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FOR CLINICIANS WHO PROVIDE CARE FOR WOMEN

Sequential Osteoporosis Treatment for Women with Postmenopausal Osteoporosis

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INTRODUCTION

The gynecologist is frequently the primary care provider responsible for treatment of women with established postmenopausal osteoporosis. Fortunately, there are now a number of effective and approved drug therapies available. There are good sources of information on the particular strengths and weaknesses of each drug[1-3] and there are guides to making an appropriate choice of therapy.[4,5] A frequently asked question is whether osteoporosis therapies should be used in combination. The purpose of this article is to show that, with rare exception, combining anti-resorptive osteoporosis therapies is not reasonable and could be potentially harmful. In addition to incurring greater costs, care providers who prescribe a second agent simultaneously will achieve little additional benefit for skeletal health, and could possibly increase the risk of fracture. For these reasons, I urge primary care providers to avoid combining anti-resorptive therapies, leaving such regimens to researchers or other osteoporosis experts. Instead, gynecologists treating women with osteoporosis should consider using osteoporosis therapies in sequence.

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HOW CURRENT OSTEOPOROSIS THERAPIES WORK

Currently approved drugs for treating osteoporosis include estrogens, bisphosphonates (such as alendronate), calcitonin, and raloxifene. All work by a similar mechanism; they depress the action of osteoclasts, bone cells that are responsible for bone breakdown (resorption), and ultimately for bone loss. We can measure this effect on bone breakdown using a variety of biochemical markers; most popular are urinary excretion of collagen cross-links and serum osteocalcin. Within a few months of starting treatment, anti-resorptive drugs slow bone breakdown 40% to 50%, and return this activity to pre-menopausal levels. However, it may take one to two years for a comparable slowing of bone formation to occur. During this phase of treatment when resorption and formation are not balanced, the bone resorption space gets a chance to fill in. The amount of available space varies with age and with estrogen status. In older women not on estrogen, it could be as large as 10% of the entire skeleton; in younger women or in those taking estrogen, it may be only 2% to 3%. In the few years after an older woman begins on a potent anti-resorptive drug (e.g., estrogen or bisphosphonate), spinal bone density will increase 6% to 8% and peripheral

FROM THE EDITOR

David F. Archer, M.D.

Dr. Bruce Ettinger presents an interesting concept, one of utilizing for maintenance of bone mineral density after a successful intervention a second medication that could have effects on organ systems other than bone. He discusses the clinical finding of plateauing or reduction in bone mineral density with continued treatment by anti-resorptive compounds. I would like to stress the importance of these concepts for the Health Care Provider.

Dr. Michael McClung shares his expertise in osteoporosis with us in this discussion of the utility of bone turnover markers for the evaluation and management of women with low bone mass and/or osteoporosis. Bone turnover markers are useful in monitoring response to therapy with bisphosphonates and hormones.

Drs. Suzanne Oparil and Stephen Bakir present the data on the use of estrogen/progestogen in women with hypertension. The message is clear that hormones appear to have a beneficial effect on blood pressure in normotensive and hypertensive postmenopausal women.

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bone density will increase about 3% to 4%. After this initial catch-up phase, bone resorption and formation are equally slowed; we see bone mass plateau for a year or so, and thereafter it declines at a small fraction of the rate observed prior to treatment. Most remarkably, within a year of starting treatment, substantial reductions in fracture risk can be demonstrated, usually in the order of 40% to 50% for spine fractures and about half this for non-spine fractures. The precise mechanisms responsible for fracture protection are not fully understood, but the effect is not simply a function of increased bone density. Most likely, protection is related to the combined effects of small increments in bone density, greater bone mineralization, and much lower bone turnover.

HOW MUCH ANTI-RESORPTION EFFECT IS REQUIRED?

In elderly women with osteoporosis, bone turnover is about twice that found in average premenopausal women. Studies of bone turnover markers in blood or urine indicate that anti-resorptive drugs differ in their abilities to suppress bone turnover; there is about a three-fold difference in effect from the weakest of these drugs (200IU nasal calcitonin, suppressing turnover about 15% to 20%) to the most potent (10mg alendronate, suppressing bone turnover about 50% to 60%). Some anti-resorptive drugs, for example estrogen, show a fairly linear dose response. Standard doses of estrogen (equivalent to 0.625mg conjugated estrogens) suppress turnover about 50%, while half this dosage suppresses turnover about 30%. Other anti-resorptive drugs show little dose effect; for example, raloxifene, a selective estrogen receptor modulator (SERM) recently approved for treatment of osteoporosis, reduces bone turnover about 35% when given in either 60mg or 120mg dosage, and alendronate reduces turnover by about half when either 5mg or 10mg dosage is given. The magnitude of these drugs' anti-resorptive effects is related to the increase they produce in bone density, but surprisingly, neither bone density change nor bone turnover change have much ability to predict the treatments' reduction in fracture risk. Thus, the pursuit of maximal drug effect may be fruitless. Using higher dosages or using very potent anti-resorptive drugs may not enhance the reduction of fracture risk.

SOME BONE TURNOVER IS REQUIRED FOR SKELETAL HEALTH

There are theoretical reasons to be concerned that excessive suppression of bone turnover may be harmful to skeletal health. Animal studies many years ago showed that high dosage bisphosphonate could produce a condition of near-complete suppression of bone turnover; in the language of bone experts, "frozen bones." These animals developed very brittle bones that fractured easily. We know that bone that has little or no capacity for resorption is unable to repair microscopic damage that is always occurring. Furthermore, the normal process of skeletal renewal is required to keep bone from aging and suffering fatigue fractures similar to the cracks that are observed over time in industrial materials that have worn out.

WHY HEALTH CARE PROVIDERS COMBINE ANTI-RESORPTIVE THERAPIES

In our experience, health care providers who prescribe combinations of anti-resorptive therapies do so for one of three common reasons: a belief that "more is better;" the belief that estrogen is not effective treatment for women with osteoporosis; or concern, based on bone density testing, that bone loss is occurring on a treatment. Let us examine each of these reasons and see their weaknesses.

The "More is Better" Fallacy

In large part, the belief that combining estrogen and alendronate doubles the skeletal effects is due to lack of knowledge that both these drugs work the same way on the skeleton. Prescribers are not aware that once a good anti-resorptive effect is obtained with one of these drugs, very little is obtained by adding a second anti-resorptive drug. Once the first drug fills in the potential resorption space in the skeleton, there is very little additional resorption space available for a second drug to fill. Lindsay and co-workers, in a multi-center clinical trial, examined the effect of adding alendronate to estrogen among 428 postmenopausal women who, on average, had been using hormone replacement therapy (HRT) nine years.[6] Half continued their usual HRT and were given calcium, while the other half continued HRT and also received alendronate 10mg/day as well as calcium. After one

year, alendronate addition resulted in only small gains in bone mineral density over simply continuing HRT. The differences were 2.6% in the spine and 0.9% in the femoral neck. Another study examined the skeletal effects of starting estrogen and alendronate simultaneously.[7] After one year, spinal density had increased, on average, 6% in women starting 0.625mg/day conjugated equine estrogens, 6% in those starting alendronate 10mg/day, and 8% in those receiving the combination of these two drugs. There were even smaller differences in the hip density changes between groups. On average, increases of 3%, 4%, and 5% were observed in these three groups, respectively. In this study, urinary cross-links, the most sensitive bone turnover biochemical marker, on average, was suppressed 52% and 61% by estrogen or by alendronate alone, and was decreased 70% among women receiving combined therapy. Thus, combined use of both drugs together did little more to suppress bone turnover or to increase bone density compared to either drug given alone. A recent one-year study examined the skeletal effects of beginning therapy with raloxifene 60mg/day alone, alendronate 10mg/day alone, and the two drugs in combination.[8] Similar to the estrogen-alendronate combination, raloxifene combined with alendronate did not substantially add to the bisphosphonate's bone effects. Those using combination therapy increased bone density at the spine and hip about 1% more than those using alendronate alone.

"Thus, combined use of both drugs together did little more to suppress bone turnover or to increase bone density compared to either drug given alone."

The Fallacy That Estrogen is Only for Preventing Osteoporosis, Not Treating It

In the past, it was commonly believed that estrogen was effective in preventing osteoporosis, and only if it was started within a few years of menopause. Now there are many studies showing that estrogen, given to older women, has quite salutary effects on bone density, bone turnover, and fracture risk – effects quite similar to alendronate's. Despite these new findings, estrogen is still widely considered to be a drug for preventing osteoporosis, coronary heart disease, and other diseases of aging, while alendronate is most often considered for treatment of established osteoporosis. The reticence to prescribe estrogen to treat elderly women with osteoporosis could also be in part due to advertising and the way physicians are detailed by company representatives of Wyeth-Ayerst and Merck. These companies have agreed to co-market Premarin® and Fosamax® non-competitively, positioning estrogen for prevention of various disorders and relieving symptoms, while promoting alendronate for treatment of older women who have osteoporosis.

The Fallacy of Bone Loss on Standard Treatment

Estrogen, alendronate, and raloxifene are all effective agents. A high proportion of women on these treatments will obtain skeletal protection.[9-12] Unfortunately, this fact is overlooked when physicians interpret the results of bone density monitoring. If a woman who has used one of these approved anti-resorptive drugs is found to have bone density somewhat below expected for her age, it is incorrect to conclude that she is losing bone and is a treatment failure. It is more likely that this woman has a low-normal bone density because she never achieved a normal skeletal density at maturity and that she is currently getting adequate bone protection. If lower than expected bone density is found in a patient receiving standard anti-resorptive therapy, measure a bone turnover marker. Typically, in such patients, collagen cross-links or osteocalcin will be in the lower one-third of the postmenopausal range, indicating a good treatment effect.

Using bone densitometry to monitor treatment effect can also be misleading. Again, because treatment failure is statistically unlikely and because densitometry machine precision is not ideal, the finding of decreasing bone density in patients taking effective treatment is usually spurious.[13] Therefore, clinicians should not change treatment (typically, by adding a second drug) on the basis of a single bone density result. In the vast majority of cases, measurement of a bone turnover marker will indicate a good treatment effect, and follow-up bone density will usually show excellent treatment results.[13] In the rare case in which bone turnover is not suppressed in a patient suspected of treatment failure, that patient should be referred to a bone specialist to have secondary causes of bone loss evaluated.

BONE-SPECIFIC VS. BROAD-SPECTRUM THERAPIES FOR OSTEOPOROSIS

Broad-spectrum therapies such as estrogen or raloxifene provide "health packages" that include lipid-lowering potential for reduction in risk of certain neoplasms (e.g., breast, colon) and possibly protection against other degenerative diseases of aging (e.g., coronary heart disease, Alzheimer's Disease, osteoarthritis). While some bone-specific drugs (e.g., alendronate) may have greater bone effects than broad-spectrum drugs (e.g., raloxifene), many postmenopausal women are in need of interventions for these other health concerns.

WHY USE SEQUENTIAL THERAPY?

Instead of combining osteoporosis treatments, prescribers should consider treating women with osteoporosis therapies in sequence. For example, the woman who has already suffered osteoporotic fractures has a very high risk of suffering new fractures in the near future (about 7% per year). Thus, these women require the "quick fix" that bisphosphonate therapy provides. Alendronate[9,10] and risedronate[14] each can reduce by half the risk of all fractures within a year or two. But if treatment is stopped, bone protection will wane rapidly. Once two years of bisphosphonate therapy has provided the "quick fix," I discuss with the patient her options for maintaining bone protection long-term. The patient could continue bisphosphonate therapy or switch to raloxifene (or estrogen) for bone mass maintenance as well as additional health benefits.

OTHER CONSIDERATIONS: ACCEPTANCE AND COST

Long-term drug therapy requires a high degree of patient acceptance that is predicated on the patient's perception that treatment benefits outweigh any risks, and that treatment is convenient, low in cost, and free of side-effects. If additional health benefits are important, then raloxifene or low-dosage estrogen may be more acceptable than a bone-specific drug. If the choice is for continuation of a bisphosphonate, then dosage can be

reduced by half, and providing this once a week (e.g., a single 40mg alendronate tablet every Sunday) adds to the convenience and reduces the cost considerably.

Using a treatment for three years that reduces fracture risk by 50%, to prevent one vertebral fracture, one would have to treat 13 older women who had one or more spine fractures, 63 older women without fracture, 50 younger women with spine fracture, and 250 younger women without fracture. Thus, using a $600 a year drug for three years, the cost per fracture prevented would be $23,400, $113,400, $90,000, and $450,000 for these four patient types. Generally, treatments that cost more than $40,000 to prevent an event are considered unreasonable use of our health resources. Thus, bone-specific drugs are warranted only for older women with fractures, or for those who have a similar high risk of fracture.

CONCLUSIONS: WHO GETS WHAT?

How should this information be incorporated into clinical practice? Prevention of osteoporosis in early postmenopausal women is best done by estrogen. Patients at low risk for fracture in the near future should not be given expensive bone-specific osteoporosis therapies. Among elderly women or those at high risk of fracture in the near future, bone-specific agents such as bisphosphonates would be the best choice, at least for a few years. Although bisphosphonates do not provide other health benefits such as improvement of the lipid profile or other attributes exhibited by estrogen and raloxifene, this therapy is appropriate for high-risk patients to quickly reduce fracture risk. A reasonable level of fracture risk that warrants bone-specific drug therapy is 5% to 7% per year. This is the level of risk observed in elderly women with vertebral fracture, women on high-dose corticosteroids, and women who have very low bone density plus multiple clinical risk factors.

Choosing the right single drug for the right woman involves assessment of short-term fracture risk and other non-skeletal health issues. While bone density may increase a bit more with two therapies, the added cost of the second agent does not result in twice the benefit. Health care providers should remain flexible about the choice of therapy and should consider sequential therapy to maximize health benefits.

Dr. Ettinger has revealed the following potential conflict of interest: Recipient of grant support and lecture honoraria from Eli Lilly, Merck, Proctor & Gamble, Aventis, Berlex, Novartis, and Solvay.

REFERENCES

1. Eastell R. Treatment of osteoporosis. *New Engl J Med*. 1998;338:736-746.
2. O'Connell M. Prevention and treatment of osteoporosis in the elderly. *Pharmacotherapy*. 1999;19:7S-20S.
3. Raisz LG. Osteoporosis: current approaches and future prospects in diagnosis, pathogenesis, and management. *J Bone Miner Metab*. 1999;17:79-89.
4. Ettinger B. Meeting the evolving therapeutic needs of postmenopausal women. *J Bone Miner Metab*. (in press).
5. Miller P, Lukert B, Broy S, et al. Management of postmenopausal osteoporosis for primary care. *Menopause*. 1998;5:123-131.
6. Lindsay R, Cosman F, Lobo RA, et al. Addition of alendronate to ongoing hormone replacement therapy in the treatment of osteoporosis: a randomized, controlled clinical trial. *J Clin Endocrinol Metab*. 1999;84:3076-3081.
7. Greenspan S, Bankhurst A, Bell N, et al. Effects of alendronate and estrogen, alone or in combination, on bone mass and turnover in postmenopausal osteoporosis. *Bone*. 1998;23 (suppl);174 (abstract).
8. Stock J, Johnell O, Scheele W, Lu Y, Lakshmanan M. Effects of raloxifene (RLX), alendronate (ALN), and RLX+ALN on bone mineral density and biochemical markers of bone turnover in postmenopausal women with osteoporosis. *Arthritis Rheum*. 1999;42 (suppl 9): (abstract 634).
9. Cauley JA, Seeley DG, Ensrud K, Ettinger B, Black D, Cummings SR, for the Study of Osteoporotic Fractures Research Group. Estrogen replacement therapy and fractures in older women. *Ann Intern Med*. 1995;122:9-16.
10. Black D, Cummings SR, Karpf DB, et al. Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures: Fracture Intervention Trial Research Group. *Lancet*. 1996;348:1535-1541.
11. Cummings SR, Black D, Thompson DE, et al. Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures. *JAMA*. 1998;280:2077-2082.
12. Ettinger B, Black DM, Mitlak BH, et al. Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene. Results from a 3-year randomized clinical trial. *JAMA*. 1999;282:637-645.
13. Cummings SR, Palermo L, Browner A, et al. Regression to the mean in clinical practice: women who seem to lose bone density during treatment for osteoporosis usually gain if treatment is continued. *JAMA*. (in press).
14. Harris S, Watts NB, Genant H, et al. Effects of risedronate treatment on vertebral and non-vertebral fractures in women with postmenopausal osteoporosis. *JAMA*. 1999; 282:1344-1352.

The Use Of Bone Turnover Markers In Clinical Practice: What They Can And Cannot Do

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INTRODUCTION

In the past few years, new highly sensitive and very specific biochemical tests have become available to assess the metabolic activity of bone remodeling.[1] These bone turnover markers (BTMs) have proven to be powerful tools in large clinical trials and have sharpened our understanding of the pathophysiology of postmenopausal and age-related bone loss. Their use has taught us much about the mechanisms of how various diseases and pharmacological intervention affects skeletal metabolism. They have even been used to select doses of antiresorptive agents for clinical trials. Several of these assays have received FDA clearance for use in clinical practice (Table 1). This review will discuss the rationale for the use of BTMs and will focus on their practical use in patient assessment and management, based on factual observations and experience in clinical trials.

BONE REMODELING, BONE MASS, AND BONE STRENGTH

In adults, bone tissue is constantly being broken down and remade by a process called bone remodeling or bone turnover. This occurs as a tightly linked and coupled interplay between osteoclasts (bone resorbing cells) and osteoblasts (bone forming cells). The exact mechanisms by which the activities of these two sets of cells are coordinated are just beginning to be understood. The remodeling activity occurs on the surface of trabecular bone and on the inner surface or, to a lesser extent, within the solid mass of cortical bone. Although cortical bone comprises about 80% of our total skeletal tissue (vs. 20% for trabecular bone), most of the

bone remodeling activity occurs in trabecular bone. In young adults, approximately 20% of our skeletal mass is remodeled each year. Because the rate of bone resorption is matched by the subsequent amount of bone formed, no net change occurs in bone mass as a consequence of bone remodeling in premenopausal women before perimenopause.

The bone loss that occurs as a result of both estrogen deficiency and aging is due to a bone remodeling imbalance. At the time of menopause, rates of bone remodeling increase about two-fold in response to estrogen deficiency. The number of specific sites engaged in bone remodeling increases substantially, and the cellular activity at each of these sites also increases. Both bone resorption and bone formation rates increase, but the relationship between these two arms of the bone remodeling process becomes unbalanced, with bone resorption exceeding bone formation. This results in a small net deficit at each of the bone remodeling sites, and that translates into bone loss, especially at sites rich in trabecular bone such as the spine. Recent studies have documented that the increased rate of bone turnover persists for many years after menopause and even increases further in the very elderly, in part due to subclinical vitamin D deficiency and secondary hyperparathyroidism.[2] This imbalance in bone remodeling contributes to increased fracture risk in two ways: progressive bone loss and deterioration in bone quality.

Therapy is currently available for the prevention of bone loss in young postmenopausal women or to decrease fractures in patients with osteoporosis. All of the drugs available (estrogen, SERMs, bisphosphonates, calcitonin) are anti-remodeling agents. Potent drugs like estrogen and bisphosphonates suppress bone turnover to or below the middle of the normal premenopausal range.[3-9] These agents initially decrease bone resorption, occurring within one month after beginning bisphosphonate therapy and within three to six months after estrogen treatment. Bone formation is indirectly suppressed, and formation markers fall more slowly, reaching a steady state between six and 12 months with bisphosphonate therapy. With estrogen therapy, there is a somewhat slower response with the full effect on resorption and formation markers being seen between six and 12 months. As a consequence of the magnitude and timing of these effects, bone mass increases during the first year or two of treatment with anti-remodeling agents. The increase in bone mass is not due to an increase in bone formation, but rather to the temporal dissociation in bone turnover such that bone resorption is suppressed more quickly than bone formation. Thus, the changes in bone density that occur with aging and in response to therapy are explicable on the basis of our understanding of bone remodeling and how it is influenced by sex steroids, calcium-regulating hormones, and pharmacologic agents.

WHAT ARE BONE TURNOVER MARKERS?

BTMs are chemical entities found in urine or serum that reflect but do not regulate the metabolic activity of the skeleton. Parathyroid hormone and vitamin D metabolites are not BTMs because they directly influence the bone metabolism. BTMs are either enzymes or structural proteins secreted by bone cells or are biochemical products released by osteoclastic resorption of bone matrix. Markers can be thought of as indices of either bone formation or bone resorption (Table 1). However, in a steady state, markers of both resorption and formation reflect the overall rate of bone turnover. Current tests cannot define the exact bone turnover balance in individual patients.

The information provided by BTMs differs substantially from that acquired by measurement of bone mineral density (BMD). BTMs assess current skeletal metabolism while BMD is influenced by skeletal changes occurring over a lifetime. BTMs reflect the bone metabolism in the entire skeleton, and regional or focal differences in remodeling activity cannot be assessed biochemically. Additionally, BTMs reflect the status of bone turnover at the time the samples are collected but provide no information about prior or future bone remodeling rates. In contrast, BMD testing assesses the state of a specific regional skeletal site (e.g., spine, femur, forearm, heel) or total skeletal mass (total body BMD). Also, a single BMD measurement integrates the effects of peak bone mass and subsequent bone loss. Thus, BTMs and BMD data are complementary and cannot substitute for each other.

CAVEATS OF BMT MEASUREMENT

All markers of bone turnover are increased at night, reaching a peak in early morning hours and then falling to much lower values in the afternoon.[10] This circadian variation in marker levels is nearly as great as the changes in BTMs with osteoporosis drug treatment. Consequently, samples for BTMs must be collected at the same time of day (usually a second morning urine sample or an early morning blood sample), especially when attempts are made to follow serial changes in marker levels. After a fracture, BTMs may be elevated for several months. The validity of BTM tests has not been evaluated in patients with impaired renal function. Marker assays vary among laboratories, making it important for all samples for a given patient to be sent to the same laboratory to maximize consistency of results.

POTENTIAL USES OF BTMS

Measuring rates of bone turnover, in principle, could be useful in evaluating the following clinical issues: predicting frac-

Table 1. Biochemical Markers of Bone Turnover

Markers of Bone Formation	Markers of Bone Resorption
*Serum bone-specific alkaline phosphatase +	*Urinary pyridinoline or deoxypyridinoline +
Serum osteocalcin	Urinary type I collagen degradation products
Serum procollagen I extension peptides	*N-telopeptide +
C-terminal	*C-telopeptide
N-terminal	Urinary hydroxyproline
	Urinary hydroxylysine glucuronide
	Serum pyridinoline or deoxypyridinoline
	Serum type I collagen degradation products
	*N-telopeptide
	C-telopeptide
	Serum tartrate-resistant acid phosphatase

* Tests approved for clinical use + Tests readily available through local or reference laboratories

ture risk, predicting bone loss, predicting response to treatment, selecting an osteoporosis drug, monitoring response to therapy, and influencing adherence to therapy. BTMs cannot be used to diagnose osteoporosis, predict a person's current bone density, differentiate among different causes of low bone mass, or determine who should be treated.

PREDICTING FRACTURE RISK

In a population of elderly women, those with the highest levels of BTMs are at increased risk for fracture, and those with both low BMD and high turnover markers are at exceptionally high risk.[11] It is not clear whether this information aids in determining which patients should receive pharmacologic therapy.

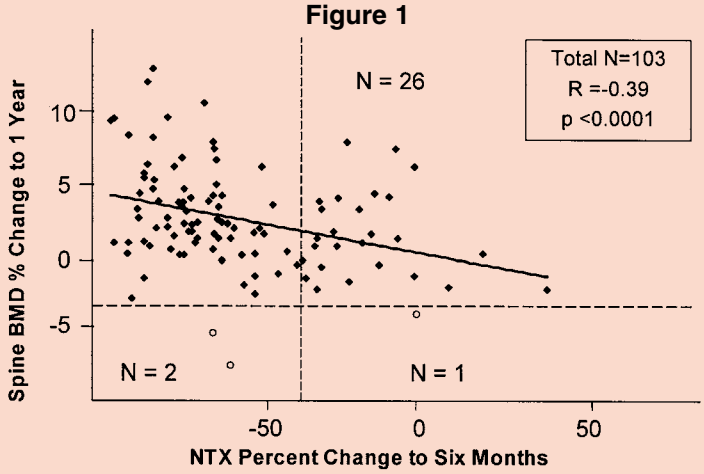
PREDICTING BONE LOSS

By knowing both a patient's current bone density and her future rate of bone loss, we could more accurately identify patients at risk for osteoporosis. In theory, women with high BTMs should lose bone density more quickly than women with lower BTMs. Combining several older markers and clinical characteristics, Danish investigators successfully predicted bone loss over 15 years.[12] In observational studies and the control groups of clinical trials, however, there is little or no correlation between a single BTM and the subsequent change in bone density.[13-15] Rosen and his colleagues evaluated this question by comparing the average of five tests collected over a one-year interval of time with a bone density change at the end of that year.[16] There was a statistical correlation between high BTM and fast rate of bone loss. Women with baseline BTM in the highest one quarter of BTM values lost 2.5% compared to no loss among women in the lowest BTM quartile. Averaging multiple BTM measurements improves the correlation with rates of bone loss by reducing the measurement error, but this approach is clinically impractical. Rogers and co-investigators evaluated the relationship between multiple formation and resorption markers and bone loss over two to four years in women whose average age was 57 years.[17] Statistically significant but modest relationships were demonstrated between higher marker values and faster rates of BMD loss. However, in these studies, a single marker measurement was not useful in predicting bone loss in individual subjects.

CHOOSING AN OSTEOPOROSIS DRUG

All of our current drugs for treating and preventing osteoporosis are anti-remodeling agents. True bone growth-stimulating drugs such as parathyroid hormone are currently being evaluated. When anabolic agents become available, it will be of value to choose the most appropriate therapy for each patient. In theory, anti-remodeling agents would be preferable for patients with high bone turnover, while growth-promoting drugs would be indicated for patients with low turnover. To date, we have no experience in selecting patients on this basis. Furthermore, even patients with low bone turnover exhibit a response to bisphosphonates and estrogen. It would be important and interesting to see if markers can be used to individualize therapy options in the future.

Figure 1



Relationship between % change in urinary N-telopeptide (NTX) at six months and % change in lumbar spine BMD at 12 months in women recently begun on estrogen therapy. Solid line is the regression line between the two variables. Dashed lines represent the threshold for observing a significant change from baseline in individual patients (40% decrease in NTX and 3% change in BMD). Open circles are the results from three subjects who experienced significant decreases in BMD. Reprinted from *American Journal of Medicine*, vol 102, 1997, pp 29-37, Chesnut et al, "Hormone replacement therapy in postmenopausal women" with permission of Elsevier Science.

PREDICTING RESPONSE TO THERAPY

BMD responses to anti-remodeling therapy vary among individuals. Women with lower levels of bone turnover are expected to have smaller BMD responses to antiresorptive drugs. Groups of women with higher markers have been shown, in some studies, to have a larger increase in BMD in response to estrogen or alendronate, but baseline markers are not predictive of whether individual patients will or will not respond to therapy.[13,18] It would be even more important if markers could predict the effectiveness of therapies in reducing fracture risk. To date, that issue has not been addressed.

MONITORING RESPONSE TO THERAPY

The objective of treating patients with osteoporosis is to reduce the incidence of new fractures. No studies have yet evaluated the correlation of changes in BMTs induced by therapy with the reduction in subsequent fracture risk. BMD testing is the most common method to monitor therapy, but it takes a year or more for spine density to change significantly in most patients (Figure 1). Measuring the change between BTM values at baseline and after three to six months of therapy provides an early opportunity to evaluate the effects of therapy.

The change in markers after three months of bisphosphonate treatment quite adequately separates the treatment group from the placebo group[3]. The performance of markers with estrogen therapy is not as robust since the percent suppression of markers is somewhat less than with bisphosphonates. This change in BMTs can be used to identify patients who may not be compliant. Alternatively, we could simply ask the patients if they are taking their medication.

Several studies have demonstrated a significant correlation (R=0.4-0.7) between changes in markers and change in BMD with estrogen or bisphosphonate therapy.[8,9,17,18] Patients with the largest decreases in markers experience greater increases in bone density. However, even patients in whom the markers fall the least do not lose bone and may actually experience an increase in bone density and, therefore, are not non-responders to treatment. Each of these studies has included both the placebo and treatment groups in the analysis. The clinician is usually faced, however, with attempts to

evaluate therapeutic response in a patient who is known to be taking the drug. If the analysis is restricted to patients on active therapy, the relationships between changes in BMTs and BMD are weak or non-existent. The BMD response cannot be predicted in individual patients on therapy by the change in markers.[13]

The major purpose of monitoring therapy is the identification of patients who are not responding; that is who have experienced a true decrease in bone density. The least significant change (95% confidence) for lumbar spine DXA is about 3%, so a true "non-responder" is someone who loses more than that amount while on therapy. With estrogen and bisphosphonate therapy, the proportion of women who exceed that rate of loss over two to three years of study is less than 3% to 5%. The incidence of non-response in clinical practice is unknown and may be greater than that.

The most enlightening data about the difficulty in using changes in BMTs to predict BMD response to therapy is that of Chesnut et al.[5] They followed 103 postmenopausal women recently begun on estrogen therapy. The percent change in urinary N-telopeptide (NTX) between baseline and six months was significantly correlated ($R=0.39$, $p=<0.001$) with the percent change in spine BMD over the year of the study (Figure 1). However, only three of the women experienced a significant loss of BMD, and NTX values fell substantially in two of them. NTX did not fall by more than 40% (the suggested threshold value) in 27 of the women (26%), but true bone loss occurred in only one of these 27 subjects. Thus the sensitivity of identifying a non-responder to treatment was only 33%, while the specificity of a lack of "response" by NTX measurement was less than 4%.

These studies show that a significant decrease in BTM is evidence that the drug is suppressing bone turnover. The amount of BTM reduction is poorly predictive of the ultimate change in bone density in women on therapy, and follow-up BMD measurements after two years of therapy may still be appropriate to assess treatment response. Not observing a decrease in BTM after three months is not evidence that the drug is ineffective or that treatment needs to be changed. Seeing no change provides an opportunity to review the patient's compliance with treatment, that the drug (especially bisphosphonates) is taken correctly, and that intake of calcium and vitamin D is adequate.

Monitoring response to less potent drugs such as raloxifene and calcitonin in individual patients is more difficult. The average change in markers or in BMD is within or near the precision error of these methods. Compared to estrogen or bisphosphonates, a much larger proportion of patients treated with these agents will not have a significant suppression of BTM or an increase in bone density. As a result, markers are not of value in monitoring patients on calcitonin or raloxifene therapy. Serial BMD testing at intervals of two to five years may identify non-responders who continue to lose bone mass despite receiving treatment.

Will better BTM assays – more precise, less variable, even more sensitive – improve their clinical usefulness for monitoring therapy? Possibly, but when the primary objective of monitoring therapy is to identify the non-responders, no method of monitoring will be useful (or necessary) with therapies to which almost everyone responds.

INFLUENCING ADHERENCE TO THERAPY

The benefit of any therapy for osteoporosis will be realized only if patients take a drug for extended intervals of time. Short-term estrogen therapy in early menopause does not provide long-term skeletal protection.[20] Adherence to estrogen therapy is notoriously poor with only 30% to 40% of women remaining on therapy after one year.

It is postulated that providing objective evidence of drug effectiveness might motivate the patient to remain on therapy. Simply providing the patient with that feedback could be an educational opportunity to reinforce the importance of therapy, its long duration, and its expected benefits. Studies evaluating the use of BTM or bone density to effect adherence to therapy are currently underway. It is not a given that these studies will document an effect of BTM measurement on adherence. Long-term adherence to lipid lowering drugs and anti-hypertensive agents is also poor, even though results of blood pressure and serum lipid levels are available to the patients as well as to the physicians. Measurement of bone turnover is a more attractive tool for providing that feedback because of the rapidity with which a response can be seen compared to bone density. In addition, the data can be collected in any office without special equipment. New point-of-care automated BTM analysis kits will provide results within only a few minutes, providing the opportunity for feedback while the patient is in the clinician's office.

SUMMARY

Our current tests of bone turnover markers are important technological advances in our ability to assess the processes of skeletal metabolism. In clinical trials, BTMs perform very well to document the magnitude in rate of changes in bone remodeling and response to treatment or withdrawal from therapy.

As with other lab tests, the use of bone turnover markers in general clinical practice is more challenging in individual patients. BTM tests themselves perform as well or better than other tests used routinely in other clinical areas (blood pressure measurements, lipid levels, etc.). However, the clinical utility of biochemical markers in the management of individual patients remains limited. A single measurement of a BTM cannot be used to select among treatment options, predict bone loss, or predict response to treatment in individual patients. The most appealing use of BTM is to monitor the response to potent antiresorptive agents such as estrogen or bisphosphonates. Observing a suppression in BTM is good (but not absolute) evidence of a therapeutic effect. Not observing a fall in values is less helpful and should not be over-interpreted as a lack of response. It remains to be demonstrated that serial measurements of BTMs will improve the likelihood that a patient will remain on therapy.

REFERENCES

1. Garnero P, Delmas PD. Biochemical markers of bone turnover. *Endocrinol Metab Clin North Am*. 1998;27:303-323.
2. Garnero P, Sornay-Rendu E, Chapuy MC, Delmas PD. Increased bone turnover in late postmenopausal women is a major determinant of osteoporosis. *J Bone Miner Res*. 1996;11: 337-349.
3. Garnero P, Shih WJ, Gineyts E, Karpf DB, Delmas PD. Comparison of new biochemical markers of bone turnover in late postmenopausal osteoporotic women in response to alendronate treatment. *J Clin Endocrinol Metab*. 1994;79:1693-1700.
4. Chesnut CH, McClung MR, Ensrud KE, et al. Alendronate treatment of the postmenopausal osteoporotic woman: effect of multiple dosages on bone mass and bone remodeling. *Am J Med*. 1995;99:144-152.

5. Chesnut CH, Bell NH, Clark GS, et al. Hormone replacement therapy in postmenopausal women: urinary N-telopeptide of Type I collagen monitors therapeutic effect and predicts response of bone mineral density. *Am J Med*. 1997;102:29-37.
6. The Writing Group for the PEPI Trial. Effects of hormone therapy on bone mineral density: results from the Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial. *JAMA*. 1996;276:1389-1396.
7. McClung M, Clemmesen B, Daifotis, et al. Alendronate prevents postmenopausal bone loss in women without osteoporosis: a double-blind, randomized, controlled trial. *Ann Intern Med*. 1998;128:253-261.
8. Bjarnason NH, Christiansen C. Early response in biochemical markers predicts long-term response in bone mass during hormone replacement therapy in early postmenopausal women. *Bone*. 2000;26:561-569.
9. Delmas PD, Hardy P, Garnero P, Dain MP. Monitoring individual response to hormone replacement therapy with bone markers. *Bone*. 2000;26:553-560.
10. Hannon R, Blumsohn A, Naylor K, et al. Response of biochemical markers of bone turnover to hormone replacement therapy: impact of biologic variability. *J Bone Miner Res*. 1998;13:1124-1133.
11. Garnero P, Hausher E, Chapuy MC, et al. Bone resorption markers predict hip fracture risk in elderly women: the EPIDOS prospective study. *J Bone Miner Res*. 1996;11:337-349.
12. Riis BJ, Hansen MA, Jensen AM, et al. Low bone mass and fast rate of bone loss at menopause: equal risk factors for future fracture: a 15-year follow-up study. *Bone*. 1996; 19:9-12.
13. Marcus R, Holloway L, Wells B, et al. The relationship of biochemical markers of bone turnover to bone density changes in postmenopausal women: results from the postmenopausal estrogen/progestin interventions (PEPI) trial. *J Bone Miner Res.* 1999;14:1583-1595.
14. Bauer DC, Sklarin PM, Stone KL, et al. Biochemical markers of bone turnover and prediction of hip bone loss in older women: the study of osteoporotic fractures. *J Bone Miner Res*. 1999;14:1404-1410.
15. Keen RW, Nguyen T, Sobnack R, et al. Can biochemical markers predict bone loss at the hip and spine? a 4-year prospective study of 141 early postmenopausal women. *Osteoporos Int*. 1996;6:399-406.
16. Rosen C, Chesnut III C, Mallinak NJS. The predictive value of biochemical markers of bone turnover for bone mineral density in early postmenopausal women treated with hormone replacement or calcium supplementation. *J Clin Endocrinol Metab*. 1997;82:1904-1910.
17. Rogers A, Hannon RA, Eastell R. Biochemical markers as predictors of rates of bone loss after menopause. *J Bone Miner Res*. 2000;15:1398-1404.
18. Ravn P, Hosking D, Thompson D, et al. Monitoring of alendronate treatment and prediction of effect on bone mass by biochemical markers in the early postmenopausal intervention cohort study. *J Clin Endocrinol Metab*. 1999;84:2363-2368.
19. Greenspan SL, Parker RA, Ferguson L, et al. Early changes in biochemical markers of bone turnover predict the long-term response to alendronate therapy in representative elderly women: a randomized clinical trial. *J Bone Miner Res*. 1998;13:1431-1438.
20. Schneider DL, Barrett-Connor EL, Morton DJ. Timing of postmenopausal estrogen for optimal bone mineral density: the Rancho Bernardo Study. *JAMA*. 1997;277:543-547.

Hypertension and the Use of Hormone Replacement Therapy in Treated Hypertensives

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INTRODUCTION

Cardiovascular disease, including coronary artery disease and stroke, is the leading cause of death in women in the United States. Although there has been an increase in the awareness of cardiovascular disease in women over the past decade, overall cardiovascular mortality in women has increased and is higher than that in men.[1,2] (Figure 1)

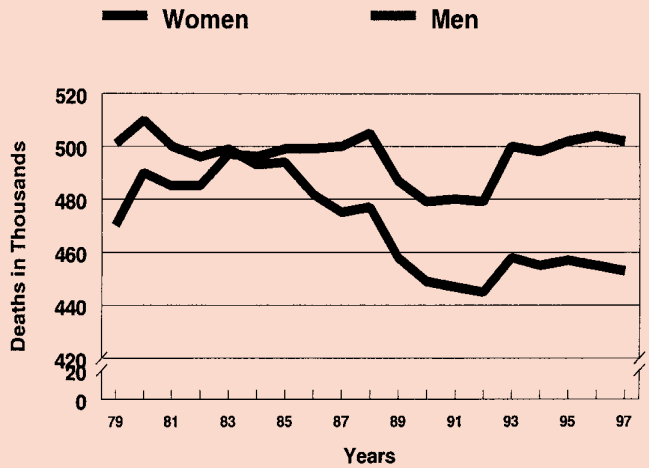
A gender-related age disparity exists in the incidence of cardiovascular disease, with women developing initial manifestations of cardiovascular disease an average of 10 years later than men.[2] Many hypotheses exist for this age-dependent disparity, but central to this issue are the sex hormones and their effects on cardiovascular disease and its risk factors. While the development of cardiovascular disease is delayed in younger women, the incidence of cardiovascular disease rises steadily in middle age, and reaches parity with men during old age.[3,4] The most obvious differentiating point between younger and older women is menopause. Determining the effects of menopause, and specifically the loss of ovarian hormones, on cardiovascular disease and its risk factors is difficult because of confounding variables: women are aging as they go through menopause, and the prevalence of more traditional cardiovascular risk factors increases as they age.[5]

Hypertension is a highly prevalent modifiable cardiovascular risk factor in middle aged and elderly women. According to the Third National Health and Nutrition Examination Survey (NHANES III), the prevalence of hypertension (BP>140/90) approaches 75% in elderly women (Figure 2).[6] The following discussion will address the effects of hormone replacement therapy on hypertension with implications for controlling blood pressure (BP) in the postmenopausal patient.

EPIDEMIOLOGY

A sexually dimorphic pattern of blood pressure (BP) development is evident in human populations.[7] NHANES III found that overall mean arterial BP is higher in both normotensive and hypertensive men than in women.[6] Gender differences in BP emerge during adolescence and persist through adulthood.[8,9] In all ethnic groups, younger men tend to have higher mean systolic (SBP) and diastolic BP (DBP) than younger women (by 6-7 mmHg systolic and 3-5 mmHg diastolic). Through

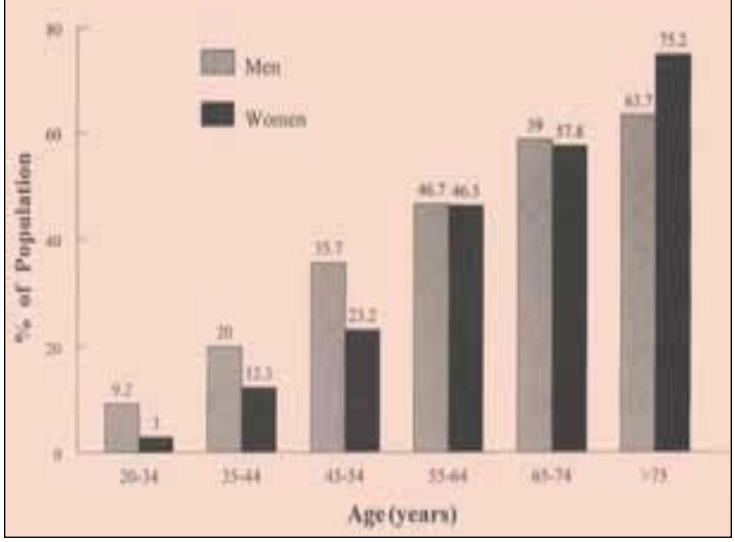
Figure 1: Cardiovascular Disease Mortality Rates for Males and Females United States: 1979-97[2]



middle age, the prevalence of hypertension is also higher among men than women (Figure 2).[6] However, NHANES III found that after age 59, hypertension is more prevalent among women than men. Further, the Community Hypertension Evaluation Clinic (CHEC) Program screened 1 million Americans between 1973 and 1975, and found that mean SBP was higher in women than in men after age 50 (for blacks) and after age 65 (for whites). Mean DPB was higher in men than in women at all ages.[10]

The influence of menopause on BP in women is also a matter of controversy. Longitudinal studies from Framingham,[11] Allegheny County,[12] and the Netherlands[13] did not document a rise in BP with menopause. In contrast, cross-sectional studies from Belgium[14] and the United States[15] found significantly higher SBP and DBP in postmenopausal compared to premenopausal women. Staessen et al reported a four-fold higher prevalence of hypertension in postmenopausal women than in premenopausal women (40% vs. 10%, P<0.001). After adjusting for age and body mass index, postmenopausal women were still more than twice as likely to have hypertension as premenopausal women.[14] In a more recent prospective evaluation of conventional and ambulatory BP in women who were pre, peri, and postmenopausal, the postmenopausal women had higher SBP (4-5 mmHg, P<0.05) compared to their pre and perimenopausal controls. The rise in SBP per decade was 5 mmHg greater in the peri and postmenopausal women than the premenopausal group (P<0.05).[16] These observations suggest that loss of the gonadal sex steroids estradiol and progesterone contributes to the rise in BP seen as women age.

Figure 2: Prevalence of Hypertension by Gender and Age [6]



HORMONE THERAPY AND HYPERTENSION: CLINICAL EVIDENCE

During the 1970s, the hypertensive effects of oral contraceptives were documented. Over the past decade, a substantial body of knowledge has accumulated indicating that postmenopausal hormone replacement therapy does not share the pressor effects of oral contraceptives. Unlike oral contraceptives, which tend to increase BP in all women and cause frank hypertension in a small percentage, the conjugated and natural estrogens used for postmenopausal replacement therapy have neutral or depressor effects on BP.

NORMOTENSIVE WOMEN

The largest prospective evaluation of hormone replacement therapy and hypertension was the Postmenopausal Estrogen/Progestin Interventions Trial (PEPI) completed in 1995.[17] PEPI evaluated cardiovascular risk factors including blood pressure in 875 normotensive postmenopausal women aged 45 to 64 years randomly assigned to treatment with a variety of different regimens of hormone replacement therapy. Office blood pressures were measured at three, six, and 12 months during the first year after randomization and thereafter every six months for a total of three years. At the end of the study period, there were no significant differences in SBP or DBP in any treatment group compared to placebo (Figure 3). There was an overall trend in mean SBP showing a decline during the first year, and an increase thereafter in all groups, including placebo. This increase paralleled a concurrent increase in body weight in all treatment groups. DBP did not change significantly during the study period.

A more recent study by Cagnacci et al evaluated the effects of two months of transdermal estrogen (50µg/day) on BP in normotensive postmenopausal women.[18] BP was assessed using a 24-hour ambulatory blood pressure monitor at the end of the two-month treatment period. Nighttime SBP, DBP, and mean BP were all significantly reduced in women receiving estrogen compared with placebo, while there was no difference between groups in daytime BP.

Seely et al evaluated the effects of transdermal estradiol (two 0.1mg patches administered twice weekly) and intravaginal progesterone (300mg nightly) on BP in healthy postmenopausal women. Patients underwent 24-hour ambulatory blood pressure monitoring after placebo, after eight weeks of biweekly transdermal estradiol, and then after two weeks of transdermal estrogen combined with intravaginal progesterone.[19] These doses of estrogen and progesterone were designed to provide premenopausal levels of circulating estrogen and progesterone. As in the Cagnacci study, nighttime SPB, DBP, and mean BP were significantly lower in both estradiol and estradiol/progesterone treated women compared to placebo. There were trends toward lower daytime SBP and DBP in patients on estradiol or estradiol/progesterone compared to placebo, but only the daytime mean BP of the estradiol group was significantly less than placebo. Similar to the data from the PEPI trial, there were no differences in office BP measurements between women treated with hormones compared with placebo. However, PEPI used conjugated equine estrogen, which may have different effects from estradiol. Further, PEPI did not utilize ambulatory BP monitors nor did it evaluate nighttime BPs, and there is now evidence that women may be particularly vulnerable to white coat hypertension[20] and that nocturnal blood pressure may be more sensitive than diurnal blood pressure to the effects of postmenopausal hormone replacement therapy.

There are two other studies of transdermal estradiol in healthy women utilizing 24-hour BP data: one used chronic transdermal estrogen in a nonrandomized, nonplacebo-controlled fashion and observed a lowering of nocturnal BP with estrogen therapy.[21] The other used 17ß-estradiol with either 5 or 10mg of progestin dydrogesterone (days 14 to 28) and observed a lowering of 24-hour ambulatory BP after

12 months of therapy.[22] It therefore appears that administration of conjugated or transdermal estradiol, alone or in combination with a progestin, to normotensive postmenopausal women has either neutral effects or tends to reduce BP (Figure 3).

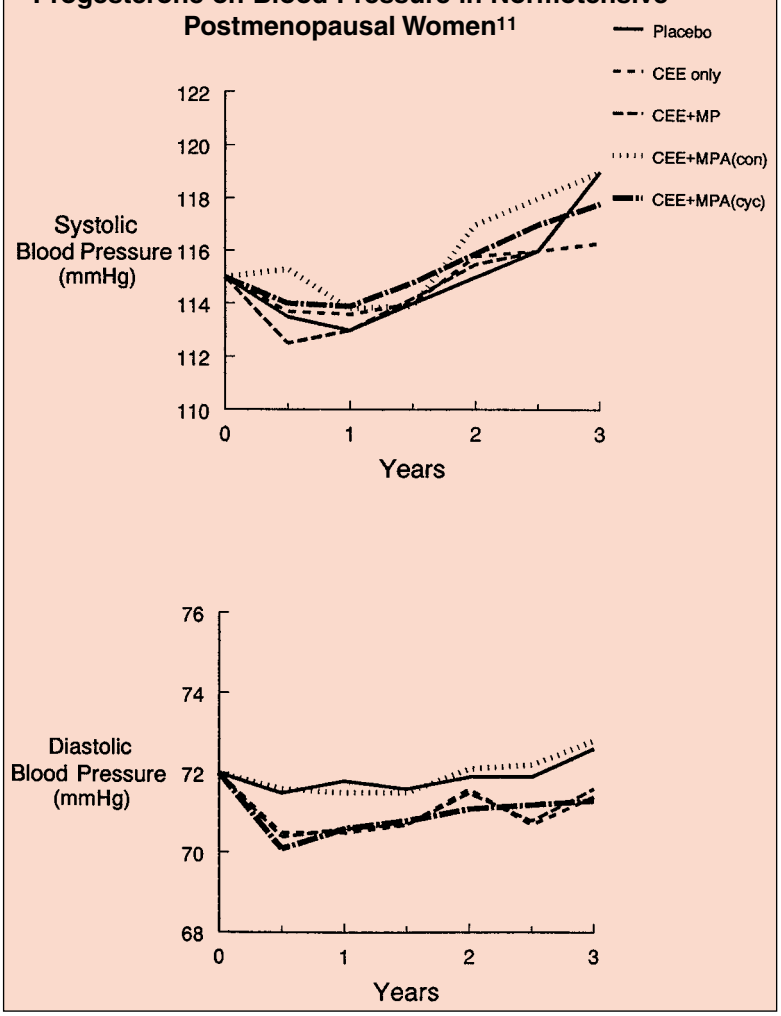
HYPERTENSIVE WOMEN

A growing body of evidence based on small clinical trials suggests that hormone replacement also has a neutral effect or lowers BP in hypertensive women. As far back as 1981, Christiansen et al demonstrated a significant drop in DBP and no change in SBP in 22 women randomized to 17ß-estradiol and estriol/norethisterone or placebo after two years follow-up.[23] More recently, in 1994, Lip et al[24] published a prospective, open study of 75 hypertensive postmenopausal women who required hormone replacement therapy to ameliorate severe menopausal symptoms. These women were followed for up to 36 months while on hormone replacement therapy with office assessments of BP every three months. During that period, there was no significant change from baseline in SBP or DBP, despite a mean weight gain of over 6kg by the end of the study.

In 1997, Kornhauser et al randomly assigned 44 postmenopausal hypertensive women to monthly injections of either saline placebo, 10mg estradiol valerianate, or 4mg estradiol valerianate plus 200mg prasterone enantate. Twenty of these women were receiving antihypertensive therapy prior to the study onset, and this was stopped prior to treatment with estrogen. Interestingly, after 90 days of follow-up, both standing and recumbent BP levels were significantly reduced in those women receiving placebo. There was no significant change in BP in women receiving estrogen or estrogen and progestin.

Manhem et al[26] performed 24-hour ambulatory blood pressure monitoring in women one day after placement of a 100µg 17ß-estradiol or placebo patch. Two weeks later, each women underwent the same protocol with the type patch not used in the first phase. Daytime DBP was significantly reduced by 3mmHg during estrogen treatment, and daytime SBP also showed a nonsignificant trend toward reduction on estrogen. There was no change in nighttime BP, HR, or in dipping phenomena with estrogen compared to placebo. Further, Mercuro et al[27] followed ambulatory BP in 30 postmenopausal women with mild hypertension during treatment with transdermal estrogen. The subjects were divided into two groups on the basis of the presence or absence of a >10% reduction in nighttime BP with respect to daytime BP ("dippers vs. nondippers"). In both groups, there was a significant decrease in SBP and DBP while on estrogen therapy. Therefore, though there are no large prospective studies, data from several studies in different populations indicate that hormone replacement therapy does not elevate – and may lower – BP in hypertensive women.

Figure 3: Effect of Conjugated Estrogens and Progesterone on Blood Pressure in Normotensive Postmenopausal Women[11]



TARGET ORGAN EFFECTS

To reduce cardiovascular complications, antihypertensive therapy should induce regression of structural abnormalities in the heart and blood vessels, as well as reduce BP. There are few studies specifically assessing target organ damage in hypertensive postmenopausal women or examining efficacy of particular antihypertensive agents in this population. Several recent observations do, however, provide some insight into this issue.

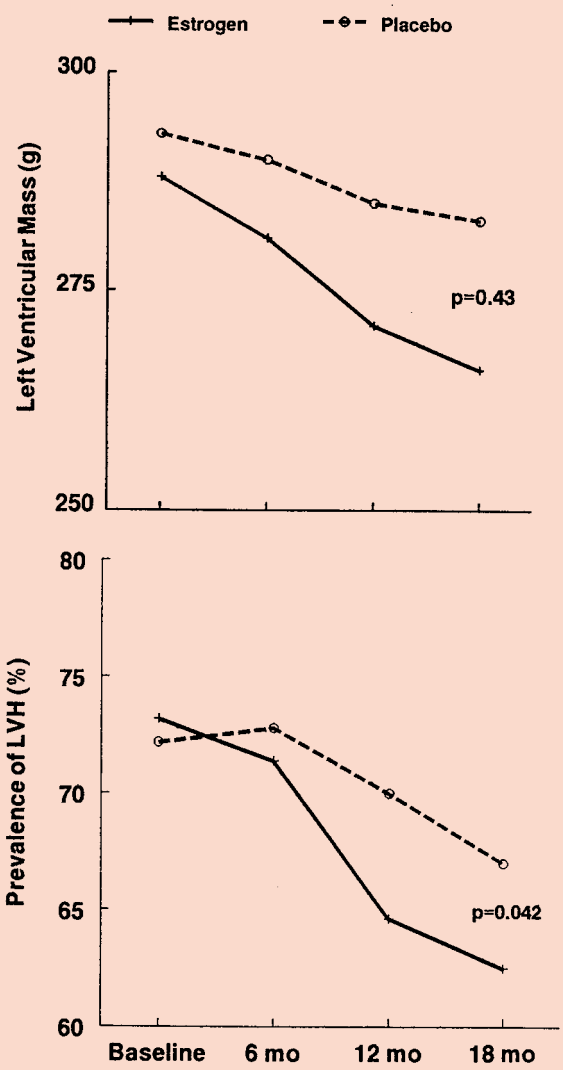
Modena et al evaluated hormone replacement therapy and its effects on left ventricular mass in hypertensive women.[28] One hundred sixty-nine postmenopausal women with controlled stage 1 and 2 hypertension (according to the Fifth Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure, JNC V) were randomized to transdermal 17ß-estradiol (50µg/24 h patches) or placebo. These women underwent an M-mode and 2-D echocardiogram at baseline, and again at six, 12, and 18 months after randomization. There were no differences between treatment and placebo in the early phases of the study, but at 18 months, women receiving estrogen had significantly reduced less left ventricular mass and left ventricular hypertrophy (Figure 4). There were no differences, however, in overall left ventricular size or function as assessed by end-systolic and end-diastolic diameters and fractional shortening, respectively. This study is one of the first pieces of evidence pointing toward a reduction in target organ damage associated with estrogen therapy in hypertensive postmenopausal women. The mechanism for this effect is unclear, but possibilities include the calcium antagonist effects of estrogen[29] or an estrogen-associated downregulation of the renin-angiotensin system.[30]

Recent studies on arterial compliance in postmenopausal women have elucidated a novel mechanism by which estrogen affects the vascular system.[31-35] Arterial stiffness, as determined by pulse wave velocity, increases with age in both sexes, but this increase is greatly accelerated in women in the perimenopausal period.[31] As a consequence, the gender difference in arterial compliance (premenopausal women > age-matched men) disappears in the postmenopausal years. This may be reflected in a perimenopausal increase in pulse pressure, a surrogate measure of arterial stiffness and a powerful independent predictor of subsequent coronary events.[32] It has been suggested that proximal aortic stiffness is a modifiable target for therapy.

This suggestion, coupled with the observation that the rapid decline in arterial compliance in perimenopausal hypertensive women is related to a fall in endogenous estrogen levels, has led to studies of the role of hormone replacement therapy in modulating arterial stiffness/compliance in postmenopausal women.[33] Short-term administration of estrogens has been shown to reduce aortic stiffness in a small group of postmenopausal women, while long-term use of the synthetic steroid Tibolone, which is structurally related to norethisterone, did not alter compliance, as derived from aortic pulse wave velocity.[34]

A larger study by Rajkumar et al tested the capacity of long-term administration of hormone replacement therapy (estrogen alone or estrogen + progestin) to modify arterial compliance in 26 postmenopausal women.[33] Control groups included 26 postmenopausal women who were not receiving hormone replacement therapy and 26 younger premenopausal women. Total systemic arterial compliance was estimated by measurement of aortic flow using continuous wave Doppler velocimetry with simultaneous carotid pressure waveform recording; pulse wave velocity, by applanation tonometry. The hormone replacement group had been treated continuously for at least 1.5 years (mean duration = seven years), while those not on therapy had not menstruated for a minimum of two years. The mean ages of those groups were 58 and 59 years, respectively. The mean age of the premenopausal group was 23 years. All participants were free of clinical cardiovascular disease. Systemic arterial compliance was greatly reduced in the untreated postmenopausal group compared to both the premenopausal and the hormone treated groups. Further, women receiving both estrogen and progestin replacement showed greater improvement in arterial compliance (0.46 + 0.03 ACU) than women receiving estrogen alone (0.37 + 0.04 ACU), reaching levels not significantly different from those in premenopausal women (0.57 + 0.04 ACU). Mean pulse wave velocity over the aortofemoral region was significantly reduced in the hormone treated group compared to the untreated postmenopausal group. Importantly, central pulse pressure was elevated in the untreated postmenopausal group (56 + 4 mmHg) compared to both the hormone treated (45 + 3 mmHg) and premenopausal (43 + mmHg) groups. This was not reflected in differences between postmenopausal groups in systolic, diastolic, or pulse pressure in the periphery, cardiac output, or total peripheral resistance.

Figure 4: Serial Changes in Echocardiographic Parameters with Estrogen Treatment[28]



Since the increased arterial compliance observed in women receiving hormone therapy was independent of BP, it must have been related to the effects of altered loading conditions on connective tissue elements in conductance vessels or to alterations in the connective tissue elements themselves. In an attempt to distinguish between these possibilities, the investigators discontinued hormone therapy in a subset (11 women) of the cohort and repeated the hemodynamic measurements after four weeks of treatment. Significant decreases in systemic arterial compliance and decreases in aortofemoral pulse wave velocity were observed, supporting the former mechanism. The rapid time course of the reduction in arterial compliance after cessation of hormone replacement therapy for four weeks is more consistent with a vasodilator mechanism than with a mechanism that requires structural remodeling of the vessel wall, which would be expected to require more time.[35] These findings are consistent with the transient nature (i.e., therapy must be continuous for benefit to be maintained) of the vasoprotective effects of postmenopausal hormone replacement therapy.[36]

A more recent study evaluated 109 postmenopausal women receiving hormone replacement therapy compared with 108 age-matched controls who did not receive hormone replacement therapy using methods similar to those of Rajkumar to study systemic arterial compliance. This study confirmed that women receiving hormone replacement therapy had a greater systemic arterial compliance than controls ($p<0.0001$).[37] These findings point to another therapeutic target for this important intervention.

TREATMENT

Little is currently know about the interaction between antihypertensive and hormone replacement therapy.

One small study by Koch et al[38] evaluated 95 postmenopausal, moderately hypertensive women (DBP between 95-114) receiving hormone replacement therapy. These women were randomized to receive either placebo or the angiotensin converting inhibitor moexipril 15mg daily. After 12 weeks of follow-up, moexipril reduced SBP and DBP to a significantly greater extent than placebo. This small study provides limited information on long-term control of BP in hypertensive women receiving hormone replacement, but it would seem to indicate that an angiotensin converting inhibitor is effective at reducing BP in this target group.

Currently, few data are available regarding the safety and efficacy of antihypertensive drugs in hypertensive postmenopausal women receiving hormone replacement. Further, no data are available on possible interactions between specific classes of antihypertensive drugs and postmenopausal hormones. Younger women of reproductive potential are excluded from most antihypertensive trials due to possible teratogenicity of these medications, and a low prevalence of hypertension. Older women are usually included in antihypertensive trials, but the results are seldom analyzed with respect to the hormone status of the participants. This is a potentially fruitful area for further clinical trials and more extensive analysis of data from existing trials. In the interim, the collective results of existing trials should be extrapolated to postmenopausal women in general as well as those receiving hormone replacement therapy. Current therapeutic recommendations for hypertension are not specific for gender and/or hormone status; however, several statements can be made from the available data:

- Postmenopausal hormone replacement therapy is administered at doses that result in "physiologic" levels of circulating estrogen, and these doses do not appear to cause hypertension.
- Hormone replacement therapy does not elevate, and may lower, BP in hypertensive women.
- Data are currently insufficient to recommend specific antihypertensive therapies in this population. However, hypertensive postmenopausal women are a high-risk patient cohort, and all traditional and non-traditional cardiovascular risk factors should be controlled as aggressively as possible.

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