non-smoker, not hypertensive, and with a reasonable HDL level, has a 1 in 100 chance of having a coronary heart disease event in the

next 10 years of life. The low incidence of coronary heart disease in recently postmenopausal women would support the use of hormone therapy in them for symptoms.

As physicians and healthcare providers we need to take a positive approach to counseling our patients to change their lifestyle. We are in a position to make a significant impact on overall cardiovascular well being in postmenopausal women. This is important since it has been shown that physicians have difficulty applying research findings to their practice. There is evidence that the use of beta blockers, lowering cholesterol, and use of aspirin in individuals who have had a previous myocardial infarction are effective intervention modalities that reduce the risk of recurrent events. In reality, only 60% of primary care physicians prescribe beta blockers, 50% of patients who have had a myocardial infarction are not screened for cholesterol levels, and only a third of patients with coronary heart disease are being prescribed aspirin.⁸ These findings provide evidence that physicians are not applying known outcome data in their practices.

Non-therapeutic intervention such as lifestyle changes can have a significant impact upon cardiovascular disease. Drs. Lewis and Pearson point out that only

25% of obstetricians and gynecologists provided cardiovascular disease prevention services such as blood pressure measurement, lipid screening, and counseling about smoking cessation and weight loss. Healthcare providers must take these national recommendations and integrate them in their practices for women at all ages.

Healthcare providers today are faced with multiple counseling issues based on current data. The healthcare provider must spend increased time in counseling the postmenopausal woman. Counseling time is important because the consumer needs information that is accurate, reliable, and balanced, and it is the healthcare provider's responsibility to provide this information. He or she must also have an opinion for the patient based on her individual medical profile. Today's risk/benefit assessment should include both the judicious use of hormone therapy and behavior modification.

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Erratum

From the Editor: I received a note from Dr. Susan Hendrix regarding the article she and Dr. Ross Prentice had published in the Spring 2003 issue of *Menopausal Medicine*. Dr. Hendrix pointed out that "The second to last paragraph in our original (article) started with 'From one gynecologist's view (SH)' while the (printed) copy...says 'From my view.' Really, this is just my view as a gynecologist and not necessarily the view of Dr. Prentice." We regret the error.

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