Endocrine, vol. 5, no. 2, 115-127, October 1996 0969-711X/96/5:115-127/$8.25

REVIEW

Salmon Calcitonin Nasal Spray

An Effective Alternative to Estrogen Therapy in Select Postmenopausal Women

Louis V. Avioli

Division of Bone and Mineral Diseases, Washington University School of Medicine, at the Jewish Hospital of St. Louis, St. Louis, MO

The efficacy and safety of estrogen replacement therapy (ERT) and salmon calcitonin in the treatment of postmenopausal osteoporosis are reviewed with special consideration given to patients for whom ERT, the primary antiresorptive therapy for osteoporosis, is not indicated, tolerable, or is refused. The various formulations of estrogen and salmon calcitonin, for which the nasal spray formulation was recently approved for use in the United States, are reviewed in depth with reference to dose ranges, side effects, and convenience. Data regarding increases in bone mineral density (BMD) produced by each agent are presented. Specifically, the range of increases in BMD induced by ERT and salmon calcitonin are comparable. Given the substantial public health consequences of postmenopausal osteoporosis and osteoporotic fractures, the primary care physician is increasingly faced with the need to educate and recruit postmenopausal patients to appropriate therapy with the optimal agent for that particular patient. In the many patients who are unable or unwilling to accept, initiate, and comply with prescribed ERT, alternative therapeutic options are necessary Based on the established safety profile of salmon calcitonin, ease of administration, an uncomplicated dosing regimen, no reported drug interactions, and the lack of uterine bleeding associated with ERT or gastrointestinal adverse effects of other agents used to treat osteoporosis, salmon calcitonin nasal spray is an appropriate alternative approach for the treatment of postmenopausal bone loss.

Key Words: Estrogen replacement therapy; salmon calcitonin; postmenopausal osteoporosis.

Received June 27, 1996; Accepted July 5, 1996.

Author to whom all correspondence and reprint requests should be addressed: L.V. Avioli, Division of Bone and Mineral Diseases, Washington University School of Medicine, at the Jewish Hospital of St. Louis, 216 South Kings Highway, St. Louis, MO 63110.

Introduction

The likelihood that today's primary care physician will evaluate and treat female patients for symptoms of estrogen deficiency is increasing secondary to the aging of the U.S. population. In fact, it is estimated that because of increased patient longevity, the average woman will be postmenopausal for approximately one third of her life (Davidson, 1995). Although many of these female patients will present with the objective and subjective symptoms most commonly associated with menopause (e.g., hot flashes, vaginal atrophy, emotional lability), many others will present initially with a vertebral crush fracture or a Colles' fracture, indicating a more potentially devastating condition, postmenopausal osteoporosis.

Defined by the World Health Organization as "a disease characterized by low bone mass and microarchitectural deterioration of bone tissue, leading to enhanced bone fragility and a consequent increase in fracture risk," osteoporosis results from a heterogeneity of skeletal and extraskeletal factors that each contribute to the disorder (World Health Organization, 1994). Specific decreases from normal values for bone mineral density (BMD) further distinguish women with osteoporosis from those with osteopenia, or low bone mass: Osteoporosis is categorized by a BMD value 2.5 standard deviations (SD) or more below the mean for young healthy adult women, whereas osteopenia is classified by a BMD value between 1 and 2.5 SD below the reference mean; by comparison, severe (established) osteoporosis is categorized by a BMD value more than 2.5 SD below the reference mean in the presence of one or more fragility fractures (Kanis et al., 1994; World Health Organization, 1994).

The prevalence of these disorders underscores the magnitude of the public health concern related to osteoporosis within the United States today. In a 1995 report by Looker et al. (1995), in which the previously cited WHO diagnostic criteria were utilized, the estimated number of non-Hispanic white women aged 50 yr or older with

osteoporosis within the United States was 5–6 million; corresponding figures for osteopenia were 10–15 million women. Melton (1995) reported 1995 estimates of 9.4 million and 16.8 million for osteoporosis and osteopenia, respectively, in white postmenopausal women in the United States. He further estimated that 4.8 million women (51% of the osteoporotic women and 16% of all white women ≥50 yr) have established osteoporosis, noting that this figure is probably an underestimate since most fractures in elderly women are related at least in part to low BMD. Based on these figures, the total population of white women in the United States at risk of fracture secondary to osteopenia or osteoporosis is 26.2 million.

The Consequences of Osteoporosis

Often called "the silent thief" (World Health Organization, 1994) because of its covert early progression, osteoporosis is associated with substantial disability and increased morbidity and mortality with advancing age, as the overt manifestations of the disease—osteoporotic fractures—occur at a markedly increased rate. In the United States, approx 1.5 million fractures attributable to osteoporosis occur each year (Peck et al., 1988; Riggs, 1991). The most common fracture sites include the vertebrae (650,000), the hip (250,000), and the distal forearm (200,000). The consequences of hip fracture are often particularly severe: In the first year after a hip fracture, the mortality rate is approx 12–20% higher than that in persons of similar age and gender without hip fracture in the general population (Miller, 1978; Gallagher et al., 1980; Lewinnek et al., 1980; Cummings et al., 1985); the excess mortality occurs primarily in the first 4–6 mo after the hip fracture (Miller, 1978; Gallagher et al., 1980; Nevitt, 1994). Of the patients who survive hip fractures, at least 50% of those who could walk before sustaining the fracture are unable to walk unassisted afterward. In addition, up to 50% of all patients with hip fracture cannot live independently following the fracture (Melton, 1993). Specifically, according to Phillips et al., hip fractures in the United States result in approx 61,000 nursing home admissions per year among white women (Phillips et al., 1988).

No less devastating are the financial costs of osteoporosis care in American women: In 1986, the total cost of treating osteoporosis—including inpatient, outpatient, and nursing home care—were approx $5.2 billion (Phillips et al., 1988). Recently reported estimated total care costs have nearly doubled and are reported to be at least $10 billion (Riggs and Melton, 1992). The enormous public health impact of osteoporotic fractures and the burden to the community and the healthcare system indicate the urgent need for prevention and necessitate that the primary care physician be able to identify appropriate patients for preventative and therapeutic treatment of osteoporosis and then select the most appropriate therapy for those patients.

Estrogen Replacement Therapy

Mechanism of the Antiresorptive Action of Estrogen

Menopause is often associated with a relatively sudden cessation of endocrine function of the ovary that significantly alters skeletal homeostasis, resulting in loss of bone tissue. Prior to menopause, the predominant estrogen is 17-β estradiol, which is secreted by the ovary (Lindsay, 1993). Postmenopause, there is a marked decline in estradiol, as well as in estrone and progesterone, producing a significant decrease in total circulating estrogen levels, which has been shown to correlate with the rate of bone loss (Lindsay, 1993).

The relatively marked decrease in total estrogen levels is thought to result in increased activation of bone remodeling and the number of bone remodeling sites, resulting in a proposed increase in the activity and number of osteoclasts and possibly altered osteoblast function (Lindsay, 1991, 1993; Compston, 1993; Lindsay et al., 1993). The net effect is a significant negative imbalance between bone resorption and bone formation at each remodeling cycle (Lindsay, 1991, 1993). An independent, age-related factor contributing to the increase in bone loss is also thought to exist in addition to an estrogen deficiency mechanism of action (Lindsay, 1993).

The reintroduction of estrogen via estrogen-replacement therapy (ERT) reverses the effects of ovarian failure (Lindsay, 1991). The minimum effective dose for conjugated equine estrogen is 0.625 mg/d, and for percutaneous estradiol, 50 μg via transdermal patch appears to achieve these levels (Lindsay, 1993).

Review of Prospective Clinical Trial Data

Two decades of prospective clinical trial results stand in support of the efficacy of ERT in the prevention and treatment of estrogen-deficient osteoporotic syndrome. These results, though frequently difficult to compare owing to inconsistencies in study design and methodology, have established the therapeutic role of estrogen in stopping and/or reversing bone resorption in the axial and appendicular skeleton.

The results of controlled studies conducted in the past 5 yr continue to corroborate the well-documented efficacy of ERT in preventing and/or minimizing bone loss and in increasing BMD in estrogen-deficient women. Of equal importance, these therapeutic effects on BMD have been clearly shown to decrease the risk of fractures in early postmenopausal women and in those with established osteoporosis. As a result, estrogen is the agent of first choice in most women for the prevention of skeletal bone loss and for the long-term treatment of primary and established osteoporosis.

The salutary effects of estrogen on bone resorption and mineral density were noted anecdotally for many years and

reported in the medical literature by several investigators (Horsman et al., 1977; Recker et al., 1977). However, these effects were first documented in a prospective, randomized, placebo-controlled study initiated by Lindsay et al. in 1968 (Aitken et al., 1973; Lindsay et al., 1976). In a 10-yr follow-up report of the study results published in 1987, bone mass measurements in 26 of the estrogen-treated women and 25 placebo-treated subjects revealed a significant increase in mean BMD values in the lumbar spine and femoral neck for the treated patients (1.17 and 0.87 g/cm^2, respectively) vs placebo patients (0.94 and 0.77 g/cm^2, respectively) ($p < 0.001$, lumbar spine; $p < 0.01$, femoral neck) (Al-Azzawi et al., 1987).

Tables 1 and 2 describe the major prospective studies conducted between 1970 and 1996 of oral and percutaneous estrogen therapy in postmenopausal and oophorectomized women (Lindsay et al., 1976, 1984; Nachtigall et al., 1979; Christiansen et al., 1980; Ettinger et al., 1987; Riis et al., 1987; Hart et al., 1987; Ribot et al., 1987, 1988; Civitelli et al., 1988; Munk-Jensen et al., 1988; Adami et al., 1989; Gallagher et al., 1989; Lindsay and Tohme, 1990; Stevenson et al., 1990; Harris et al., 1991; Motta et al., 1991; Lufkin et al., 1992; Aloia et al., 1994; Lafferty and Fiske, 1994; Cantatore et al., 1995). In studies utilizing oral doses of 0.625 mg of conjugated estrogen (Lindsay et al., 1984; Lindsay and Tohme, 1990; Stevenson et al., 1990; Harris et al., 1991; Aloia et al., 1994; Lafferty et al., 1994) or a 50-μg patch (Ribot et al., 1988; Adami et al., 1989; Stevenson et al., 1990; Motta et al., 1991; Cantatore et al., 1995; Marcus et al., 1996), annual increments in BMD ranged from stabilization of bone loss (i.e., 0% annual increase in BMD) to as high as 12%; in most studies, however, annual increases in BMD ranged from 2–5%.

In addition to these prospective studies, a variety of cross-sectional studies have been undertaken that attest to the ability of estrogens to prevent and/or minimize bone loss caused by estrogen deficiency, in either surgically induced or natural menopause (Jensen et al., 1982; Ettinger et al., 1985; Savvas et al., 1988; Moore et al., 1990; Villareal et al., 1992).

Estrogen replacement therapy is effective in early postmenopausal women as well as in women with established osteoporosis. The efficiency of estrogen in halting and/or minimizing bone loss and in increasing BMD during rapid bone loss in the early postmenopausal phase (i.e., ≤ 6 mo and up to 2 yr postmenopause) is supported by findings from several clinical investigations (Lindsay et al., 1984; Ettinger et al., 1987; Hart et al., 1987; Riis et al., 1987; Munk-Jensen et al., 1988; Stevenson et al., 1990; Aloia et al., 1994; Cantatore et al., 1995). Munk-Jensen et al. (1988) reported an increase of greater than 6% in BMD in the lumbar spine, and in a very recent study, Cantatore et al. (1995) documented increases in both cortical and trabecular bone mass in the first 6 mo of estrogen treatment in women who were less than 6 mo from clinical menopause.

Women with established osteoporosis also clearly benefit from therapy with estrogen. Jensen et al. (1982) demonstrated a continuous increase in BMD in 70-yr-old women treated with oestradiol. Results of a more recent study by Lindsay et al. (1990) in women with established osteoporosis revealed a 2.7% increase in BMD in the femoral neck and a 5.3% increase in the lumbar spine. Similarly, Lufkin et al. (1992) reported increases in BMD of 7.6 and 5.3% in the femoral trochanter ($p < 0.03$) and lumbar spine, respectively, in osteoporotic women up to 25 yr from menopause who had received transdermal ERT.

It should be noted that broad generalizations based on an in-depth analysis of the studies cited in Tables 1 and 2 can be fraught with interpretative difficulties for many reasons. Coefficients of variations in separate studies using identical densitometric methods vary from 1% (Munk-Jensen et al., 1988) to 4% (Riis et al., 1987). In addition, some methods of measuring bone density (i.e., quantitative computed tomography [QCT]) can be criticized because they appear to overestimate bone loss (Laval-Jeantet et al., 1984). Moreover, differences in menopausal ages and in estrogen preparations, as well as the established heterogeneity of bone loss in oophorectomized (Orimo et al., 1993) and postmenopausal osteoporotic women (Civitelli et al., 1988; Eriksen et al., 1990; Arlot et al., 1993) often confound the interpretation of the derived data. The heterogeneous bone-loss patterns can result in serious misconceptions regarding the efficacy of estrogen, since postmenopausal patients with more rapid remodeling or "high-turnover" skeletal status respond better to attempts at therapeutic intervention with drugs that suppress bone resorption (Civitelli et al., 1988; Gennari et al., 1993). Finally, women with earlier onset of menopause are also more likely to have a sustained response to estrogens (Nachtigall et al., 1979).

Impact of Estrogen Replacement Therapy on Fracture Rate

Of significance from a broader clinical and public health perspective, results of a limited number of retrospective and prospective studies, as well as case-controlled studies, indicate that long-term ERT reduces fracture risk at specific fracture sites. More specifically, Ettinger et al. (1985) reported in one retrospective study that long-term estrogen therapy was associated with a 53.7% decrease in the number of vertebral fractures. In addition, case-controlled studies have consistently reported significant reductions in the risk of hip and Colles' fractures in postmenopausal osteoporotic women receiving ERT (Hutchinson et al., 1979; Weiss et al., 1980; Paganini-Hill et al., 1981; Kreiger et al., 1982; Kiel et al., 1987).

Two recently published retrospective cohort studies have also shown that long-term ERT confers statistically significant protection against both peripheral and vertebral compression fractures (Lafferty and Fiske, 1994; Maxim et al., 1995). In a long-term study from 1964 to 1989, Lafferty

Table 1
Prospective Studies Demonstrating Effects of Oral Estrogens on Bone Density

Author	Year	Therapy/ daily dose	No. of patients	Length of follow-up (yr)	Menopausal Age (yr)	% Change in BMD	Site measured	Method of assessment	Statistical significance
Lindsay	1976	Mestranol	63	5	0	0	Metacarpal	SPA	NA
et al.		24 mg		5	3	–0.8	Metacarpal	SPA	$p < 0.001$
				5	> 6	–0.8	Metacarpal	SPA	$p < 0.004$
Nachtigall	1979	Premarin	30	10	< 3	1	Metacarpal	SPA	$p < 0.001$
et al.		2.5 mg	37	10	> 3	0	Metacarpal	SPA	$p < 0.001$
Christiansen	1980	Trisequens	56	2	0.5–3.0	1.2	Distal forearm	SPA	$p < 0.01$
et al.		Forte							
Lindsay	1984	Premarin	150	2	1.5	0	Metacarpal	SPA	NS vs baseline;
et al.		0.625 mg							placebo loss $p < 0.01$
		1.25 mg							vs baseline
Ettinger	1987	Premarin	15	2	1.0–2.0	1.2	Lumbar spine	QCT	NA
et al.		0.3 mg							
Civitelli	1988	Premarin	10	1	3.0–7.0	8.3	Lumbar spine	DPA	$p < 0.05$
et al.		1.25 mg				2.6	Femur	DPA	$p < 0.05$
Munk-Jensen	1988	Oestradiol	50	1.5	0.5–2.0	6.4	Lumbar spine	DPA	$p < 0.01$
et al.		2 mg							
Gallagher	1989	Premarin							
et al.		0.3 mg	21	2	1.5–6.0	0.5	Lumbar spine	DPA	NA
		0.6 mg	21	2	1.5–6.0	1			
Lindsay	1990	Premarin	40	2	15	5.3	Lumbar spine	DPA	$p < 0.01$
et al.		0.625 mg				2.7	Femoral neck	DPA	NS
Stevenson	1990	Premarin	33	1.5	0–7.0	2	Lumbar spine	DPA	$p < 0.001$
et al.		0.625 mg				1.3	Femoral trochanter	DPA	$p < 0.001$
Harris	1991	Estrone sulfate	120	2	2.5	0	Lumbar spine	QCT	$p < 0.05$ vs
et al.		0.625 mg							placebo at
		1.25 mg							18 mo
Aloia	1994	Premarin	118	3	0.5–6.0	1.32	Trochanter	SPA	$p < 0.005$ vs baseline
et al.		0.625 mg				0.1	Femoral neck	SPA	NS
						–0.23	Spine	SPA	NS
						0.54	Radius	SPA	NS
Lafferty	1994	Premarin	81	11.5	4.7	12	Radius	SPA	$p < 0.02$ vs control
et al.		0.625 mg					(distal third)		
PEPI	1996	Premarin	875	3	5.0	5	Lumbar spine	DEXA	$p < 0.05$ vs baseline
Trial		0.625 mg				2	Femoral neck		$p < 0.05$ vs baseline

Abbreviations used: BMD = bone mineral density; SPA = single photon absorptiometry; NA = not available; NS = not statistically significant; QCT = quantitative computed tomography; DPA = dual photon absorptiometry; DEXA = dual energy x-ray absorptiometry.

Table 2
Prospective Studies Demonstrating Effects of Percutaneous Estrogens on Bone Density

Author	Year	Therapy/ daily dose	No. of patients	Length of follow-up (yr)	Menopausal Age (yr)	% Change in BMD	Site measured	Method of assessment	Statistical significance
Riis et al.	1987	Cream 3 mg	20	2	0.5–3.0	4.5	Lumbar spine	DPA	NA
Hart et al.	1987	Implant 50 mg 6/12	35	2	0–2.0	4.3	Lumbar spine	DPA	$p < 0.001$
Ribot et al.	1987	Patch 0.05 mg	30	1.5	2.9 ± 1.8 (mean)	5.4	Lumbar spine	DPA	$p < 0.02$ vs baseline
Ribot et al.	1988	Patch 50 mcg	15	2	1.0–5.0	6	Lumbar spine	DPA	$p < 0.001$ vs baseline
Adami et al.	1989	Patch 50 mcg	17	1.5	2.0–4.0	4.3	Forearm	DPA	$p < 0.01$ vs baseline
Stevenson et al.	1990	Patch 50 mcg	33	1.5	0.5–7.0	2	Lumbar spine	DPA	$p < 0.001$
						0	Femoral trochanter	DPA	$p < 0.001$ vs controls
Motta et al.	1991	Patch 50 mcg	38	2	0–14.0	0	Lumbar spine	QCT	NS loss in treated group; significant loss in control group ($p < 0.001$ vs baseline)
Lufkin et al.	1992	Patch 100 mcg	75	1	5.0–25.0	5.3	Lumbar spine	DPA	$p < 0.007$
						7.6	Femoral trochanter	DPA	$p < 0.03$
						1	Mid-radius	DPA	$p < 0.001$
Cantatore et al.	1995	Patch 0.05 mg (1st 6 mo)	12	1	< 0.5	Cortical 1.5 Trabecular 2.2	Distal forearm	SPA	Cortical NS Trabecular NS
		0.025 mg (2nd 6 mo)				Cortical –2.4 Trabecular –3.6	Distal forearm	SPA	Cortical $p < 0.03$ Trabecular $p < 0.03$
		0.1 mg (1st 6 mo)	12	1	< 0.5	Cortical 1.5 Trabecular 2.1	Distal forearm	SPA	Cortical NS Trabecular $p < 0.05$
		0.05 mg (2nd 6 mo)				Cortical 0.2 Trabecular 0.03	Distal forearm	SPA	Cortical NS Trabecular NS

Abbreviations used: BMD = bone mineral density; DPA = dual photon absorptiometry; NA = not available; QCT = quantitative computed tomography; NS = not statistically significant; SPA = single photon absorptiometry.

et al. reported a 12% increase in BMD in osteoporotic postmenopausal women treated with oral estrogens; this increase was accompanied by a significantly reduced risk of both vertebral fractures (fracture rate: 6.50 [control group] vs 1.09 [ERT group]) and peripheral fractures (fracture rate: 12.00 [control group] vs 2.19 [ERT group]) (relative risk for vertebral and peripheral fractures, 0.28) (Lafferty and Fiske, 1994). The optimal length of therapy needed to reduce fracture risk has not been firmly established. However, ERT was administered for at least 5 yr in most studies showing a reduction in fracture risk. The results of a recent prospective cohort study by Cauley et al. (1995) suggests that to decrease fracture risk, ERT should be initiated within 5 yr of menopause and continued for longer than 10 yr. In this study, current long-term estrogen use was associated with a 75% decrease in the risk of wrist fractures (relative risk, 0.39; CI, 0.24–0.06) and a 30–40% decrease in the risk of all nonspinal fractures (relative risk, 0.66; CI, 0.54–0.80) when compared with no estrogen use. There was no difference in the effect of ERT (i.e., unopposed estrogen) and estrogen plus progestin on fracture risk (Cauley et al., 1995).

Estrogen Dosing and Initiation and Duration of Therapy

An oral dose of 0.625 mg of conjugated estrogens or 1.5–2.0 mg of estradiol is considered to be the optimal therapy for both preventing bone loss and treating existing osteoporosis (Christiansen et al., 1980). Insignificant differences have been reported between the two therapies in maintaining bone mass long-term (Lindsay et al., 1976). Furthermore, lower levels of estrogen have been shown to be ineffective in reducing bone loss in postmenopausal and oophorectomized women (Lindsay et al., 1984). Results of Felson et al. (1993) and evidence from controlled clinical trials (Weiss et al., 1980; Ettinger et al., 1985; Moore et al., 1990; Naessén et al., 1993) consistently point to the benefit of initiating ERT as soon as menopause has been clinically confirmed and of continuing therapy for at least 5–10 yr. The earlier therapy is started, the greater the effect in preserving bone mass and decreasing fracture risk if therapy is continued (Hutchinson et al., 1979; Weiss et al., 1980; Paganini-Hill et al., 1981; Ettinger et al., 1985; Lindsay et al., 1991).

Traditionally, oral forms of estrogen have been the most widely prescribed. With oral estrogen formulations, however, relatively large doses must be administered to compensate for the significant first-pass effect in the liver during drug metabolism; during the first pass, as much as 60–90% of the administered dose will be metabolized, leaving only 10–40% of the active drug in the systemic circulation (Lievertz, 1987). Newer formulations of estrogen include gels, transdermal patches, subcutaneous implants, and vaginal suppositories. These formulations deliver the lowest effective estrogen dose directly into the systemic circulation. The transdermal patch has been found to be as effective as oral therapy (Stevenson et al., 1990; Lufkin et al., 1992).

Patient Risk Perceptions of Estrogen Replacement Therapy

Although ERT has been used for several decades, evidence regarding long-term benefits, safety, and risks continues to emerge, along with therapeutic and monitoring strategies to preclude the development of therapy-associated adverse outcomes. Yet despite these data, many patients for whom ERT is clearly indicated and/or prescribed for the treatment of osteoporosis remain noncompliant with the physician's prescribed regimen.

In a British study, Ryan et al. (1992) reported that of 127 postmenopausal women recommended to start (n = 105) or continue (n = 22) ERT for the treatment of osteoporosis, 28% of the new patients and a total of 39% of the women prescribed ERT discontinued treatment within an average of 8 mo, mostly due to side effects (17%). Ravnikar (1987), reporting preliminary results (5-yr data) from the retrospective Massachusetts Women's Health Survey of 2500 women given a prescription for ERT, found that 20% of new ERT patients discontinued therapy within 9 mo. An additional 20–30% of new ERT patients never had their prescriptions filled. Groeneveld et al. (1995) recently corroborated the high discontinuation rate of ERT in their follow-up study of 1689 women in an open population. These investigators reported that although the cumulative incidence of initial ERT prescription was high, 66% of patients stopped taking ERT within 21 mo of prescribed therapy. Reasons for noncompliance with prescribed ERT are usually related to adverse side effects—predominantly uterine withdrawal bleeding, or return of menses, and weight gain—and patient fears of endometrial and/or breast cancer (Ravnikar, 1987; Ryan et al., 1992). Other side effects and subjective complaints such as nausea, vomiting (especially with high doses), headaches, and depression, can also complicate ERT therapy (Yang et al., 1990).

Fear of cancer is probably the most common reason given by women who decline or are noncompliant with prescribed ERT (Lafferty and Fiske, 1994; Ravnikar, 1987; Ryan et al., 1991; Stumpf and Trolice, 1994). Although ERT has not been definitively linked as an etiologic factor in any type of cancer other than endometrial carcinoma in patients with an intact uterus receiving unopposed estrogen (Smith et al., 1975; Mack et al., 1976; Perrson et al., 1986; Grady et al., 1995), this fear remains in the forefront of many patients' minds. The most recent results from breast cancer studies in patients receiving estrogen-progestin therapy continue to reflect conflicting outcomes (Colditz et al., 1995; Stanford et al., 1995). Lafferty and Fiske (1994), reviewing the conclusions of four meta-analyses of a total of 94 ERT studies, concluded that the small increases in relative risks noted in the meta-analyses most likely reflect detection bias introduced by more frequent physical examinations and mammography among women receiving ERT. These investigators further stated that if a link does exist between ERT and an increased incidence of

breast cancer, it is probably confined to women using more potent estradiol preparations for ≥15 yr. Patient fears regarding the association between ERT and cancer can therefore be tempered by a clear explanation of these findings and of the therapeutic rationale for ERT in the treatment of osteoporosis.

Many women are unable to initiate ERT, however, secondary to medical contraindications. Current contraindications include:

1. Known or suspected estrogen-dependent neoplasias, particularly cancer of the breast or uterus;
2. Abnormal genital bleeding;
3. A history of severe thrombophlebitis or thromboembolic disease; and
4. Acute liver disease.

Even a prospective candidate's family history of these conditions or of diabetes mellitus, prophyria, or severe hypertension requires careful analysis of the benefit-to-risk ratio of ERT for that patient (Hammond and Maxson, 1982; Young et al., 1990).

In the face of the reported obstacles related to ERT and the clinical need for osteoporosis therapy, the practitioner is faced with analyzing not only the alternative therapeutic options for patients at risk for initial or continued postmenopausal bone loss, but also with the task of appropriately matching patients and optimal therapy. While ERT is generally considered to be the treatment of first choice for antiresorptive therapy in postmenopausal osteoporosis (Avioli, 1992; Carr et al., 1993; Marsh and Stevenson, 1993; Gennari et al., 1994), alternative modes of therapy are necessary in select patients. Recently, the Food and Drug Administration (FDA) approved salmon calcitonin nasal spray as a treatment option in individuals for whom ERT therapy is contraindicated, intolerable, or refused.

Salmon Calcitonin in the Prevention and Treatment of Osteoporosis

Mechanism of the Antiresorptive Action of Salmon Calcitonin

Calcitonin, a 32-amino-acid polypeptide, is secreted by the thyroidal C cells and is rapidly degraded after oral administration by the high concentrations of peptidase in the gastric secretions. Endogenous calcitonin production and secretion are dependent on the circulating level of ionized calcium. Specifically, low levels of calcium decrease calcitonin secretion; high levels of calcium stimulate calcitonin release. Diets consistently low in elemental calcium result in increased parathyroid hormone (PTH) secretion, decreased calcitonin secretion, and the subsequent stimulation of osteoclastic-regulated bone resorption. By comparison, diets high in calcium result in decreased PTH levels, increased calcitonin production, and a resultant decrease in osteoclastic-stimulated bone resorption.

Osteoclasts possess specific calcitonin-binding receptors and cause the brush borders of the osteoclasts to disappear, resulting in osteoclast movement away from the bone resorption surface (Reginster, 1991). The potent effects of calcitonin on osteoclasts are dose-related and occur within 30 min of administration. Other direct actions of calcitonin on osteoclasts include marked alterations of the internal structure of isolated osteoclasts, resulting in restricted cytoplasmic motility of the cells, and a reduction in the lifespan and number of osteoclasts. The net effect of these antiosteoclastic functions is a significant reduction in the bone resorptive activity and a consequent reduction in bone loss (Reginster, 1991).

Current Indications and Formulations of Calcitonin

The principal calcitonins used therapeutically are porcine, human (synthetic), salmon (synthetic), and eel. Of these substances, salmon calcitonin is the most potent (Reginster, 1991). Injectable forms of salmon calcitonin were first indicated for use in the treatment of Paget's disease in the United States and later received an indication for use in the treatment of postmenopausal osteoporosis. The injectionable (intramuscular [IM] or subcutaneous [SC]) formulations of salmon calcitonin, however, were often associated with a high rate of noncompliance in elderly patients. The recently approved nasal spray formulation has ameliorated the difficulties inherent in parenteral administration and is considered a suitable option as an alternative therapy in patients who are not appropriate candidates for ERT.

Review of Prospective Clinical Trial Data

The possibility that calcitonin might be effective in treating osteoporosis was first investigated in 1970 (Caniggia et al., 1970). Since that time, calcitonin—primarily salmon calcitonin—has been evaluated in therapeutic trials in healthy, early postmenopausal women and in osteoporotic women in the United States and abroad. In these studies, therapeutic responses vary from stabilization of bone loss to striking dose-related increments in vertebral and peripheral bone mass.

Tables 3 and 4 describes the many prospective trials that have been conducted in the past decade to analyze the effects of salmon calcitonin, administered by IM and SC injection and by the newer nasal spray formulation, on BMD in early postmenopausal women and those with established osteoporosis. In all but one of the trials (Mazzuoli et al., 1990), the female participants underwent natural menopause as opposed to oophorectomy.

Injectable Salmon Calcitonin Formulations

Controlled, prospective clinical trials utilizing the IM and SC formulations of salmon calcitonin at doses of 40, 50, and 100 IU administered at daily, every-other-day, or twice-a-week intervals have established the efficacy and safety of salmon calcitonin as a potent antiresorptive agent

Table 3
Prospective Studies Demonstrating the Effects of Injectable Salmon Calcitonin on Bone Density

Author	Year	Therapy/ daily dose	No. of patients	Length of follow-up (yr)	Menopausal Age (yr)	% Change in BMD	Site measured	Method of assessment	Statistical significance
Mazzuoli et al.	1986	IM 100 IU (qod)	21	0.5	17.3	10	Distal radius	DPA	$p < 0.001$
			16	1		13			$p < 0.05$
Civitelli et al.	1988	SC 50 IU (qod)	53	1	7.0–9.0	7.4	Lumbar spine	DPA	$p < 0.001$
						–3	Femoral mid-shaft	DPA	$p < 0.01$
Agnusdei et al.	1989	SC 100 IU (qod)	10	1	NA	7	Distal radius	DPA	$p < 0.01$
Mazzuoli et al.	1990	IM 100 IU (qod)	13	0.5	0	0	Distal forearm	DPA	NS vs baseline; $p < 0.01$ vs control
Meschia et al.	1992	IM 40 IU (× 2 d/wk)	26	1	5	0	Lumbar spine	DPA	NS
		IM 40 IU (× 2 d/wk) + Premarin 1.25 mg	26	1	4	10	Lumbar spine	DPA	$p < 0.001$
Rico et al.	1995	IM 100 IU (× 10 d/mo)	36	2.0	18	30.7	Pelvis	DPA	$p < 0.001$
						6.2	Arm	DPA	$p < 0.001$

Abbreviations used: BMD = bone mineral density; IN - intramuscular; DPA = dual photon absorptiometry; NS = not statistically significant; SC = subcutaneous; SPA = single photon absorptiometry.

Table 4
Prospective Studies Demonstrating the Effects of Salmon Calcitonin Nasal Spray on Bone Density

Author	Year	Therapy/ daily dose	No. of patients	Length of follow-up (yr)	Menopausal Age (yr)	% Change in BMD	Site measured	Method of assessment	Statistical significance
Reginster et al.	1987	IN 50 IU (× 5 d/wk)	30	1	<3	0.8	Lumbar spine	DPA	NS vs baseline; $p < 0.01$ vs control
Overgaard et al.	1989	IN 100 IU	19	2	2.5–5.0	2.5	Lumbar spine	DPA	$p < 0.001$ vs placebo
						–2	Total skeleton	DPA	NS
						–2	Distal forearm	SPA	NS
						–2	Proximal forearm	SPA	NS
Overgaard et al.	1989	IN 200 IU	17	1	18.0	0.8	Proximal forearm	SPA	NS
						–1	Distal forearm	SPA	NS
						1.4	Lumbar spine	DPA	NS
Agnusdei et al.	1989	IN 100 IU	20	1	NA	5	Distal radius	DPA	$p < 0.01$
Overgaard et al.	1992	IN 50 IU	40	2	21	–1	Distal forearm	SPA	NS
						1	Lumbar spine	Dual energy X-ray absorptiometry	$p = 0.008$
		IN 100 IU	43	2	24	–1	Distal forearm	SPA	NS
						2	Lumbar spine	Dual energy X-ray absorptiometry	$p = 0.008$
		IN 200 IU	41	2	21	–0.9	Distal forearm	SPA	NS
						3	Lumbar spine	Dual energy X-ray absorptiometry	$p = 0.008$
Reginster et al.	1994	IN 50 IU (× 5 d/wk)	91	3	<3	1.8	Lumbar spine	DPA	$p < 0.05$ vs baseline
Ellerington et al.	1996	IN 200 IU daily	18	2	<5	0.5	Lumbar spine	DPA	NS vs placebo
			18	2	>5	3.1	Lumbar spine	DPA	$p < 0.01$ vs placebo
		IN 200 IU (3×/wk)	17	2	<5	–0.1	Lumbar spine	DPA	NS vs placebo
			18	2	>5	0.6	Lumbar spine	DPA	NS vs placebo

Abbreviations used: BMD = bone mineral density; IN - intranasal; DPA = dual photon absorptiometry; NS = not statistically significant; SPA = single photon absorptiometry.

(Mazzuoli et al., 1986, 1990; Civitelli et al., 1988; Agnusdei et al., 1989; Meschia et al., 1992; Rico et al., 1995). In these studies, all patients had been postmenopause for at least 4 yr (range, 4–18 yr), except those in the study by Mazzuoli et al. (1990) who were evaluated following oviarectomy. Five of six studies demonstrated either statistically significant stabilization of bone loss (i.e., 0% increase in BMD) (Mazzuoli et al., 1990) or significant increases in BMD ranging from 7–30.7% (Mazzuoli et al., 1986; Civitelli et al., 1988; Agnusdei et al., 1989; Rico et al., 1995). Typical increases in BMD in the latter studies ranged from 7–13%.

Early observations of an analgesic effect associated with injectable salmon calcitonin in patients with osteoporotic fractures led to further evaluation of this therapeutic effect in other studies. Lyritis et al. (1991) conducted a double-blind placebo-controlled clinical study of the analgesic effect of 100 IU salmon calcitonin IM in patients with osteoporotic vertebral fractures; a significant reduction ($p < 0.001$) in pain intensity was observed in the group receiving calcitonin vs the placebo group. The beneficial effect of salmon calcitonin therapy was observed from the second day of treatment onward and was associated with early and increased mobility in the treatment group. Additional studies utilizing salmon calcitonin in other pain states have been conducted with significant increases in analgesia associated with therapy (Gennari et al., 1985; Roth and Kolaric, 1986; Szanto et al., 1986).

In studies of injectable salmon calcitonin in osteoporotic patients, therapy was well tolerated, with only occasionally reported side effects, such as nausea and flushing. Compliance may be hindered, however, with the injectable salmon calcitonin formulations, especially in elderly patients and those receiving long-term treatment (Meschia et al., 1992). The nasal spray formulation was developed to overcome these limitations to therapy and to enhance patient convenience and compliance.

Nasal Spray Formulation

The efficacy and safety of salmon calcitonin nasal spray has been evaluated in seven prospective trials in doses of 50, 100, and 200 IU in osteoporotic women with menopausal ages ranging from less than 3 yr to 24 yr (Reginster et al., 1987, 1994; Agnusdei et al., 1989; Overgaard et al., 1989a,b, 1992; Ellerington et al., in press). Administration protocols studied in these trials include daily dosing in the majority of studies (Agnusdei et al., 1989; Overgaard et al., 1989a,b, 1992; Ellerington et al., in press), five consecutive days per week, (Reginster, et al., 1987, 1994) and alternate days three times per week (Ellerington et al., in press).

Lower-Dose (50 IU and 100 IU) Regimens. In the two clinical trials conducted by Reginster et al., (1987, 1994) doses of 50 IU of salmon calcitonin nasal spray were administered daily on five consecutive days per week to postmenopausal women less than 3 yr from menopause. Statistically significant increases in lumbar spine BMD values of 0.8% ($p < 0.01$ vs control patients) (Reginster et al., 1987) and 1.8% ($p < 0.05$ vs baseline) (Reginster et al., 1994) were observed in these studies after 1 and 3 yr of therapy with salmon calcitonin nasal spray, respectively.

Overgaard et al. (1989a) studied doses of 100 IU salmon calcitonin nasal spray in osteoporotic women 2.5–5 yr from menopause. These investigators also reported statistically significant increases in lumbar spine BMD values of 2.5% in treated patients vs placebo patients ($p < 0.001$); BMD values for the total skeleton and distal and proximal forearm were not significantly increased over placebo, however. In a similar study by Agnusdei et al. (1989), in which 100 IU doses were utilized, BMD values at the distal radius were increased by 5% ($p < 0.01$) after 1 yr of continuous therapy with intranasal salmon calcitonin.

Higher-Dose (200 IU) Regimens. In the first study of 200 IU salmon calcitonin administered daily, Overgaard et al. (1989b) evaluated changes in BMD at the proximal and distal forearm and lumbar spine in 17 women with established osteoporosis (mean years from menopause, 18) after 1 yr of continuous therapy. The calcitonin group did not lose BMD at any site measured vs the placebo and control groups ($p < 0.001$): Increases of 0.8 and 1.4% in BMD were documented at the proximal forearm and lumbar spine, respectively (p = NS) (Overgaard et al., 1989b).

To further clarify the relationship between outcome and dose, Overgaard et al. (1992) conducted a follow-up dosing study evaluating outcome in patients with established osteoporosis who received 50 IU ($n = 40$), 100 IU ($n = 43$), or 200 IU ($n = 41$) of salmon calcitonin nasal spray daily for 2 yr. Measured sites were the distal forearm and lumbar spine. In this double-blind placebo-controlled study, statistically significant increases in BMD were observed in lumbar spine BMD values at each dose vs placebo ($p = 0.008$), although these increases were greatest in the 200 IU group (mean, 3%; range, 1.8–4.2%) (Table 4). Thus, spinal bone mass increased in a dose-dependent manner to a statistically significant degree at both 1 yr ($p = 0.007$) and 2 yr ($p = 0.008$) (Fig. 1). At the distal forearm, BMD decreased in all patients but to a lesser degree in the 200 IU salmon calcitonin group (–0.9%) vs placebo-treated patients (–1.2%) at 2 yr (p = NS). In addition, there was no difference in the incidence side effects reported in the salmon calcitonin groups—regardless of dose—vs the placebo group (Overgaard et al., 1992).

Ellerington et al. studied two administration protocols utilizing 200 IU doses of intranasal salmon calcitonin: daily dosing and alternate-day dosing three times per week (i.e., Monday–Wednesday–Friday schedule) for 2 yr in 36 and 37 patients, respectively. The investigators further subdivided patients into groups according to menopausal age within each dosing group. Patients who were 5 yr or less from menopause were classified as "early postmenopause" patients and those who were >5 yr from menopause were

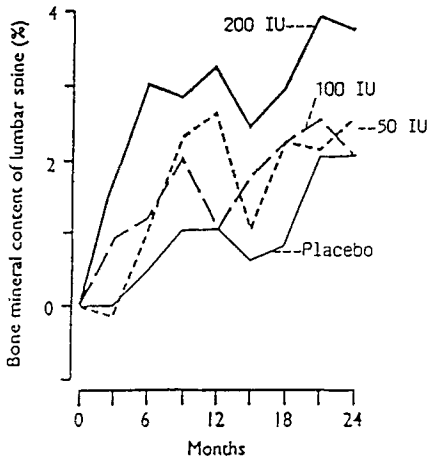

Fig. 1. Bone mineral content of the lumbar spine during a 2-year study with salmon calcitonin nasal spray: (——) placebo; (- - -) 50 IU salmon calcitonin; (- - -) 100 IU salmon calcitonin; (——) 200 IU salmon calcitonin. (Reproduced from Overgaard et al., 1992).

patients and those who were >5 yr from menopause were classified as "late postmenopause" patients (Ellerington et al., 1996). Women who were >5 yr from menopause (and who had the lowest baseline BMD values) and who received daily salmon calcitonin 200 IU showed the greatest response to treatment: lumbar spine BMD increased 3.1% vs placebo ($p < 0.01$). Women who received thrice-weekly salmon calcitonin 200 IU or placebo had significant decreases in lumbar spine BMD vs baseline values. Therapy with salmon calcitonin nasal spray was well tolerated by all patients, and no significant treatment-related adverse events were reported (Ellerington et al., 1996).

On the basis of the results in each of the studies of 200 IU salmon calcitonin nasal spray by Overgaard et al. (1992) and Ellerington et al. (1996) the most significant and consistent improvements in BMD measures occurred with daily doses of 200 IU in women with established osteoporosis. Although vertebral bone mass was preserved by 50–100 IU/d, (Reginster et al., 1987; Overgaard et al., 1989a) the peripheral bones were not protected by these dosages (Overgaard et al., 1989a). In addition to these findings, the beneficial effects of 200 IU of salmon calcitonin nasal spray on fracture rates have also been reported.

Impact of Salmon Calcitonin on Fracture Rates

Therapy with salmon calcitonin clearly decreases fracture rates in patients with established osteoporosis. A Mediterranean osteoporosis study that examined the incidence of hip fracture in women 50 yr or older from six countries in southern Europe demonstrated that calcitonin, like estrogen therapy, significantly decreased the incidence of hip fractures (Kanis et al., 1992). In this study, calcitonin therapy and ERT were associated with the greatest reduction in risk of hip fracture of all osteoporosis therapies (adjusted relative risk values: calcitonin 0.69 [95% CI, 0.51–0.92], $p = 0.015$, estrogen, 0.55 [95% CI, 0.36–0.85], $p = 0.01$) (Kanis et al., 1992).

Calcitonin therapy for 2 yr also produced a significant reduction in vertebral fracture rates in elderly osteoporotic postmenopausal women who previously had one or more vertebral fractures (Rico et al., 1992). In fact, preliminary data reveal that salmon calcitonin nasal spray 200 IU daily administered for 2 yr to women with established osteoporosis reduced the incidence of new fractures by 66% when compared with placebo (Overgaard et al., 1992). As previously stated, these changes were accompanied by a statistically significant difference in lumbar spine BMD between the calcitonin- treated and placebo groups (Overgaard et al., 1992). Epidemiologic data further suggest that every 3% increase in BMD corresponds to a 15–20% decrease in fracture rates at either the spine or femoral neck (Slemenda, personal communication, 1994).

Summary

The nasal spray formulation of salmon calcitonin has made available in a convenient dosage form an osteoclastic agent with the potency of estrogen in altering markers of bone turnover and metabolism. While the results of ongoing studies will continue to expand the knowledge base of the primary care physician in the management of the potentially devastating personal and public health problem of postmenopausal osteoporosis, available data serve as a current guide to the clinician in developing an optimal therapeutic regimen suited to the medical and personal needs of the patient. As delineated in this review, the range of increases in BMD induced by salmon calcitonin and ERT is comparable.

Given the enormous public health consequences of postmenopausal osteoporosis and osteoporotic fractures, the primary care physician is faced with the challenge of not only educating the growing segment of elderly patients regarding the ubiquitous and inevitable decline in bone mass, but of actively recruiting appropriate patients for antiresorptive therapy based on current epidemiologic statistics. Estrogen replacement therapy is currently considered the primary antiresorptive therapy for osteoporosis, yet many patients are unable or unwilling to accept and initiate prescribed therapy. Significant, documented noncompliance is also associated with ERT in patients who do start treatment. Nasal salmon calcitonin should be considered an appropriate alternative in all such patients since the efficacy of this agent in increasing BMD is comparable to ERT.

Importantly, the safety profile of salmon calcitonin has been demonstrated in clinical trials since the early 1970s when the first injectable formulation was approved for use in various European countries; the safety of injectable salmon calcitonin was further established by wider clinical trials, leading to the 1986 FDA approval for its use in the United States. The nasal spray formulation of salmon calcitonin—more recently approved by the FDA—offers fur-

ther advantages in ease of administration, an uncomplicated dosing regimen, and lack of restrictions related to drug administration with food—all factors that may increase the likelihood of potentially improved compliance with long-term therapy. Furthermore, salmon calcitonin does not induce uterine bleeding and is associated with little to no gastrointestinal upset. In patients with vertebral crush fractures, the analgesic action of salmon calcitonin provides additional pharmacotherapeutic benefit (Pun and Chan, 1989). Drug interactions, a common concern in elderly patients receiving multiple agents, have not been reported with salmon calcitonin. It appears justifiable to conclude, therefore, that salmon calcitonin nasal spray provides the physician with an appropriate alternative approach for the treatment of postmenopausal bone loss.

References

Adami, S., Suppi, R., Bertoldo, F., et al. (1989). *Bone Miner.* **7,** 79–86.

Agnusdei, D., Gonnelli, S., Camporeale, A., et al. (1989). *Minerva Endocrinol.* **14,** 169–176.

Aitken, J. M., Hart, D. M., and Lindsay, R. (1973). *BMJ* **3,** 515–518.

Al-Azzawi, F., Hart, D. M., and Lindsay, R. (1987). *BMJ* **294,** 1261,1262.

Aloia, J. F., Vaswani, A., Yeh, J. K., et al. (1994). *Ann. Intern. Med.* **120,** 97–103.

Arlot, M. E., Bradbeer, J. N., Edouard, C., et al. (1993). *Calcif. Tissue Int.* **52,** 10–15.

Avioli, L. A. (1992). *Geriatrics* **47,** 58–67.

Caniggia, A., Gennari, C., Bencini, M., et al. (1970). *Clin. Sci.* **38,** 397–407.

Cantatore, F. P., Cicinelli, E., Galantino, P., et al. (1995). *Arthritis Rheum.* **38,** 292–294.

Carr, B. R., Dawson-Hughes, B., and Ettinger, B. (1993). *Patient Care* **7,** 31–56.

Cauley, J. A., Seeley, D. G., Ensrud, K., et al. (1995). *Ann. Intern. Med.* **122,** 9–16.

Christiansen, C., Christensen, M. S., McNair, P., et al. (1980). *Eur. J. Clin. Invest.* **10,** 273–279.

Civitelli, R., Agnusdei, D., Nardi, P., et al. (1988). *Calcif. Tissue Int.* **42,** 77–86.

Civitelli, R., Bonnelli, S., Zacchei, F., et al. (1988). *J. Clin. Invest.* **82,** 1268–1274.

Colditz, G. A., Hankinson, S. E., Hunter, D. J., et al. (1995). *N. Engl. J. Med.* **332,** 1589–1593.

Compston, J. E. (1992). *Br. Med. Bull.* **48,** 309–344.

Cummings, S. R., Kelsey, I. L., Nevitt, M. C., and O'Dowd, K. J. (1985). *Epidemiol. Rev.* **7,** 178–208.

Davidson, N. E. (1995). *N. Engl. J. Med.* **332,** 1638,1639.

Ellerington, M. C., Hillard, T. C., Whitcroft, S. I. J., et al. (1996) *Calcif. Tissue Int.* **59,** 6–11.

Eriksen, E. F., Hodgson, S. T., Eastell, R., et al. (1990). *J. Bone Miner. Res.* **5,** 311–319.

Ettinger, B., Genant, H. K., and Cann, C. E. (1985). *Ann. Intern. Med.* **102,** 319–324.

Ettinger, B., Genant, H. K., and Cann, C. E. (1987). *Ann. Intern. Med.* **106,** 40–45.

Felson, D. T., Zhang, Y., Hannan, M. T., et al. (1993). *N. Engl. J. Med.* **329,** 1141–1146.

Gallagher, J. C., Goldgar, D., and Kable, W. T. (1989). *Sixth International Workshop on Bone and Soft Tissue.* Ontario, Canada.

Gallagher, J. C., Melton, L. J., Riggs, B. L., and Bergstrath, E. (1980). *Clin. Orthop.* **150,** 163–171.

Gennari, C., Agnusdei, D., and Camporeale, A. (1993). *Osteoporosis. Int.* **1 (Suppl),** S208–S210.

Gennari, C., Chierichetti, S. M., Piolini, M., et al. (1985). *Curr. Ther. Res.* **38,** 298–308.

Gennari, C., Nuti, R., Agnusdei, D., et al. (1994). *Drug Saf.* **11,** 179–195.

Grady, D., Gebretsadik, T., Kerlikowske, K., et al. (1995). *Obstet. Gynecol.* **85,** 304–313.

Groeneveld, F. P. M. J., Bareman, F. P., Barentsen, R., et al. (1995). *Maturitas* **20,** 81–89.

Hammond, C. B. and Maxson, W. S. (1982). *Fertil. Steril.* **37,** 5–25.

Harris, S. T., Genant, H. K., Baylink, D. J., et. al. (1991). *Arch. Intern. Med.* **151,** 1980–1984.

Hart, D. M., Al-Azzawi, F., Farish, E., et al. (1987). In: *Osteoporosis 1987.* Christiansen, C., Johansen, J. S., and Riis, B. J. (eds.). International Symposium on Osteoporosis. *Osteopress ApS* **1,** 572–574.

Horsman, A., Gallagher, J. C., Simpson, M., and Nordin, B. E. C. (1977). *BMJ* **2,** 789–792.

Hutchinson, T. A., Polansky, S. M., and Feinstein, A. R. (1979). *Lancet* **2,** 705–709.

Jensen, G. F., Christiansen, C., and Transbøl, I. B. (1982). *Obstet. Gynecol.* **60,** 493–496.

Kanis, J. A., Johnell, O., Gullberg, B., et al. (1992). *BMJ* **305,** 24–28.

Kanis, J. A., Melton, L. J., III, Christianson, C., et al. (1994). *J. Bone Miner. Res.* **9,** 1137–1141.

Kiel, D. P., Felson, D. T., Anderson, J. J., et al. (1987). *N. Engl. J. Med.* **317,** 1169–1174.

Kreiger, N., Kelsey, J. L., Holford, T. R., and O'Connor, T. (1982). *Am. J. Epidemiol.* **116,** 141–148.

Lafferty, F. W. and Fiske, M. E. (1994). *Am. J. Med.* **97,** 66–77.

Laval-Jeantet, A. M., Cann, C. E., Roger, B., and Dallant, P. (1984). *J. Comput. Assist. Tomogr.* **8,** 1164–1167.

Lewinnek, G. E., Kelsey, J., White, A. A., III, and Kreiger, N. J. (1980). *Clin. Orthop.* **152,** 35–43.

Lievertz, R. W. (1987). *Am. J. Obstet. Gynecol.* **156,** 1289–1293.

Lindsay, R. (1991). *Am. J. Med.* **91 (Suppl 5B),** 5B-10S–5B-13S.

Lindsay, R. (1993). In: *The Osteoporotic Syndrome: Detection, Prevention, and Treatment.* Avioli, L. V. (ed.). Wiley-Liss: New York, pp. 123–136.

Lindsay, R. and Tohme, J. F. (1990). *Obstet. Gynecol.* **76,** 290–295.

Lindsay, R., Aitken, S. M., Anderson, J. B., et al. (1976). *Lancet* **1,** 1038–1041.

Lindsay, R., Cosman, F., and Nieves, I. (1993). *Osteoporos. Int.* **1 (Suppl),** S150– S152.

Lindsay, R., Hart, D. M., and Clark, D. M. (1984). *Obstet. Gynecol.* **63,** 759–763.

Looker, A. C., Johnston, C. C., Jr., Wahner, H. W., et al. (1995). *J. Bone Miner. Res.* **10,** 796–802.

Lufkin, E. G., Wahner, H. W., O'Fallon, W. M., et al. (1992). *Ann Intern. Med.* **117,** 1–9.

Lyritis, G. P., Tsakalakos, N., Magiasis, B., et al. (1991). *Calcif. Tissue Int.* **49,** 369–372.

Mack, T. M., Pike, M. C, Henderson, B. E., et al. (1976). *N. Engl. J. Med.* **294,** 1262–1267.

Marsh, M. S. and Stevenson, J. C. (1993). *Baillieres Clin. Rheumatol.* **7,** 549–560.

Maxim, P., Ettinger, B., and Spitalny, G. M. (1995). *Osteoporos. Int.* **5,** 23–29.

Mazzuoli, G. F., Passeri, M., Gennari, C., et al. (1986). *Calcif. Tissue Int.* **38,** 3–8.

Mazzuoli, G. F., Tabolli, S., Bigi, F., et al. (1990). *Calcif. Tissue Int.* **47,** 209–214.

Melton, L. J., III (1993). In: *Size Osteoporotic Syndrome: Detection, Prevention, and Treatment,* 3rd ed. Avioli, L. V. (ed.). Wiley-Liss: New York, pp. 17–38.

Melton, L. J., III (1995). *J. Bone Miner. Res.* **10,** 175–177.

Meschia, M., Brincat, M., Barbacini, P., et al. (1992). *Eur. J. Obstet. Gynecol. Reprod. Biol.* **47,** 53–57.

Miller, C. W. (1978). *J. Bone Joint Surg. Am.* **60-A,** 930–934.

Moore, M., Bracker, M., Sartoris, D., et al. (1990). *J. Bone Miner. Res.* **5,** 659–664.

Motta, T., Santoro, L., Messina, C., et al. (1991). *Ital. J. Mineral Electrolyte Metab.* **5,** 21–25.

Munk-Jensen, N., Nielsen, S. P., Obel, E. B., and Eriksen, P. B. (1988). *BMJ* **296,** 1150–1152.

Nachtigall, L. E., Nachtigall, R. H., Nachtigall, R. D., and Beckman, E. M. (1979). *Obstet Gynecol.* **53,** 277–281.

Naessén, T., Persson, I., Thor, L., et al. (1993). *Br. J. Obstet. Gynaecol.* **100,** 454–459.

Nevitt, M. C. (1994). *Rheum. Dis. Clin. North Am.* **20,** 535–559.

Orimo, H., Shiraki, M., and Inoue, S. (1993). *Osteoporos. Int.* **1 (Suppl),** S153–S156.

Overgaard, K., Hansen, M. A., Jensen, S. B., and Christiansen, C. (1992). *BMJ.* **305,** 556–561.

Overgaard, K., Riis, B. J., Chnstiansen, C., and Hansen, M. A. (1989). *BMJ* **299,** 477–479.

Overgaard, K., Riis, B. J., Christiansen, C., et al. (1989). *Clin. Endocrinol.* **30,** 435–442.

Paganini-Hill, A., Ross, R. K., Gerkins, V. R., et al. (1981). *Ann. Intern. Med.* **95,** 28–31.

Peck, W. A., Riggs, B. L., Bell, N. H., et al. (1988). *Am. J. Med.* **84,** 275–282.

PEPI Trial Investigators Writing Group (1996) *JAMA,* in press.

Perrson, I. R., Adami, H. -O., Eklund, G., et al. (1986). *Acta Obstet. Gynecol. Scand.* **65,** 211–217.

Phillips, S., Fox, N., Jacobs, I., and Wright, W. E. (1988). *Bone* **9,** 271–279.

Pun, K. K. and Chan, L. W. L. (1989). *Clin. Ther.* **11,** 205–209.

Ravnikar, V. A. (1987). *Am. J. Obstet. Gynecol.* **156,** 1332–1334.

Recker, R. R., Saville, P. D., and Heaney, R. P. (1977). *Ann. Intern. Med.* **87,** 649–655.

Reginster, J. Y., Albert, A., Lecart, M. P., et al. (1987). *Lancet* **2,** 1481–1483.

Reginster, J. Y., Denis, D., Deroisy, R., et al. (1994). *J. Bone Miner. Res.* **9,** 69–73.

Reginster, J.-Y. (1991). *Am. J. Med.* **91 (Suppl 5B),** 19S–22S.

Ribot, C., Pouillès, J. M., and Tremollières, F. (1988). *Proceedings of the Twelfth World Congress of Obstetrics and Gynaecology.* Rio de Janeiro, Brazil, 35–42.

Ribot, C., Trémollières, F., Pouillès, J. M., et al. (1987). In: *Osteoporosis 1987.* Christiansen, C., Johansen, J. S., and Riis, B. J. (eds.). Intemational Symposium on Osteoporosis. *Osteopress ApS* **1,** 546–548.

Rico, H., Hemandez, E. R., Revilla, M., and Gomez-Castresana, F., (1992). *Bone Miner.* **16,** 131–138.

Rico, H., Revilla, M., Hernández, E. F., et al. (1995). *Calcif. Tissue Int.* **56,** 181–185.

Riggs, B. L. (1991). *West J. Med.* **154,** 63–77.

Riggs, B. L. and Melton, L. J., III (1992). *N. Engl. J. Med.* **327,** 620–627.

Riis, B. J., Thomsen, K., Strøm V., and Christiansen, C. (1987). *Am. J. Obstet. Gynecol.* **156,** 61–65.

Roth, A. and Kolaric, K. (1986). *Oncology* **43,** 283–287.

Ryan, P. J., Harrison, R., Blake, G. M., and Fogelman, I. (1992). *Br. J. Obstet. Gynaecol.* **99,** 325–328.

Savvas, M., Studd, J. W. W., Fogelman I., et al. (1988). *BMJ* **297,** 331–333.

Smith, D. C., Prentice, R., Thompson, D. J., and Herrmann, W. L. (1975). *N. Engl. J. Med.* **293,** 1164–1167.

Stanford, J. L., Weiss, N. S., Voigt, L. F., et al. (1995). *JAMA* **274,** 137–142.

Stevenson, J. C., Cust, M. P., Gangar, K. F., et al. (1990). *Lancet* **336,** 265–269.

Stumpf, P. G. and Trolice, M. P. (1994). *Obstet. Gynecol. Clin. North Am.* **21,** 219–229.

Szanto, J., Jozsef, S., Rado, J., et al. (1986). *Oncology* **43,** 69–72.

Villareal, D. T., Rupich, R. C., Pacifici, R., et al. (1992). *Osteoporos. Int.* **2,** 70–73.

Weiss, N. S., Ure, C. L., Ballard, J. H., et al. (1980). *N. Engl. J. Med.* **303,** 1195–1198.

World Health Organization. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. WHO *Technical Report Series 843, 1994,* World Health Organization, Switzerland.

Young, R. L., Kumar, N. S., and Goldzieher, J. W. (1990). *Drugs* **40,** 220–230.