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# Key Information from NAMS 11th Annual Meeting Satellite Symposia

The Satellite Symposia held in conjunction with the annual meetings of The North American Menopause Society are unique to national meetings. Satellite subjects, topics and speakers are chosen solely by the program scientific committee, based largely on the needs assessment of the congress participants, and designed not to overlap or duplicate material already in the main program. Despite having no input on selection of topics or speakers, the sponsoring pharmaceutical companies continue to be supportive through provision of unrestricted grants. This certainly confirms their commitment to promoting unbiased medical information, for which we are appreciative.

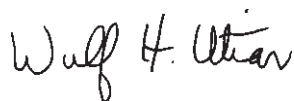
The NAMS 2000 satellites were so highly rated by congress participants that we have decided to make key summaries available to a wider audience. Summaries of three of the four satellites are presented in these pages.

The rapidly evolving area of postmenopausal hormone replacement therapy is scrutinized from three perspectives; David F. Archer takes a fresh look at vasomotor symptoms, J. Christopher Gallagher considers the challenging question of when to commence pharmacoprevention of bone loss, and the critically important question, and rapidly evolving puzzle, regarding HRT and cardiovascular disease is scrutinized by Sandra J. Lewis.

A symposium on osteoarthritis and musculoskeletal pain provided a forum in which three prominent experts considered pathogenesis (Margaret D. Smith), clinical features and diagnosis (Marc C. Hochberg) and treatment (Thomas J. Schnitzer). This important topic previously received less than adequate attention by menopause healthcare providers.

Osteoporosis, on the other hand, despite receiving widespread attention in recent years, remains an area of diagnostic and treatment confusion for numerous clinicians. This satellite symposium, covering the basic science background to clinical therapies, provided an opportunity for three internationally prominent investigators to present their current viewpoints; Robert P. Heaney explains why bones break, Robert Lindsay summarizes current clinical applications, and John P. Bilezikian tells us what's new and next.

We hope you find these easy-to-read summaries helpful. If, however, you'd like to get the full flavor of NAMS satellites and, indeed, the entire annual meeting, please accept my invitation to attend our 12th Annual Meeting, to be held in the exciting city of New Orleans, October 4-6, 2001. See you there!



**Wulf H. Utian, MD, PhD**

Editor-in-Chief, *Menopause Management*

Executive Director, The North American Menopause Society

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# Evaluating ERT/HRT for Postmenopausal Women

September 6, 2000 • Orlando, Florida

11th Annual Meeting of The North American Menopause Society

Supported by an Unrestricted Educational Grant provided by Wyeth-Ayerst Pharmaceuticals

## Menopausal Symptoms: Their Occurrence and Treatment

David F. Archer, MD

Professor, Department of Obstetrics and Gynecology  
Eastern Virginia Medical School, Norfolk, Virginia

### Overview

Dr. Archer discussed the pathophysiology of hot flashes and reviewed the findings from trials of hormonal and nonhormonal treatment regimens.

Forty percent of premenopausal women and an estimated 85% of postmenopausal women experience hot flashes. While they can occur at any time, hot flashes are most common in the 5 years immediately preceding or following menopause. In general, the hot flash is experienced as a subjective feeling of intense heat followed by reddening of the skin, head, neck and chest, followed shortly thereafter by profuse sweating (the cooling phenomenon). An increase in heart rate (to 100-120 beats/minute), changes in skin temperature and a drop in skin resistance also occur. Duration is variable, but hot flash episodes usually last for 1-2 minutes. Reports of hot flash frequency and intensity are highly variable, accounting for women's differing perceptions.

In the 1980s a high level of concordance between the hot flash and the episodic secretion of luteinizing hormone (LH) from the pituitary was shown, purportedly caused by the release of gonadotrophin-releasing hormone from the hypothalamus. This was explained as a generalized brain activation pattern that manifests with episodic release of LH secretion and the hot flash. Other studies have shown that LH, *per se*, is not the cause of the hot flash, which can occur in the absence of LH release.<sup>1</sup>

The transition from deep to light sleep that occurs prior to the nighttime hot flash (night sweat) fre-

quently causes awakening, and results in disrupted sleep with a reduction in rapid eye movement (deep) sleep. The likely result is daytime fatigue. While a recent report cites the hot flash as the most common symptom at menopause,<sup>2</sup> Dennerstein et al<sup>3</sup> recently reported that 53% of their postmenopausal study population cited aches or stiff joints, and only 42% reported hot flashes as a symptom.

### Hormonal Treatments

In 1979 Schiff et al<sup>4</sup> clearly showed a decrease in sleep latency with conjugated equine estrogens (CEE), as compared to placebo. CEE significantly reduced hot flash occurrence in the Postmenopausal Estrogen/Progestin Interventions<sup>5</sup> trial. The addition of cyclic or continuous medroxyprogesterone acetate (MPA) neither inhibited nor synergized with the estrogen in terms of hot flash reduction or increase, and a comparable reduction in hot flashes was seen with conjugated equine estrogens and micronized progesterone. Similarly, there is a rapid reduction in the number of hot flashes in the first 3-4 weeks of therapy with other oral agents, particularly estradiol.

Notelovitz et al<sup>6</sup> recently reported a reduction in hot flash frequency and intensity over 12 weeks with continued estrogen administration, and a much more rapid and greater impact on hot flash reduction with

oral estrogen plus norethindrone acetate than with placebo. It has also been argued that androgen, used concurrently with estrogen, improves hot flash frequency in a manner comparable to estrogen alone. Watts et al<sup>7</sup> have shown a similar reduction in hot flash intensity with esterified estrogen or esterified estrogen with methyltestosterone.

Estrogen appears to be the key, regardless of the way in which it is administered. Steingold et al<sup>8</sup> showed that transdermal estradiol exhibited a dose-response effect in reducing hot flash frequency/hour. Transdermal estradiol—via matrix patch, reservoir system or gel—reduces the number of hot flashes/day. Recently, Utian et al<sup>9</sup> reported a minimal difference in the reduction of hot flashes/day regardless of whether 25, 50 or 100 µg of transdermal estradiol was used. The progestin in the recently introduced transdermal estradiol with norethindrone acetate does not appear to increase or decrease the transdermal estrogen's efficacy in reducing hot flashes.<sup>6</sup> In a study without placebo, estradiol vaginal rings reduced the number of hot flashes/week, compared to baseline.<sup>10</sup> Because of this effect on hot flashes, it is assumed that there is some increase in serum estrogen levels related to the use of these experimental vaginal rings; ideally, however, a placebo-controlled study that includes measurement of plasma estradiol is needed.

In a 1980 crossover study, Schiff et al<sup>11</sup> reported an 80% reduction in hot flash incidence with MPA, compared to placebo. Findings from a follow-up study<sup>12</sup> showed a reduction in the frequency of objectively measured temperature elevations associated with MPA. This study also demonstrated the significant placebo effect seen in many clinical trials of agents used to reduce hot flashes. Megestrol acetate (MA) has been shown to rapidly reduce the number and intensity of hot flashes<sup>13</sup> in a dose-dependent manner.

We are well aware that transdermal progesterone is absorbed, albeit in small amounts, and consumer interest in such products continues to grow. In the one published report of a compounded progesterone cream (20 mg) applied to the arms,<sup>14</sup> vasomotor symptoms purportedly improved or resolved in 83% of patients, versus 19% of those receiving placebo. The report does not state if this is a direct progesterone effect or secondary metabolism of progesterone in the body.

### Nonhormonal Treatments

Recently, selective serotonin reuptake inhibitors

(SSRIs) have been found to reduce hot flash frequency and, to some extent, severity in women who have lost gonadal function secondary to treatment for neoplasia.<sup>15,16</sup>

Tibolone, a steroid available in Europe but not in the United States, was as effective as estradiol 2.0 mg in reducing hot flash incidence after 12 weeks.<sup>17</sup> Clonidine, an alpha-andronergic agent, was somewhat more effective than placebo, but not as effective as steroids.<sup>18</sup>

The placebo effect and anecdotal reporting pose problems with respect to evaluating the efficacy of "alternative therapies." There is some evidence that black cohosh can reduce the incidence of hot flashes, compared to placebo.<sup>19</sup> Findings from a recent controlled clinical trial<sup>20</sup> strongly suggest that soy isoflavones are significantly better than placebo in reducing hot flash incidence, but an earlier literature review and meta-analysis<sup>21</sup> did not provide a clear-cut answer, possibly because of the preparations and types of isoflavones studied.

### Conclusions

It appears that estrogen and other steroids reduce the number, frequency and intensity of hot flashes. For women in whom hormonal therapy is cause for concern, a number of nonhormonal alternatives are being studied for the treatment of this potentially debilitating disturbance; SSRIs do have a role, androenergetic-blocking agents are minimally effective and, while difficult to predict based on currently available data, soy proteins—particularly soy isoflavones—might yet prove effective.

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**Dr. Archer receives research/grant support from Novo Nordisk Pharmaceuticals, Inc.; Pharmacia & Upjohn; Organon, Inc.; Ortho-McNeil Pharmaceutical and Wyeth-Ayerst Pharmaceuticals. He is a consultant for Organon, Inc.; Rhône-Poulenc-Rorer Pharmaceuticals, Inc.; Solvay Pharmaceutical Products, Inc., and Wyeth-Ayerst Pharmaceuticals, and he serves on the speakers' bureaus of Ortho-McNeil Pharmaceutical, Pharmacia & Upjohn, Solvay Pharmaceuticals, Inc., and Wyeth-Ayerst Pharmaceuticals.**

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## Preventing Bone Loss With Estrogen Therapy: When to Start

### J. Christopher Gallagher, MD

Professor of Medicine and Director, Bone Metabolism Unit  
Creighton University School of Medicine, Omaha, Nebraska

#### Overview

Dr. Gallagher discussed the diagnosis of osteoporosis using BMD measurements, and their use in osteoporosis treatment and prevention.

A diagnosis of osteoporosis is based on bone density, which is defined according to a *T*-score (individual's bone density compared to peak bone mass) or *Z*-score (individual's bone density compared to that of women of comparable age).

According to the World Health Organization's definition of osteoporosis (*T*-score of -2.5 or below)<sup>1</sup> it is estimated that 20% of the population will have the disease by age 60-69, and 35% by age 70-79. The need for improvement in both diagnosis and treatment is evidenced by NHANES data,<sup>2</sup> showing that as many as 77% of osteoporotic women in the 10-

state study population were undiagnosed, 14% were diagnosed but untreated and only 9% were diagnosed and treated.

#### Bone Density Measurement

Bone density measurement with dual-energy x-ray absorptiometry (DEXA) provides high-quality images via extremely low-dose radiation. BMD measured at a specific site is the best predictor of fracture at that site<sup>3</sup>; in other words, there is a very high correlation between a *T*-score obtained from direct BMD measurement of the femur, for example, and femoral-neck

fracture risk.

While there is a relationship between indirect (e.g., ultrasound) density measurement of sites, such as the finger and calcaneus, and fracture risk,<sup>4</sup> the predictive value of such measurements is much less than that of direct, site-specific measurement (i.e., hip and spine). Because bone densitometry instruments aren't readily available in many clinical practices, the practicality and availability of indirect BMD measurement technologies—peripheral densitometry and, especially, ultrasound—might ultimately be key in implementing widespread BMD evaluation.

Ultrasound is widely available and inexpensive, and its nonradiation source eliminates the need for certain regulations and licensing. Calcaneus measurement is the best-characterized and can provide a reading (stiffness index) similar to a *T*-score. This enables fairly accurate indirect measurement of femoral-neck and, to a lesser degree, spine density. While calcaneus measurement can be quite useful for screening in the absence of DEXA technology, very low values suggest the need for follow-up with DEXA, to obtain a more precise measurement.

### BMD, Estrogen and Fracture Risk

Estrogen's positive effects on bone are, by now, well known. Estrogen produces a dose-related increase in bone density. Ideally, the hormone dose should be individualized which, at present, requires that dosing be based on BMD. As addressed in the National Osteoporosis Foundation's (NOF) *Physician's Guide to Prevention and Treatment of Osteoporosis*,<sup>5</sup> prophylactic treatment should be considered in women with a *T*-score below -2.0 (a diagnosis of osteopenia) and in those with a *T*-score below -1.5 with one or more risk factors.<sup>9</sup> Of course, the NOF recommends treating all vertebral and hip fractures, since the latter are always associated with low BMD (i.e., no need for diagnostic BMD testing).

Follow-up is needed for women with low BMD values; repeat DEXA is suggested in 3 to 5 years for women with a *T*-score below -2.0 without additional risk factors, and for those below -1.5 with at least one risk factor.<sup>5</sup> These practices place an emphasis on identifying and diagnosing women with osteopenia (*T*-score below -1.5 and risk factors).

*Early postmenopausal bone loss.* The best study of estrogen for prevention of postmenopausal bone loss is the Postmenopausal Estrogen/Progestin Interventions Trial (PEPI);<sup>6</sup> there was an increase in spine BMD of approximately 4-5% and an approximate 2.5-

3% increase in hip BMD over 3 years. Progestin given as medroxyprogesterone acetate or micronized progesterone did not inhibit estrogen's effect on BMD. There is now evidence of a small additional effect of other progestins, such as norethindrone; namely, an antiresorptive effect that leads to an additional 1 or 1.5% increase in BMD above that achieved with estrogen.<sup>7</sup> This has the benefit of allowing one to use a lower dose of estrogen.

In the 5 years since the completion of PEPI, many trials of different forms and doses of estrogen have been initiated. Ongoing studies of 0.45 and 0.3 mg of conjugated estrogens, and yet-unpublished studies of low-dose (25 and 37.5 µg) transdermal estrogens, will likely demonstrate that some women respond well to low-dose treatment, while others require larger doses.

Although observational data on estrogen/estrogen plus progestins for hip fracture prevention suggest a benefit,<sup>8</sup> there are no large, prospective studies of estrogen's effect on hip fracture, and useful prospective data will not be available until completion of the Women's Health Initiative in 2005.

*When to start prevention therapy.* Although estrogen will prevent bone loss at any age, beginning therapy at age 70-75 years might not be optimum, since patients have already lost 25-30% of their bone mass. There is good evidence that starting estrogen early after the menopause (age 50-60) results in much better fracture prevention than starting later in life (after age 70).<sup>9</sup> This is due primarily to preservation of bone mass; in general, the woman who takes estrogen for 15 years after the menopause will have bone density that is 1.5 *T*-scores higher than a nonuser of estrogen of the same age.

### Conclusions

It is important to note that, as shown by patient response to agents such as alendronate and raloxifene, fracture risk is related not just to bone mass, but also to the subtle changes in the quality of bone itself—something we can't measure with densitometry. This caveat notwithstanding, BMD measurement remains our most useful tool for predicting fracture risk. The NOF recommends that BMD testing be performed for all women under 65 with a risk factor, and for all those over 65 regardless of additional risk factors.<sup>5</sup>

BMD evaluation is only one part of a multifaceted equation. NOF and The North American Menopause Society also recommend that all women be counseled about osteoporosis risk factors. Counseling that emphasizes healthy lifestyle choices (e.g., adequate cal-

cium and vitamin D intake, and weight-bearing and muscle-strengthening exercises) and elimination of risk factors (e.g., smoking, caffeine) are key to osteoporosis prevention.

**Dr. Gallagher receives research/grant support from Wyeth-Ayerst Pharmaceuticals.**

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# Prevention of Cardiovascular Disease and the Role of ERT/HRT and Other Therapies

**Sandra J. Lewis, MD**

Clinical Associate Professor of Medicine  
Oregon Health Sciences University, Portland Cardiovascular Institute

## Overview

Dr. Lewis reviewed the latest data on ERT/HRT and statins for primary and secondary cardiovascular disease prevention.

**H**ear disease is the number-one cause of death in American women. One-third of all women over age 64 have cardiovascular disease, and more than 80,000 women under age 65 are diagnosed with myocardial infarction (MI) each year.<sup>1</sup> Even so, research on heart disease in women lags behind that in men.

### Primary Prevention

Recent Nurses' Health Study findings<sup>2</sup> confirm that reducing risk factors in women—through diet and lifestyle modification, hormone replacement therapy (HRT) and smoking cessation—yields tremendous reductions in cardiovascular events. Some patients are unaware of, or chose not to modify, their cardiovascular risk factors. For example, only 27% of hypertensive individuals in the United States are adequately controlled (BP consistently <140/90 mmHg), 31% are unaware that they have hypertension, 16% are

aware but are not on treatment and 29% are treated but not controlled.<sup>1</sup>

Fifty million women in the United States have total cholesterol above the ideal 200 mg/dl level, and more than 50% of women older than 55 years have total cholesterol levels >240 mg/dl, considered high.<sup>1</sup> While limited data are available from studies of cholesterol lowering in women for primary prevention of heart disease, women were included in the Air Force/Texas Coronary Artery Prevention Study,<sup>3</sup> in which significant event reduction occurred with cholesterol lowering with lovastatin.

The National Cholesterol Education Panel<sup>4</sup> recommends lipid screening (total and high-density lipoprotein [HDL]) for all patients. Specific recommendations are shown in the table.

Note: While HDL <35 mg/dl is identified as an independent risk factor by the National Cholesterol Education Program, a higher level—perhaps 45 mg/

**Table. Total- and HDL-Cholesterol-Based Primary Prevention\***

Status		Intervention
Total Cholesterol (mg/dl)	HDL (mg/dl)	
<200	≥35 <35	recheck in 5 yrs fasting lipoprotein analysis
200-239	≥35 and <2 other risk factors <35 or ≥2 other risk factors	recheck in 1-2 yrs fasting lipoprotein analysis
≥240		fasting lipoprotein analysis

\*Based on Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. *JAMA* 1993;269:3015-23.

dl—should probably be considered a risk factor for women, and might be adjusted as such in the program's new guidelines.

### Secondary Prevention

As in primary prevention, prospective data now demonstrate event reduction from aggressive lipid lowering with statins in women with established coronary heart disease (CHD)—in low-risk patients from the Cholesterol and Recurrent Events (CARE) trial<sup>5</sup> and in high-risk patients in the Scandinavian Simvastatin Survival Study.<sup>6</sup> In the CARE trial, a subgroup analysis of women with documented CHD but total cholesterol levels <240 mg/dl (women who would not have been treated previously with cholesterol-lowering medications) showed a remarkable 43% reduction in CHD death or nonfatal MI with 5 years of pravastatin 40 mg/day—even more so than in the men. The marked reductions in stroke incidence and the need for coronary artery bypass or angioplasty have considerable quality-of-life implications.

### ERT/HRT and Heart Disease

Women develop CHD approximately 10 years later than do men. It has long been postulated that estrogen provides protection against the development of atherosclerosis.

In observational studies, HRT does appear to provide protection against CHD events. A summary of these studies<sup>7</sup> shows a 34-58% improvement in CHD risk, but the results of randomized, prospective trials of HRT in women have led to reevaluation of these studies for possible confounding population features (e.g., healthy-user, compliance and surveillance biases). ERT/HRT has been shown to have a benefi-

cial effect on lipid profiles, decreasing low-density lipoprotein (LDL) cholesterol and increasing HDL. The issue of a beneficial effect on lipid profiles as the only surrogate marker for cardiovascular event reduction is called into question.

The Heart and Estrogen/Progestin Replacement Study (HERS)<sup>8</sup> was the first large, randomized, double-blind, placebo-controlled trial evaluating the effectiveness of estrogen plus progesterone in reducing the risk of myocardial infarction and CHD death in postmenopausal women with CHD. In HERS, HRT produced the anticipated positive effects on lipids in women with CHD but, unexpectedly, failed to reduce cardiovascular events in the treatment, versus placebo, groups. HRT users had more CHD events (versus placebo) during year 1, fewer in years 4 and 5, and more venous thrombosis and gallbladder disease throughout. The accompanying editorial cites the limitations of observational data, and emphasizes the need for randomized prospective studies of women, hormones and heart disease.

The discrepancy between the observational and prospective data on HRT in cardiovascular risk prevention is leading to in-depth examinations of the complex role of HRT on the cardiovascular system. Markers of inflammation, hemostasis, thrombosis and vascular reactivity change with HRT, and might be keys to understanding the disease mechanisms in CHD. One marker of inflammation, C-reactive protein (CRP), is an independent risk factor for the development of CHD. Ridker et al<sup>9</sup> identified high-sensitivity CRP using an assay to stratify CRP levels within the normal range (1.66-7.3 mg/l). Women in the lowest quartile of CRP in the Women's Health Study database, used by Ridker et al, had the lowest

risk of cardiovascular events; this increased over the quartiles of normal CRP levels. This novel risk factor increases in women on combined estrogen/progesterone therapy, and increases further in those on estrogen alone.

After 3.2 years of follow-up in a second prospective trial of women with CHD, the Estrogen Replacement and Atherosclerosis trial,<sup>10</sup> there was no change in angiographic coronary artery diameter (a surrogate endpoint), and no difference in events among 309 postmenopausal women with established CHD receiving unopposed estrogen, estrogen/medroxyprogesterone acetate or placebo. There was a lowering of LDL, slightly less than that seen with statins. This lack of change in CHD progression is consistent with the HERS findings; however, a small beneficial effect from estrogen cannot be ruled out.

The role of ERT/HRT for primary CHD prevention has not been explored prospectively in randomized clinical trials. Prospective data on hormone therapy's effects on cardiovascular events in women without CHD remain to be shown in the Women's Health Initiative (WHI), to be completed in 2005. However, unpublished interim WHI data are reported to support the HERS data, with early increases in MI, stroke and thrombosis in the hormone-treated groups, which decrease with time.

### Conclusions

Many questions about ERT/HRT and CHD risk remain to be answered. While new data are causing us to rethink some long-held beliefs, the study of HRT's effects on the cardiovascular system provides a unique opportunity to gain new insight into the vascular biology and molecular basis of atherosclerotic cardiovascular disease. The importance of aggressive cardiovascular risk intervention remains clear. Epidemiologic findings support ERT/HRT as protective in primary CHD prevention, with prospective data awaiting the WHI results. In the meantime, continuing ERT/HRT might be appropriate in women with CHD who have taken hormones for longer than 1 year. For the non-HRT user with es-

tablished CHD, treatment should be individualized, and other modalities with proven event reduction, including statin therapy, should be considered.

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# Osteoarthritis and Musculoskeletal Pain: Special Considerations for the Postmenopausal Woman

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Supported by an Unrestricted Educational Grant provided by Merck & Co., Inc.

## Pathogenesis of Osteoarthritis

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### Overview

Dr. Smith discussed the range of factors involved in the pathophysiology of osteoarthritis.

While, occasionally, osteoarthritis (OA) can be attributed to an old injury, it is most often the result of more than just wear and tear. In actuality, a wide range of factors are at play in OA pathogenesis (Figure), and their relative roles are the source of much ongoing research and debate.<sup>1-3</sup>

### Altered Chondrocyte Function

Articular cartilage, a complex avascular system, is structurally unparalleled in terms of allowing frictionless motion but has limited repair capabilities. Articular cartilage is composed of chondrocytes, multipotent cells that produce not only the collagen fibers that provide structure to the cartilage, but also the matrix glycoaminoglycans. Chondrocytes also can be induced to produce metalloproteinases (MMPs), prostaglandins (PGs) and nitric oxide (NO), cytokines and other substances.<sup>2</sup> With aging, chondrocyte responsiveness to TGF-beta, its principal stimulating growth factor, is diminished, with decreased cell proliferation and increased production of calcium pyrophosphate (PPi), leading to chondrocalcinosis.<sup>4</sup> Matrix protein production is also altered by aging, and decreased amounts of glucosamine and chondroitin sulfate can be observed.

### Degradation of Cartilage Extracellular Matrix

A central event in OA development, matrix deterioration can result from inadequate collagen fibers, from increased production or response to MMPs or other degrading substances produced largely by chondrocytes, and also by apoptotic bodies of chondrocytes that remain in the avascular area (not removed by macrocytes). The metabolically active apoptotic bodies continue to produce PPi as well, which further entraps them where the destructive products accumulate.

The histologic picture is one of a progressive decrease in the cartilage matrix, a decrease in the number of chondrocytes—beginning with the surface cells and, later, at all levels—synovial inflammation, early increased hydration and later dehydration of the matrix and, finally, fibrillation and splitting of the cartilage surface.

### Mediators of Inflammation

Not long ago OA was thought to be noninflammatory. We now recognize, however, that there is an inflammatory response involved in OA, albeit not to the extent seen in rheumatoid or other types of arthritis

traditionally thought to be inflammatory, and mediated via cytokines rather than leukocytes. Cytokines are first produced by the synoviocytes, and then diffuse through the cartilage and stimulate the chondrocytes to produce more proinflammatory products, including cytokines. These also cause direct injury to the cartilage and the subchondral bone. Analysis of cartilage surgically removed during total joint replacement reveals that OA chondrocytes produce excessive amounts of both PGE<sub>2</sub> and NO, the significance of which is now being investigated. In addition, the enzyme cyclooxygenase-2 is also significantly increased in OA articular cartilage. NO production continues after PG is switched off, probably relating in some way to both pain and joint destruction.

### Subchondral Bone Damage

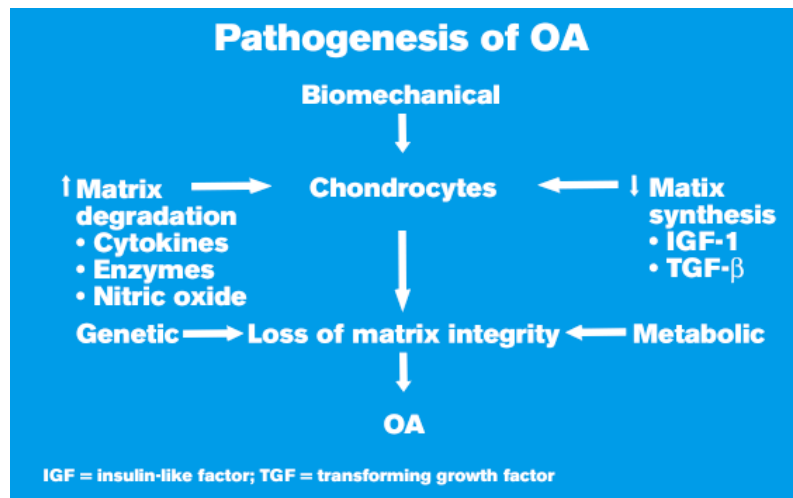
The subchondral bone, which is cancellous, serves as a “shock absorber” to the joint and is, thereby, protective of articular cartilage (absorbing some stress with weight bearing). Mechanical stress and degradation by way of cytokines and destructive enzymes can lead to the development of microfractures in the subchondral bone plate, compromising its ability to protect the cartilage. Progressive sclerosis of the subchondral bone (one of the radiologic manifestations of OA) leads to increased stiffness.

### Genetic Factors

Genetic factors have been recognized as important in OA, especially in the nodal type usually seen in a familial pattern in women with Heberdene’s and Bouchard’s nodes with involvement of five or more joints. In some of these patients the gene responsible for the production of type II collagen has been implicated.<sup>5</sup> It is hypothesized that poor-quality type II collagen, the framework that gives tensile strength to cartilage by entrapping aggregated proteoglycans, allows increased hydration of the cartilage, leading to softening and swelling—precisely the picture seen in early OA. In addition, the association of premature or severe OA with other inherited diseases has led to research, as yet unrevealing, that might link other genetic factors to OA in the settings of, for example, diabetes and hemochromatosis.

### Other Factors

Exercise is very important in OA management, and muscle atrophy, muscular instability, proprioceptive disorders or other situations leading to abnormal bio-



mechanical joint stress can certainly accelerate OA progression.

While obesity is clearly an important risk factor for OA of the knees, many unknowns about the possible contribution of nutritional factors to OA development remain. It is known that adequate vitamin C is required for normal cartilage metabolism. Possible roles of other antioxidants, minerals, glucosamine and additional nutrients are being investigated. Estrogen’s role in this picture is uncertain and requires investigation.

### Conclusions

OA pathogenesis is a complex process involving many actors; poor joint function caused by pathologic articular cartilage is the end result. The process might begin with biomechanical or genetic problems and accelerate with chondrocyte malfunction, including the production of excess destructive enzymes, PGs, NO or cytokines, as well as PPI, ultimately resulting in matrix degradation. The resulting loss of integrity of the matrix of articular cartilage leads to changes in subchondral bone, which further aggravates the situation. Radiologic changes typical of OA include joint space narrowing (articular cartilage loss), subchondral sclerosis, subchondral cysts and osteophyte formation (new bone growth in response to the cartilage destruction).

Recent emphasis on normal cartilage physiology has led to identification of a range of mechanisms at play in OA pathogenesis. Our challenge, as clinicians and scientists, is to use this knowledge to change our view of OA from that of a nuisance to be endured during the last years of life, to a disease that can be prevented and treated effectively.

Dr. Smith has disclosed no financial interests (presentation did not include discussion of any commercial products or services).

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## Clinical Features and Diagnosis of Osteoarthritis

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### Overview

Dr. Hochberg discussed the clinical presentation and diagnosis of osteoarthritis, focusing on associated pain and debilitation.

Osteoarthritis (OA) is a chronic disorder characterized by joint pain and joint line tenderness, crepitus (grating sensation caused by irregular opposing surfaces of articular cartilage) and limited joint motion, usually related to osteophyte presence (ossification of new cartilage formed during repair). Occasionally, there is effusion within the joint, with varying degrees of local inflammation.

OA is generally expressed during middle age (40-65 years); incidence increases with age, beginning at 40. OA is more common in overweight than in normal-weight women; a woman's weight in her 20s and 30s has been shown to predict later development of knee OA, and joint injury sustained during early life predicts later OA in weight-bearing joints.<sup>1</sup>

OA can involve the distal and proximal interphalangeal (DIP and PIP) joints, the thumb base, the knee, the first metatarsophalangeal (MTP) joint of the foot, the hip, and the apophyseal joints of the cervical and lumbar spine. Generalized OA is especially common during peri- and early postmenopause. In this OA syndrome, three or more joint groups are involved. The nodal form of generalized OA demonstrates familial aggregation and is inherited in an autosomal-dominant form in women.<sup>2</sup>

### OA Pain and Disability

Severity of pain accounts for the greatest loss of function with OA. Among patients with rheumatoid arthritis (RA), OA and other rheumatic diseases, pain was the most important factor in explaining physi-

cian-assessed disease activity, patient-assessed general health/arthritis status and medication use, and subsequent pain and physical disability.<sup>3</sup> Providing further evidence of the relationship between pain and disability, an association between higher-grade radiographic changes and higher mean disability scores disappeared after adjusting for knee pain<sup>4</sup>; in other words, radiographic findings correlate with the presence of pain, but it is both the presence and severity of pain that correlate best with disability.

Knee pain has been associated with increased self-reported disability<sup>5</sup> and dependence.<sup>6</sup> Significant excess mortality, documented in women with radiographic OA,<sup>7</sup> does not appear to be due to the relationship of obesity to OA; instead, findings might result from, at least in part, excess mortality from complications of peptic ulcer disease and upper gastrointestinal bleeding, probably related to traditional nonsteroidal anti-inflammatory therapy.

### OA Diagnosis and Assessment

During clinical evaluation, patient histories should elicit information about the presence, severity and characteristics of pain (via Likert or visual analogue scale) and other symptoms, such as joint stiffness and instability, and crepitus.

Physical function assessment, which can be accomplished rapidly with the eight-question Modified Health Assessment Questionnaire,<sup>8</sup> provides information about the patient's ability to carry out routine tasks. For example, OA symptoms generally worsen

with activity, are exacerbated by movement and relieved by rest. After rest, patients often develop stiffness ("gel phenomenon"). In lower limb OA, pain worsens with activity (walking, ascending/descending stairs, prolonged standing, bending, stooping, rising from a low chair or toilet, getting in or out of a car or bathtub, etc.).

On physical examination, swelling, limitation of motion, bony enlargement, tenderness of the joint line and joint deformities can be observed in patients with OA. Importantly, pain arising from the joint could be coming from the synovium (from inflammation or from stimulation of nociceptive fibers within the synovial membrane or joint capsule); from the bone (from microfractures caused by remodeling in the subchondral bone, or increased intraosseous pressure); from the periarticular structures (from muscle spasm due to weakness, bursitis or tendonitis); or from periosteal reaction over the osteophyte. Studies have shown a significant relationship between osteophyte presence and past or current knee pain, and that the odds of having pain increase with radiographic severity (more osteophytes and joint space narrowing).<sup>9</sup>

Osteoarthritis is diagnosed radiographically; findings include narrowing of the joint space caused by loss of articular cartilage, changes (usually thickening or sclerosis) in the subchondral bone and formation of osteophytes or bony prominences on the joint margins.

### Differential Diagnosis: OA Versus RA

Because of differing treatment strategies, it is important to differentiate between OA, which affects about 25% of peri- and postmenopausal women, and RA, which affects about 3% of this population.

While generally absent in OA, rheumatoid factor is usually present in patients with RA. RA typically involves the PIP and metacarpophalangeal (MCP) joints of the hands, wrists, elbows, shoulders, MTP joints of the feet, ankles and knees, and usually spares the spine. While both OA and RA can involve multiple joints with symmetrical distribution, there are differences in terms of the specific joint groups involved, as seen with inspection of the hand. OA involvement is limited to the distal and proximal interphalangeal joints and the thumb base, in a mostly bilateral distribution, with sparing of the MCPs and wrist. In RA there is involvement of the PIP and MCP joints, and the radiocarpal and intercarpal joints at the wrist, with sparing of the DIP joints.

In OA, hand radiographs reveal the typical changes of joint space narrowing, osteophyte formation and sclerosis or increase in subchondral bone density, involving the distal and proximal interphalangeal joints and the thumb base. In RA, radiographs reveal the typical changes of joint space narrowing, juxtaarticular demineralization of bone and marginal erosions involving the proximal interphalangeal and MCP joints and intercarpal joints of the wrist.

### Conclusions

As the population continues to age, OA is becoming increasingly common in the practices of clinicians caring for midlife women. It is, therefore, incumbent upon clinicians to gain a working knowledge of the clinical features of this potentially debilitating disease.

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**Dr. Hochberg has disclosed no financial interests (presentation did not include discussion of any commercial products or services).**

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# Treatment of Osteoarthritis and Musculoskeletal Pain in Postmenopausal Women

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## Overview

Dr. Schnitzer focused on the role of COX-2-specific inhibitors in the treatment of osteoarthritis and musculoskeletal pain.

Nearly two-thirds of Americans over age 65 have daily or chronic pain, and almost 75% cite arthritis as the source of their pain.<sup>1</sup> Pain changes with age; older individuals experience more pain which, in turn, is perceived as more severe and debilitating. Pain is associated with an increased risk for other comorbidities and problems, such as depression, agitation, poor sleep and diet, decreased physical activity, a marked decrease in quality of life, and increased healthcare utilization and costs. The combination of increased longevity, comorbidities and polypharmacy makes treating pain in older patients a particular challenge.

The types of drugs generally used to treat osteoarthritis (OA)/musculoskeletal pain include acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), centrally acting drugs (e.g., opiates, antidepressants, anticonvulsants) and the recently introduced cyclooxygenase-2 (COX-2)-specific inhibitors, upon which the bulk of this article focuses. In addition, “nutriceuticals,” such as glucosamine, are being used by an increasingly large segment of the older adult population.

Treating OA-related pain is not without its challenges. The relief obtained with even the most effective agents is rarely complete or even adequate; well-established drugs provide only ~30-50% relief from severe pain. Furthermore, some of the most widely used agents are associated with potentially serious adverse effects. Finally, episodic flares superimposed over the chronic pain of OA create the need for effective treatment of both acute and chronic pain.

## COX-2-Specific Inhibitors

Acetaminophen remains the first-line therapy for OA and other musculoskeletal pain, based on its efficacy and safety. Traditional NSAIDs, the most widely used of all drugs, effectively relieve pain but are responsible for as many as 16,000 deaths per year, and an estimated 103,000 hospital admissions for

acute gastrointestinal (GI) bleeds.<sup>2</sup>

With the identification of the COX-2 enzyme one decade ago came the realization that two different pathways are responsible for prostaglandin production. Traditional NSAIDs inhibit both pathways—the pathway that mediates pain, fever and inflammation (COX-2), and the pathway responsible for normal physiologic functions, such as stomach/GI tract protection (COX-1). COX-2-specific inhibitors, however, inhibit only the pathway responsible for pain, fever and inflammation mediation, leaving the protective COX-1 constitutive enzyme intact. The resulting pharmacologic activity without the GI morbidities represents, in my view, the most significant advance in pain treatment in several years.

Of the two FDA-approved COX-2 inhibitors, celecoxib (a sulfonamide) and rofecoxib (a sulfone), rofecoxib is more selective and has a longer half-life, supporting once-daily dosing. Celecoxib can be dosed once or twice daily.

*Efficacy.* Studies have shown that both drugs are as effective as traditional NSAIDs and that rofecoxib 25 mg is more effective than acetaminophen. In general, more patients will respond to the COX-2 inhibitors than have traditionally responded to acetaminophen (which should remain first-line therapy). In approval studies<sup>3</sup> celecoxib was shown to relieve pain, compared to placebo. Comparable pain relief was achieved with rofecoxib (12.5 and 25 mg/day) and high-dose (150 mg/day) diclofenac.<sup>4</sup> In a head-to-head comparison<sup>5</sup> rofecoxib 25 mg/day provided better pain relief than either acetaminophen 4 g/day or once-daily celecoxib 200 mg.

In acute pain models, rofecoxib reduced post-operative opioid analgesic use,<sup>6</sup> and ~74% of dental patients reported good, very good or excellent pain relief with rofecoxib 50 mg/day, versus 73% with ibuprofen 400 mg, 51% with celecoxib 200 mg<sup>7</sup> and only 19% with placebo.

*GI Safety.* GI safety superior to that seen with traditional NSAIDs has recently been shown in two large

outcome studies. In one study<sup>8</sup> celecoxib-treated OA and rheumatoid arthritis (RA) patients demonstrated a 40-50% reduction in the incidence of serious GI events, versus those treated with diclofenac or ibuprofen. When participants using even low doses of aspirin were removed from the analysis, there was a statistically significant (~10%) increase in relative risk reduction. A similar magnitude of risk reduction for serious GI events was seen in RA patients taking rofecoxib,<sup>9</sup> and data from studies of rofecoxib in OA patients clearly demonstrate the same 50-60% reduction in serious GI events.<sup>10</sup>

With the availability of COX-2 inhibitors, traditional NSAIDs should, in my opinion, be avoided in patients with a history of GI events, as well as in older patients, who are already at markedly increased risk for GI events with traditional NSAIDs. When not contraindicated, NSAID therapy should be combined with appropriate gastroprotective agents.

**Adverse Effects.** Early, acute sodium retention has been observed with rofecoxib, celecoxib and traditional nonsteroidals, such as indomethacin. While most patients excrete the sodium without incident, a small number develop peripheral edema, but at the same level and rate seen with traditional NSAIDs.<sup>11</sup> Because COX-2 occurs in the kidney, where it is important for normal physiologic function, renal effects can occur with inhibition, potentially leading to congestive heart failure (CHF). CHF associated with NSAIDs is a significant problem. In patients with a history of heart disease the risk of recurrent hospitalization for CHF is 10 times higher when NSAIDs are used; even without underlying heart disease this risk is doubled.<sup>12</sup>

### Other Pharmacologic Options

There are, in addition to acetaminophen and NSAIDs, a vast array of agents that may be considered for OA/musculoskeletal pain treatment. Opioids, which are sometimes appropriate for short-term treatment, especially when other agents fail to provide sufficient pain relief, are effective but are associated with a number of side effects. Tramadol, a centrally acting nonopioid analgesic, lacks the GI, renal and hepatic effects seen with NSAIDs. Because tramadol interacts with mu opioid receptors, opiate-like side effects (constipation, nausea and dizziness) are relatively common but can be reduced with slow titration. Tramadol is an effective alternative to traditional NSAIDs and COX-2 inhibitors, for patients in whom those agents are contraindicated, and it can

also be used as an adjunct to NSAID/COX-2 treatment. While a number of studies have demonstrated potential pain-related benefit with glucosamine therapy, further studies are necessary before any definitive statements can be made.

### Conclusions

Pain is not an inevitable part of aging; clinicians have at their disposal a range of treatment options that can make a difference in patients' health and quality of life. In our search for more effective pain management strategies, some basic tenets should be kept in mind: encouraging positive lifestyle changes as the first-line approach to pain management; considering the patient's unique needs and risk profile when considering pharmacologic treatment; relying upon evidence-based medicine in selecting effective agents; and ensuring that those agents will not increase disease risk in patients already at risk for a number of other comorbidities.

Furthermore, no single agent works all the time; there is, to some extent, a role for polypharmacy and for switching drugs to achieve optimal, safe pain relief.

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# Therapies for Postmenopausal Osteoporosis: Basic Science to Clinical Application

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## Why Bones Break: Approaches to the Problem

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### Overview

Dr. Heaney explained the importance of nonmass factors in relation to bone strength/fragility and fracture risk.

**B**ones break because they are subjected to more force than their intrinsic strength can sustain. Despite our focus on bone mass density (BMD), it is only one of several features that determine bone strength. Prior fracture, positive family history, prior disease (e.g., hyperthyroidism) and even geographic/ethnic variability<sup>1</sup> have all been shown to affect osteoporotic fracture risk, independent of BMD. Increasing evidence points to the importance of nonmass factors—bone architecture and inherent mechanical properties—in determining whether a fracture will occur.

### Architecture

The human skeleton is designed to produce maximum strength for minimum mass, making structure critically important.

*Connectivity.* Pathologists have identified 250–400 healed or healing microfractures per vertebral body in elderly individuals at autopsy.<sup>2</sup> Loss of cross-bracing leads to lateral bending of the bone structure. When loaded vertically the structure will snap with excessive bending, causing trabecular microfractures. These usually-silent microfractures explain, in part, why prior fracture is often a herald of future fractures, indicating that some damage

has already been sustained.

Connectivity loss occurs with age and is greater in women than in men.<sup>3</sup> Kleerekoper et al<sup>4</sup> reported more connectivity loss in osteoporotic patients than in age-matched controls, and osteoporotic men with fractures have been shown to have more connectivity loss than those without fractures, independent of BMD.<sup>5</sup>

*Bone size.* BMD measurement actually factors out bone size, obscuring a major strength determinant. Indeed, individuals with small bones are more likely to sustain fractures than those with large bones. In one study<sup>6</sup> 32 pairs of women were matched for age, BMD and body weight; one member of each pair had vertebral compression fractures. The women without fractures had larger bones, and those with smaller skeletons were sustaining ~10% greater axial compression during daily activity. With forward bending, the smaller vertebral bodies were subjected to approximately 15% more stress at the anterior edge.

*Bone geometry.* The importance of bone geometry with respect to hip axis length and hip angle has been shown in at least five studies.<sup>7–11</sup> A shorter hip axis produces a stronger structure, as evidenced by data from Faulkner et al,<sup>7</sup> who showed a substantial increase in hip fracture risk with long axes—an effect

similar to that observed when BMD drops from high to low. Other anatomic features positively correlated with bone strength include the Singh index, femoral cortical thickness at the shaft and neck, tensile trabeculae and trochanteric width.

### Mechanical Properties

**Remodeling.** While remodeling positively affects bone quality by removing foci of weakness and replacing them with fresh, strong bone, it also negatively affects local structural properties during remodeling. Overall bone strength is the algebraic sum of these two effects.

High remodeling rates have been shown to predict fracture.<sup>12</sup> A remodeling pit in the middle of the vertical trabecular element creates a point of weakness, at which stresses are concentrated manyfold. Since less remodeling now appears to be better than more in most patients with osteoporosis, remodeling suppression (with antiresorptive agents) should produce a substantial benefit. These agents also reduce fragility by producing positive bone balance through osteoclast antagonism.

**Fatigue damage.** The point of remodeling is to identify and replace the microscopic cracks in the fabric of the bony material (fatigue damage). The available data clearly show that the strength of bone is an inverse function of the crack density, and the more cracks, the weaker the bone.

Crack density in bone increases with age, and a significant increase occurs in women at menopause. Failure to repair fatigue damage leads to an accumulation of fatigue cracks, resulting in local weakness, poorer quality bony material and increased fracture risk.

Microdamage also leads to increased remodeling, which results in locally increased stress, which in turn leads to further increases in local microdamage. Fractures tend to occur in elderly individuals at sites where little fatigue damage repair is occurring.

**Collagen cross-linkage.** Cross-links hold the collagen fibrils together, providing toughness to the bone. In animal studies,<sup>13</sup> reducing cross-linkage clearly reduces bone strength. In clinical studies,<sup>14</sup> substantially less cross-linkage has been observed in osteoporotic versus nonosteoporotic bone.

### Conclusions

Nonmass features of bone—largely ignored because they are difficult to measure *in vivo*, and because of our enormous investment in BMD—contribute

significantly to skeletal strength and fragility. Impairment of one or more nonmass features can create potentially dangerous situations—even more so when combined with decreasing BMD. Much more intensive study of the causes, detection and management of the nonmass characteristics of bone is needed.

**Dr. Heaney has disclosed no financial interests (presentation did not include discussion of any commercial products or services).**

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# Current Clinical Applications

**Robert Lindsay, MBChB, PhD, FRCP**

Chief of Internal Medicine, Helen Hayes Hospital  
Professor of Clinical Medicine, Columbia University, New York

## Overview

Dr. Lindsay focused on the agents being used to treat osteoporosis and prevent fractures.

The management of patients who might be at risk for osteoporosis, or who are diagnosed with osteoporosis-related fractures, has changed significantly within the past few years. The 1998 *Guide to Prevention and Treatment of Osteoporosis*, published by the National Osteoporosis Foundation (NOF), recommended, for the first time, fairly broad use of bone densitometry in the postmenopausal population, those generally considered at greatest risk. In that Guide, densitometry was recommended for all women 65 years and older, and for postmenopausal women under age 65 with risk factors other than menopause. (NOF considered personal history of a fracture after age 40, a family history of hip fracture, low body weight [ $<127$ lbs] and cigarette use as the major risk factors, although others have been suggested).

When used in this fashion, bone mineral density (BMD) testing is a clinically useful tool for determining the need for intervention. While treatment should be considered for those whose BMD is below the range for young adults ( $T$ -score  $\leq -2.5$ ), the "cut-point" for treatment can be raised to a  $T$ -score of  $-1.5$  when risk factors are present. The intent is to identify those most at risk of fracture and to treat before fractures begin to occur.

It has been known for some time that the presence of a vertebral fracture, usually found by chance, increases the risk of further fractures. Recently, we demonstrated that new vertebral fractures further increase that risk, to the extent that individuals who sustain a vertebral fracture have, on average, a 20% chance of fracturing again within 1 year of the incident. Furthermore, although osteoporosis treatments reduce fracture risk in patients with and without fractures, it is now clear that the risk reduction in those with fractures is insufficient to return risk to the prefracture level.

## Pharmacologic Therapy

The initial approach to patients with, or thought to be at increased risk for, osteoporosis is to attempt to reduce the impact of risk factors, where possible.

Thus, improving calcium intake to 1,200 mg/day, increasing vitamin D intake to 400-800 IU/day, initiating an exercise program, and cutting smoking and alcohol intake are integral to patient management.

Pharmacologic therapy includes the use of drugs with broad effects on many bodily systems (estrogens and selective estrogen receptor modulators) and agents that are skeleton-specific (bisphosphonates and calcitonin). All these drugs have the same net effect on the skeleton—reducing the rate of bone remodeling—which results in a small but significant (in most cases) increase in bone mass.

*Estrogen.* Estrogen, given as estrogen replacement therapy (ERT) or combined with a progestin as hormone replacement therapy (HRT), has generally been regarded as the prime approach to osteoporosis prevention and treatment. While there are considerable data supporting a skeletal effect of estrogen in postmenopausal women, with the exception of two studies that demonstrated a reduction in vertebral fracture risk, data from controlled clinical trials showing beneficial effects on nonvertebral fractures, and especially hip fractures, are largely observational. Findings from these clinical trials indicate a 50-75% reduction in vertebral fracture risk, and the observational data support similar levels of risk reduction for hip fracture, particularly in women who begin therapy in early postmenopause and continue long-term. Recently, data from controlled clinical trials have begun to confirm the nonvertebral fracture effects of estrogen; however, because no clinical fracture reduction was observed with HRT in the Heart and Estrogen/progestin Replacement Study (HERS), further data from the Women's Health Initiative are eagerly awaited.

The effects of estrogen on bone mass are generally not modified by medroxyprogesterone acetate, although there is some suggestion that norethindrone, a 19-nortestosterone derivative, might add to the estrogen effect. Similarly, improved calcium intake and higher levels of physical activity might also enhance estrogen's effect on bone mass. Whether those effects will confer an additional effect on fractures is un-

known, but using an androgenic progestin or increasing calcium intake and physical activity might mean that, for many lower doses of estrogen, the current standard of 0.625 mg conjugated equine estrogens might be sufficient to conserve bone mass. Studies to evaluate this concept are under way.

ERT/HRT is associated with an increase in the risk of deep-vein thrombosis, and data suggest a small but significant increase in breast cancer risk with long duration of use (>5-10 years). In addition, uterine bleeding, bloating and weight gain are problems for many women that limit the more general long-term use of HRT. Concerns that some of the other proposed benefits might be less than those anticipated from epidemiologic studies have also arisen after publication of the cardiovascular data from HERS.

*Selective estrogen receptor modulators (SERMs).* The development of agents that might produce the beneficial effects of estrogen without the perceived problems has provoked considerable interest in recent years. Raloxifene is approved for osteoporosis prevention and treatment. Initially, studies demonstrated that raloxifene could prevent bone loss in women less than 5 years from menopause. In the Multiple Outcomes of Raloxifene Effects (MORE) trial, some 7,700 women with osteoporosis were enrolled into a controlled clinical trial comparing two doses of raloxifene with placebo. Patients with osteoporosis and prevalent vertebral fractures had a 30% reduction in the risk of new vertebral fractures. In patients with osteoporosis—as defined by the World Health Organization as BMD <-2.5 SD from young average mean—a 55% reduction in vertebral fractures was achieved. With the exception of ankle fractures, for which a significant protective effect was evident, no significant effects on nonvertebral fractures were seen. This finding might, in part, be related to the relatively young (67 years) mean age at recruitment and to the small numbers of fractures that occurred, particularly in the placebo group in the early part of the study.

Raloxifene was associated with a significant reduction (~76%) in the appearance of invasive breast cancer during 40 months of observation in the MORE study; the effect was most pronounced for estrogen-receptor-positive tumors (~90% reduction). More than any factor, this decrease in breast cancer risk drives the use of raloxifene in practice, especially for younger women (<70 years) concerned about osteoporosis, but also for a peer group for whom breast cancer is a concern. Raloxifene is not associated with

an increase in endometrial cancer but has the same effect on deep-vein thrombosis as that seen with HRT (relative risk 2-3 times).

*Bisphosphonates.* Bisphosphonates are analogues of pyrophosphate that have effects only in the skeleton, by virtue of their capacity to bind to calcium. Alendronate and risedronate are both approved in the United States for postmenopausal osteoporosis prevention and treatment. In both situations, these agents reduce skeletal remodeling and stabilize bone mass, with observed increases in BMD, particularly in the spine. Alendronate reduces vertebral fracture risk and also produces a reduction in nonvertebral fractures that is evident in the BMD of individuals with osteoporosis (with or without prevalent fractures). Risedronate also reduces vertebral fractures significantly within the first year of treatment. In the only study completed in which hip fracture was the primary outcome, risedronate reduced risk by about 40% in older postmenopausal patients with osteoporosis. Risedronate is also approved for prevention and treatment of glucocorticoid-induced osteoporosis. Alendronate is approved for treatment of glucocorticoid-induced osteoporosis and for osteoporosis in men.

Alendronate has been found postmarketing to be associated with an increased risk of upper gastrointestinal (GI) irritation. Risedronate might have a better GI profile. All bisphosphonates are poorly absorbed and must be taken with water on an empty stomach to facilitate absorption.

*Calcitonin.* Calcitonin delivered by intranasal spray also reduces vertebral fractures by about 30% in patients with osteoporosis, with little apparent effect on nonvertebral fractures. Calcitonin has little in the way of side effects, except for local effects in the nostrils. Calcitonin is approved for the treatment of postmenopausal osteoporosis.

*Novel Agents.* All of the agents currently available for osteoporosis prevention/treatment act by reducing bone remodeling. Anabolic agents that might repair the underlying damage to the skeleton provide a new paradigm for the treatment of osteoporosis. Parathyroid hormone (PTH) has been known to be anabolic for more than 70 years, but it is only recently that controlled clinical trials have been developed in which subcutaneously injected PTH, both in conjunction with standard antiresorptive treatment and as monotherapy, has been shown to reduce both vertebral and nonvertebral fracture risk.

### Conclusions

Osteoporosis is easily diagnosed using bone density evaluation, which can also be used as a case-finding tool in postmenopausal women. BMD results can be used to guide the need for therapy. While important as a first step in osteoporosis treatment, risk factor reduction alone is likely to be insufficient for patients with the disease. Osteoporosis treatment falls into two basic categories: use of agents with multiple effects throughout the body (ERT/HRT, raloxifene) and use of agents that act only on the skeleton (alendronate, risedronate). All available agents reduce

the risk of vertebral fractures, but the effects on peripheral fractures are more variable and established for bisphosphonates, especially risedronate. Novel agents, such as PTH, raise the possibility of even more effective therapies in the future.

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**Dr. Lindsay is a consultant for Eli Lilly and Company, Wyeth-Ayerst Laboratories and Pfizer US Pharmaceutical Group. He is on the speakers' bureaus for Eli Lilly and Company and Pfizer US Pharmaceutical Group, and has served as an investigator for Aventis and Wyeth-Ayerst Laboratories.**

*References available from Dr. Lindsay, upon request.*

## What's New; What's Next?

### John P. Bilezikian, MD

Professor of Medicine and Pharmacology  
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#### Overview

Dr. Bilezikian discussed innovative new approaches to osteoporosis management.

Currently being investigated, several novel approaches to osteoporosis management—with bisphosphonates, anabolic agents and combination therapies—are showing great promise.

#### Bisphosphonates

While bisphosphonates have demonstrated efficacy in increasing bone mass density (BMD) and reducing fracture incidence, restrictive dosing requirements—intended, in part, to minimize possible esophageal irritation and to optimize absorption—have prompted investigation of new approaches to dosing.

*Weekly/biweekly dosing.* In a yearlong, double-blind, randomized study,<sup>1</sup> reduction in bone markers, along with an increase in lumbar spine, total hip, trochanter and total body BMD, were essentially indistinguishable across three oral alendronate regimens—10 mg once daily (standard regimen), 35 mg twice weekly and 70 mg once weekly. The low (~2%) incidence of upper gastrointestinal events (even lower for serious events) was reduced even further with the weekly and biweekly regimens. [The FDA approved weekly alendronate in October 2000.]

*Intravenous infusion.* Intravenous (IV) bisphosphonates might ultimately allow even further intermittent dosing. In one study<sup>2</sup> IV ibandronate (1 or 2 mg)

given every 3 months produced a significant increase in BMD; a significant fracture reduction was not, however, observed. In our practice IV pamidronate (30 mg every 3 months for 1 year) has yielded an approximate 6% increase in lumbar spine BMD and a smaller, but still impressive, increase in hip BMD.

*Special populations.* In a small but well-controlled, 2-year, double-blind study involving osteoporotic men,<sup>3</sup> alendronate effectively increased lumbar spine and femoral neck BMD, compared to placebo, and reduced clinical vertebral fractures (with no difference in nonvertebral fractures). These data are consistent with those reported for alendronate in postmenopausal women.

In a recent placebo-controlled trial,<sup>4</sup> 2 years of alendronate 10 mg/day (plus calcium and vitamin D) produced a significant (6.4%) BMD increase and a 4.1% increase in total hip BMD in osteoporotic African-Americans. The drug was well tolerated, and BMD increases and bone turnover reductions were similar to those seen in Caucasian women.

#### Anabolic Agents

Anabolic agents that increase bone mass by stimulating bone formation are receiving increasing attention.

*Parathyroid hormone.* In primary hyperparathyroidism, a disease of excess parathyroid hormone (PTH),

the cancellous skeleton seems to be relatively preserved in comparison to the cortical skeleton,<sup>5</sup> which is vulnerable to the catabolic actions of PTH. These observations suggest that PTH might be beneficial for the cancellous bone loss that occurs typically in postmenopausal women.

In a recent 18-month, double-blind, placebo-controlled trial,<sup>6</sup> osteoporotic men had an impressive 13-14% increase in lumbar spine BMD with low-dose, intermittent PTH (400 units), versus no significant change in controls. A smaller, slower rise in femoral neck BMD reached significance by 18 months. The distal radius remained unchanged in the placebo and PTH groups. Serum calcium, 24-hour urinary calcium, 25-hydroxyvitamin D, and 1,25-dihydroxyvitamin D were unchanged.

Findings from a large study in more than 1,600 postmenopausal women receiving PTH alone<sup>7</sup> showed significant reductions in the relative risks of vertebral and nonvertebral fractures, with impressive increases in bone density. Although PTH is currently the most promising anabolic agent being evaluated for osteoporosis, the fact that it is administered by injection is a relative drawback. Moreover, PTH's long-term safety has not been established. Potential adverse effects include hypercalcemia and hypercalciuria.

*Manipulating PTH.* The findings above have prompted ideas about the plausibility of raising endogenous PTH levels by "tricking" the parathyroid gland in an intermittent, low-dose fashion—perhaps with molecules that inhibit its calcium receptor. Calcilytics antagonize the calcium receptor, lower the cellular calcium level and ultimately raise intracellular and circulating PTH.<sup>8</sup>

### Combination Therapy

Combination therapy—2 antiresorptives or an antiresorptive with an anabolic—represents a new treatment paradigm. Bone et al<sup>9</sup> reported a greater increase in BMD—more impressive in the lumbar spine than in the total hip—with combined estrogen and alendronate than with either agent alone. Lindsay and colleagues<sup>10</sup> have shown that sequential combination therapy—hormone replacement therapy (HRT) followed by alendronate—results in even more impressive BMD increases than continuing HRT alone. Similar results have been reported with the selective estrogen receptor modulator raloxifene combined with alendronate.<sup>11</sup>

Examining another approach, Watts et al<sup>12</sup> have shown that adding androgens to HRT produces a

greater change in bone density than does HRT alone. While not yet approved for osteoporosis treatment, tibolone, a synthetic steroid with both antiresorptive and anabolic properties, shows promise as a potentially more acceptable approach to combination therapy in women. Tibolone has been shown to sequentially increase both lumbar spine and total hip BMD, in a dose-related fashion.<sup>13</sup>

Combined estrogen and PTH might prove highly effective for postmenopausal and glucocorticoid-induced osteoporosis, as suggested by an impressive increase in lumbar spine BMD in patients with glucocorticoid-induced osteoporosis.<sup>14</sup>

To date, there have been no studies showing improved fracture reduction with any of these combination regimens, compared to single-agent therapy.

### Conclusions

New agents, coupled with promising data from studies of innovative dosing regimens and drug combinations, are stimulating us to look beyond improving bone density and reducing fracture risk. The potential now exists to actually commute a diagnosis of osteoporosis to one of "normal."

**Dr. Bilezikian has no significant relationships with the grantor, Eli Lilly and Company, or any other commercial company whose products and services were discussed in his presentation.**

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1. According to Dr. Lewis ("Prevention of Cardiovascular Disease and the Role of ERT/HRT and Other Therapies"), all of the following are correct, **except**:

- a) Heart disease is the number-one cause of death in American women.
- b) Lipid lowering with statins has been shown to reduce cardiovascular events in women with heart disease, but not in those without.
- c) The National Cholesterol Education Panel recommends total and HDL cholesterol screening for all patients, regardless of risk factors.
- d) Interim WHI data appear to support HERS findings regarding early cardiovascular events in hormone-treated women.

2. According to Dr. Hochberg ("Clinical Features and Diagnosis of Osteoarthritis"), which of the following accounts for the greatest loss of function in patients with osteoarthritis?

- a) severity of pain
- b) number of involved joints
- c) distribution of involved joints
- d) presence of an osteophyte

3. According to Dr. Schnitzer ("Treatment of Osteoarthritis and Musculoskeletal Pain in Postmenopausal Women"), COX-2-specific inhibitors act by inhibiting both pathways responsible for prostaglandin production.

- a) True
- b) False

4. With which of the following statements would Dr. Heaney ("Why Bones Break: Approaches to the Problem") disagree?

- a) Connectivity loss is greater in women than in men.
- b) Individuals with large bones are more likely to sustain fractures than those with small bones.
- c) Remodeling both positively affects bone quality and negatively affects local structural properties.
- d) Less collagen cross-linkage has been observed in osteoporotic versus nonosteoporotic bone.

5. In the study by Bone and colleagues cited by Dr. Bilezikian ("What's New; What's Next?"), the authors reported:

- a) impressive BMD increases with sequential therapy (HRT followed by alendronate)
- b) a greater change in BMD with combined HRT and androgens than with HRT alone
- c) an impressive increase in lumbar spine BMD among patients with glucocorticoid-induced osteoporosis treated with estrogen and PTH
- d) a greater increase in BMD (more so in the lumbar spine than in the total hip) with combined estrogen and alendronate than with either agent alone

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