Gonadotropin-releasing hormone agonists and the skeleton

Ignac Fogelman, M.D.*

Department of Nuclear Medicine, Guy's Hospital, St. Thomas Street, London, United Kingdom

Objective: To review and evaluate published studies that have assessed the effect on the skeleton of treatment with gonadotropin-releasing hormone agonists (GnRH-a). The effects on bone biochemistry and bone density are presented.

Data Identification: Major studies reporting on bone and GnRH-a use were identified through Excerpta Medica and Medline searches.

Study Selection: Those that have reported on GnRH-a treatment in patients where data relating to skeletal metabolism or bone density were obtained.

Results: Changes in bone biochemistry during GnRH-a therapy indicate that there is altered skeletal metabolism associated with GnRH-a use. The data on changes in bone density after a 6-month course of GnRH-a therapy generally indicate some bone loss. The magnitude of any detected change in bone density depends on the skeletal site assessed and the method of assessment. No significant bone loss has been documented in cortical bone; any bone loss occurring is usually associated with trabecular bone and is partially or completely reversible on withdrawal of GnRH-a treatment.

Conclusions: A 6-month course of GnRH-a therapy may result in a small reduction in trabecular bone density that is partially or completely reversible on withdrawal of treatment. The magnitude of any persistent residual bone loss is unlikely to be of clinical relevance and the benefits of a single 6-month course of GnRH-a therapy should not be withheld on the basis of a possible effect on bone. Fertil Steril 1992;57:715–24

Key Words: GnRH agonists; bone density; bone metabolism; hypoestrogenemia

In recent years several potent agonistic analogues of gonadotropin-releasing hormone (GnRH) have become available for use in clinical practice (1). These compounds are decapeptides, and oral use is not possible because GnRH agonists (GnRH-a) would be degraded in the gastrointestinal tract. Therefore, preparations with alternative routes of administration such as intranasal (IN) spray and subcutaneous (SC) or intramuscular (IM) injections have been developed. Gonadotropin-releasing hormone agonists cause initial stimulation of the pituitary-ovarian axis. However, with repeated dosing this stimulatory response is attenuated, and within a few days to a few weeks there is progressive suppression of gonadal steroidogenesis and reduction in serum estradiol (E₂) levels in women. The explanation for this apparently paradoxical effect of an agonist is that normally GnRH is secreted from the hypothalamus in a pulsatile fashion, but in the presence of continuous GnRH stimulation the receptors for GnRH on the gonadotrophs are not capable of being regenerated (down regulation) (2). The induction of estrogen (E) deficiency may be of clinical benefit, for example, in endometriosis (3, 4). It is, however, well recognized that E deficiency leads to bone loss, and this is a potentially serious complication of what may otherwise be an effective treatment. This review will evaluate the current data relating to the effect of GnRH-a on the skeleton.

GnRH-a THERAPY AND SKELETAL METABOLISM

After a natural menopause (5) or oophorectomy (6), there are profound changes in bone biochem-
istry. Because GnRH-a rapidly induce hypoestrogenism, it is reasonable to expect an effect on skeletal metabolism. Several studies have addressed this issue. Gudmundsson et al. (7) studied 47 healthy women (average age 29.4 years) who were menstruating normally. Twenty-five women received 100 \( \mu g/d \) nafarelin IN, whereas 22 women received 200 \( \mu g/d \) IN for 6 months. The dose was reduced in 14 women taking the higher dosage because of symptoms such as hot flushes, with several patients subsequently discontinuing therapy. Evaluative data were present for 42 women. While on treatment, serum calcium and phosphate rose with a fall in parathyroid hormone levels. Serum osteocalcin rose, but there was no significant change in serum alkaline phosphatase (parameters reflecting bone formation). Urinary calcium/creatinine and hydroxyproline/creatinine ratios (parameters reflecting bone resorption) were also elevated. The data were, in addition, analyzed on the basis of whether women were smokers or nonsmokers, and in general all changes were more marked in the nonsmokers. No direct correlation was found between \( E_2 \) levels and the indices of bone metabolism, but a subgroup of 8 women, whose average \( E_2 \) levels were above 200 pmol/L during the last month of treatment, did not show any significant change in either the serum or urinary parameters. In other words, the biochemical changes were related to a significant fall in \( E_2 \) levels. Similar changes were found with both regimens. No follow-up data were presented.

Similar results on bone resorption were obtained by Steingold et al. (8) who studied 16 women with endometriosis, between 21 and 38 years of age, who were treated with goserelin 100 \( \mu g/d \) SC for 6 months. Two women withdrew from the study because of emotional side effects. Urinary calcium/creatinine and hydroxyproline/creatinine ratios were obtained before treatment and at 1, 3, and 6 months of therapy. Values were compared with those from 10 women who had bilateral oophorectomy carried out at least 6 months before the study. Both calcium/creatinine and hydroxyproline/creatinine ratios were lower at baseline when compared with the oophorectomy group, but values rose significantly by 3 months of treatment to be indistinguishable from the oophorectomy group, and elevated values persisted at 6 months. After treatment, values fell and were not significantly different from baseline. No biochemical parameters reflecting bone formation were obtained in this study.

This increase in bone resorption and subsequent return to pretreatment levels has also been shown by Johansen et al. (9). In this study, 25 women with endometriosis, between 19 and 43 years of age, received nafarelin IN, 16 receiving 200 \( \mu g \) and 9 receiving 400 \( \mu g/d \) for 6 months. Measurements were obtained every 3 months, and patients were followed up for 6 months after treatment. Serum alkaline phosphatase and osteocalcin were measured together with urinary calcium/creatinine and hydroxyproline/creatinine ratios. For both therapy groups, there was a significant rise in all variables by 6 months of treatment, which was not dose dependent. After withdrawal of treatment the values fell, but serum alkaline phosphatase and osteocalcin were still elevated 3 months after treatment, although by 6 months levels were similar to pretreatment values.

A change in the parameters reflecting bone formation has also been demonstrated by Dlugi et al. (10) in a randomized, double-blind, multicenter study involving 52 patients with endometriosis. Patients received either leuprolide acetate (LA) 3.75 mg by monthly depot IM injections or a placebo for 6 months. Those receiving the active compound had significantly elevated values of serum calcium and alkaline phosphatase at the end of 6 months when compared with baseline values and control subjects.

In a study involving patients with leiomyomas, Van Leusden and Dogterom (11) concluded that their results reflected increased bone turnover rather than bone loss. In this study, 10 women were treated with depot injections of triptorelin 4 mg monthly for 6 months and evaluative data were available for 9 subjects. There were significant rises in serum calcium, alkaline phosphatase, and osteocalcin at the end of therapy when compared with baseline values. However, urinary excretion of calcium and hydroxyproline was not increased. The authors’ (11) conclusions, however, are not in keeping with what is known about bone remodeling, in that bone formation invariably follows an initial phase of resorption. The implication is that there is direct stimulation of osteoblastic activity (as happens, for example, with fluoride therapy) which does not occur with GnRH-a. It should be noted that 24-hour urine collections were obtained for total calcium and hydroxyproline excretion. The data were not normalized for creatinine, and therefore results would have been affected by dietary changes.

The above results are, nevertheless, in general agreement and show that there is altered skeletal metabolism in association with GnRH-a use. A rise in both the urinary calcium/creatinine and hydroxyproline/creatinine ratios is among the earliest demonstrable changes and may be expected to be
found within 3 months. This reflects an increase in bone resorption after withdrawal of the protective effect of E on the skeleton. Serum calcium rises with suppression of parathyroid hormone. As would be expected from the bone remodeling cycle, there is coupling between resorption and formation, and after the increase in resorption there is an increase in those parameters reflecting bone formation, i.e., serum alkaline phosphatase and osteocalcin.

GnRH-a THERAPY AND BONE DENSITY

Many studies have been reported (9, 10, 12–24) on the effects of GnRH-a on bone density as measured by single photon absorptiometry, dual photon absorptiometry, and quantitative computed tomography (CT). However, the results obtained have varied depending on the skeletal site studied and the method of measurement. It should also be noted that precision of these methods is variable and relevant when changes that may be as small as 1% or 2% are being measured.

In addition to assessing biochemical changes, Johansen et al. (9) and Dlugi et al. (10) also assessed bone density. Johansen et al. (9) used single photon absorptiometry on the distal forearm and dual photon absorptiometry on the spine in women with endometriosis, 16 of whom received nafarelin 200 μg/d and 9 of whom received 400 μg/d. Treatment was for 6 months with 6 months’ follow-up after treatment. Two women in the first group and 3 women in the second group became pregnant and did not complete the study. Follow-up data were only available for 6 women 6 months after discontinuation of therapy. It was found that those receiving 200 μg/d did not lose bone. Those receiving 400 μg/d lost between 2% and 6% at both sites. However, all values had returned to pretreatment levels at 6 months after treatment. Dlugi et al. (10) reported a randomized, double-blind, multicenter study of 52 patients with endometriosis receiving either LA 3.75 mg monthly by IM depot injection or placebo for 6 months. Different methodologies were used to measure bone density, but evaluative data with dual photon absorptiometry in the spine were available for 15 treated patients who lost 3.6% at the end of 6 months, and using quantitative CT in the spine in 8 patients who lost 11.8%. It is stated that further follow-up data were available for 8 patients at 1 year; in 6 patients there was complete resolution and in 1 a partial recovery of bone lost.

One of the largest studies was carried out by Cann et al. (12) who studied 42 women undergoing 6 months’ treatment of nafarelin (18 patients receiving 400 μg/d and 24 receiving 800 μg/d) for endometriosis or leiomyoma, who were compared with 18 women receiving 800 mg/d of danazol. Subjects were randomized into three blind treatment groups. Cortical bone in the hand was evaluated using radiogrammetry and spinal bone density by quantitative CT. Measurements were obtained after 3 and 6 months of treatment and at 3 and 6 months after treatment. At the end of 6 months’ treatment, the nafarelin groups had lost 7.3% and 8.0% of spinal bone density, respectively, whereas those treated with danazol gained 3.6%. At 3 months after treatment with nafarelin, spinal bone mass was decreased by 3.8% from baseline, whereas at 6 months the decrease was 0.3%, which was not significant. Metacarpal cortical thickness measurements did not change during treatment or follow-up.

In both of the above studies, it was concluded that bone loss occurred during nafarelin therapy, but that this was rapidly reversible with no residual bone loss documented. These results are supported by a study by Whitehouse et al. (13) using the dual energy quantitative CT method. The rationale for this is that when significant loss of bone occurs in the spine, marrow fat may increase and could affect the accuracy of quantitative CT measurements. Dual energy quantitative CT corrects for marrow changes and is more accurate than single energy quantitative CT but at the expense of some loss in precision. Whitehouse et al. (13) studied 24 women with endometriosis (age range of 24 to 44 years) who were randomly allocated, in a ratio of 2:1, to receive either nafarelin 400 μg/d or danazol 600 mg/d for 6 months. Spinal measurements were obtained using both quantitative CT (single energy) and dual energy quantitative CT. Twelve of the 15 women receiving nafarelin lost bone while on treatment, and for the group as a whole, the average loss was 5.9% measured by single energy quantitative CT and 4.9% measured by dual energy quantitative CT. Follow-up values at 6 months after discontinuation of treatment were available for 13 patients and showed loss of 1.23% with single energy quantitative CT and 0.36% with dual energy quantitative CT, neither of which were significantly different from baseline. In view of the similarity in the magnitude of change, as assessed by both single energy and dual energy quantitative CT, it would appear that there is little change in trabecular fat content. In addition, the authors found that although individual plasma E2 levels did not correlate with the fall in bone mineral, values did fluctuate considerably from month to month.
month, and the mean values of all the $E_2$ measurements for each patient during treatment were significantly related to the change in bone mineral density ($r = 0.655, P < 0.005$). Further, the 12 patients who lost bone mineral during treatment had lower mean levels of $E_2$ (92.1 pmol/L) than had the 3 patients who did not lose bone (172.6 pmol/L). However, two previous studies have failed to demonstrate any significant correlation between changes in bone mineral and the degree of hypoestrogenemia (14, 15) although in one, no significant bone loss was demonstrated (15). The main conclusion from this study is that although spinal bone loss occurs during 6 months of nafarelin treatment, this is rapidly reversible, and measurements obtained at 6 months after treatment did not show any residual deficit.

Similar results relating to the spine were obtained after buserelin acetate therapy in a study by Matta et al. (16). Thirteen women with endometriosis (mean age of 22.4 years) received 1.2 mg/d of buserelin acetate IN for 6 months. Bone density measurements were performed on the spine using quantitative CT, and dual photon absorptiometry measurements of the midright femur (cortical bone) were also obtained. Results at the end of therapy were not available for one patient. At the end of treatment, there was 4.6% loss in the spine and 0.9% loss in the femur. In a subsequent report (14), the results of 6 months' follow-up were presented. It was found that there was no residual loss of bone at either site. Indeed the absolute value for bone density in the spine had risen slightly, but this was not significant.

Three further studies have reported changes in bone density ranging from 2% to 7%. Dawood et al. (17) studied 31 women with endometriosis. Twenty women received buserelin acetate; of these, 9 received 1.2 mg/d IN for 6 months, 4 received 200 $\mu$g/d SC for 6 months, and 7 were treated for 9 months with 1.2 mg/d IN. Eleven women received 400 mg/d of danazol, 3 for 6 months and 8 for 9 months. Measurements were performed at baseline, end of therapy, and 6 months after discontinuation of therapy, using quantitative CT in the spine and single photon absorptiometry in the distal forearm. Evaluative data were available for 18 of the 20 women treated with buserelin acetate. There was no significant change in single photon absorptiometry in either the buserelin acetate or the danazol group.

With quantitative CT, there was 7.4% and 7.7% loss at the end of 6 and 9 months of buserelin acetate therapy, respectively. At 6 months after discontinuation of treatment, these values were 4.2% and 5.2%, respectively. The authors concluded that significant loss of spinal bone occurs during buserelin acetate therapy and that this persists, albeit slightly reduced, at 6 months after discontinuation of treatment.

In addition, Devogelaer et al. (18) studied nine women with endometriosis (mean age of 32 years) who received IN 900 $\mu$g/d of buserelin acetate. Measurements were obtained, with dual photon absorptiometry in the spine and single photon absorptiometry at three different sites in the forearm, before, at the end of 6 months' treatment, and 3 months after withdrawal of the drug. It was found that at the end of treatment, bone mineral loss was significant in the lumbar spine at 2.1%, but complete restoration of bone mass was found 3 months after withdrawal of therapy. Bone mineral loss was also significant at the distal radius at 4.6%, and at 3 months after discontinuation of therapy the value, although not at pretreatment levels, was no longer significantly decreased. Purely cortical measurements of bone were not affected by treatment.

Finally, Stevenson et al. (19) studied 11 women with endometriosis (mean age of 31.5 years) who were treated for 6 months with goserelin 3.6 mg by SC depot injection every 28 days. Measurements were obtained using dual photon absorptiometry in both the spine and femur. At the end of treatment, there was 2% loss in the spine with 1.83% loss in the femoral neck. Follow-up measurements were obtained in 9 women at 6 months after treatment with no recovery documented.

In addition to the above results, several studies have been published reporting no significant bone loss after GnRH-a therapy. Tummon et al. (15) evaluated 38 women with endometriosis (mean age of 31.4 years). A variety of therapies were employed including two GnRH-a (buserelin acetate and LA). Eight women received LA 1.6 mg/d IN, 8 received buserelin acetate 1.2 mg/d IN, 9 received buserelin acetate 200 $\mu$g/d SC, and 13 women received danazol for 6 months. Measurements were obtained in the spine using dual photon absorptiometry. Four women receiving GnRH-a and 1 receiving danazol did not complete the protocol. There was no loss of bone found in the spine after treatment. The explanation for this is not apparent, but all women were taking 1 g/d of calcium supplementation.

Assessment of bone density has also been reported in studies on women with leiomyomas. Bianchi et al. (20) reported a study of 18 women with leiomyomas who were treated with buserelin acetate 1.5
mg/d SC for 10 days, then 800 μg/d IN for 6 months. There was a control group of 18 normal premenopausal women (mean age of 41.3 years) who were matched for age and body mass index. Bone density was measured by single photon absorptiometry in both proximal and distal forearm, and although treatment was successful in reducing the size of the fibroids, no significant bone loss was reported at either site at the end of treatment or at the end of a further 6 months' follow-up.

In another study, using single photon absorptiometry at the distal third of the forearm, Vollenhoven et al. (21) studied 40 women (mean age of 36.6 years) with leiomyomas. Patients were randomly allocated to receive either 1,200 μg/d of buserelin acetate IN (21 patients) or 200 μg/d of buserelin acetate SC (19 patients) for 6 months. Treatment was successful in reducing the size of fibroids with a 66% reduction in size in 70% of patients. Bone density was measured in 31 women at the end of treatment. Results were compared with a normal data base and were not significantly different. Bone density values were only available for 6 patients both before and at the end of treatment, and again there was no significant bone loss. However, the study is of no value with regard to assessing the effect of GnRH-a on the skeleton; there are very little matched data before and after treatment, and measurements were obtained only at one site, which is cortical bone where one would not expect to document bone loss.

Damewood et al. (22) studied 26 women (14 endometriosis, 12 leiomyomas with mean age of 37 years) who had been treated with LA 1 mg/d SC for 6 months using dual photon absorptiometry in the spine and at three sites in the femur (neck, Ward's triangle, and trochanter). They did not find any significant bone loss at any site and further commented that the bone density results for the study population were not significantly different from normal population values.

In assessing the combined use of a GnRH-a and progesterone (P), Friedman et al. (23) carried out a randomized, double-blind study in 16 premenopausal women (between 28 and 54 years of age) who received either LA 0.5 mg/d SC plus two placebo tablets (7 patients) or LA 0.5 mg/d SC plus 20 mg/d medroxyprogesterone acetate (MPA) (9 patients) for 6 months. At the end of treatment, those patients receiving LA alone had a 51% reduction in the size of fibroids, whereas those receiving additional P had a reduction of 14%, which was not significant. Those patients receiving P did, however, have a significant reduction in symptoms (hot flushes). Bone density was measured using single photon absorptiometry at both the proximal and distal forearm, and no significant loss was found in either group at the end of treatment.

Another study demonstrating the efficacy of GnRH-a in fibroid reduction was reported by Golan et al. (24) who studied 26 women with leiomyomas (mean age of 37.8 years). Patients received treatment with triptorelin 3.2 mg/mo by depot injection for 6 months; bone density was measured by dual photon absorptiometry in the spine. There was a significant reduction in the size of the fibroids, and it was stated that there was no significant loss of bone mineral at the end of treatment.

Finally, Van Leusden and Dogterom (11) studied 10 women (mean age of 43 years) with leiomyomas after treatment with depot injections of triptorelin 4 mg monthly for 6 months. An x ray of the left hand was obtained before and after completion of treatment. It was commented that no significant change was noted on x ray. However, x rays provide a crude means of assessing bone density, and one could not expect to document change in cortical bone over this period of time. A summary of the results for bone density changes in these published studies with GnRH-a is presented in Table 1.

**PREVENTION OF BONE LOSS ASSOCIATED WITH GnRH-a THERAPY**

Clearly, to prevent the bone loss associated with GnRH-a therapy is an attractive concept, and several approaches are being investigated. The effects of the addition of low doses of E (or so-called “add back” therapy) are currently being studied. In a pilot study by Friedman (25), five premenopausal women with leiomyomata, 45 to 49 years of age, were treated with 0.5 mg of LA SC for 27 months. After the initial 3 months of treatment, 0.625 mg of conjugated equine Es were added from day 1 to day 25 of each month, and 10 mg of MPA was added from day 16 to day 25 of each month. Single photon absorptiometry was performed at the distal third of the radius and at the ultradistal radius. Mean bone densities at these sites did not change significantly during the 27 months. Other possible approaches include the addition of diphosphonates and calcitonin as well as progestogens.

Riis et al. (26) studied the effect of adding the progestogen norethisterone (NET) to GnRH-a treatment. Their study population consisted of 17 premenopausal women with endometriosis who...
received 400 μg of nafarelin IN each day for 6 months, combined with 1.2 mg of NET each day; the NET was continued for an additional 6 months. All 17 patients completed 6 months’ treatment, and 15 completed the 6 months’ follow-up, with 2 excluded because of pregnancy. Bone density measurements were obtained in the forearm and spine using single photon absorptiometry and dual photon absorptiometry, respectively, and, in addition, total body calcium was measured with dual photon absorptiometry. Results were compared with those obtained from 20 premenopausal women not receiving any treatment and also with cases of endometriosis previously treated with nafarelin. Although the authors (9) had previously found significant bone loss of between 2% and 6% in both forearm and spine with nafarelin therapy, when NET was added there was only significant bone loss in the distal forearm. Further, on analysis of biochemical changes, it was found that NET prevented the rise of urinary hydroxyproline, which reflects bone resorption, but there was a rise in serum osteocalcin and alkaline phosphatase, although much smaller than seen with nafarelin alone. Thus the authors concluded that the addition of a small dose of progestogen could have a bone sparing effect.

The study of Friedman et al. (23) has already been commented on. They studied 16 women with leiomyomas who received 0.5 mg/d SC of LA, either alone or with 20 mg/d of MPA for 6 months. Bone loss was not found in either group at the end of treatment using single photon absorptiometry of proximal and distal forearm. Progestogen could well have a protective effect on the skeleton in this situation.

Table 1 Bone Density Results

<table>
<thead>
<tr>
<th>Author (Ref)</th>
<th>Drug; dose; route; duration; subjects</th>
<th>Bone density assessments</th>
<th>Bone density results at end of treatment</th>
<th>Bone density results after treatment-free follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Johansen et al. (9)</td>
<td>N*; 200 μg; IN; 6/12; n = 16</td>
<td>Forearm (SPA)†</td>
<td>200 μg: no loss</td>
<td>n = 6: no loss (6/12)‡</td>
</tr>
<tr>
<td>Dlugi et al. (10)</td>
<td>LA; 3.75 mg; D; 6/12; n = 52</td>
<td>Spine (DPA)§</td>
<td>400 μg: 2% to 6% loss in both sites</td>
<td>n = 6: complete recovery (12/12)‡</td>
</tr>
<tr>
<td>Cann et al. (12)</td>
<td>N; 400 μg; IN; 6/12; n = 18</td>
<td>Hand-radiodensitometry</td>
<td>Hand: no loss</td>
<td>No significant loss (6/12)‡</td>
</tr>
<tr>
<td>Whitehouse et al. (13)</td>
<td>N; 400 μg; IN; 6/12; n = 15</td>
<td>Spine (QCT)</td>
<td>Spine-400 μg: 7.3% loss</td>
<td>No significant loss (6/12)‡</td>
</tr>
<tr>
<td>Tummon et al. (15)</td>
<td>B**: 1.2 mg; IN; 6/12; n = 8</td>
<td>Spine and dual energy QCT</td>
<td>No loss</td>
<td>No loss</td>
</tr>
<tr>
<td>Matta et al. (16)</td>
<td>B; 1.2 mg; IN; 6/12; n = 13</td>
<td>Spine (QCT)</td>
<td>Spine: 4.6% loss</td>
<td>No loss (6/12)‡</td>
</tr>
<tr>
<td>Dawood et al. (17)</td>
<td>B; 1.2 mg; IN; 6/12; n = 9</td>
<td>Distal Forearm (SPA)</td>
<td>Femur: 0.9% loss</td>
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<tr>
<td>Devogelaer et al. (18)</td>
<td>B; 900 μg; IN; n = 9</td>
<td>Distal Forearm (SPA)</td>
<td>Forearm: no loss</td>
<td></td>
</tr>
<tr>
<td>Stevenson et al. (19)</td>
<td>G††; 3.6 mg; D; 6/12; n = 11</td>
<td>Distal Forearm (SPA)</td>
<td>Forearm: 4.6% loss</td>
<td>No recovery documented at (6/12)‡</td>
</tr>
<tr>
<td>Bianchi et al. (20)</td>
<td>B; 1.5 mg; SC; 10 days then 800 μg IN; 6/12; n = 18</td>
<td>Proximal and distal forearm (SPA)</td>
<td>Spine-200 μg: 2.1% loss</td>
<td>No loss (6/12)‡</td>
</tr>
<tr>
<td>Vollenhoven et al. (21)</td>
<td>B; 1.2 mg; IN; 6/12; n = 21</td>
<td>Distal forearm (SPA)</td>
<td>Spine: 2% loss</td>
<td></td>
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<tr>
<td>Damwood et al. (22)</td>
<td>LA; 1.0 mg; SC; 6/12; n = 26</td>
<td>Spine (DPA)</td>
<td>Femur: 1.83% loss</td>
<td>No recovery documented at (6/12)‡</td>
</tr>
<tr>
<td>Friedman et al. (23)</td>
<td>LA; 0.5 mg; SC; 6/12; n = 7</td>
<td>Proximal and distal forearm (SPA)</td>
<td>No loss</td>
<td></td>
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<tr>
<td>Golan et al. (24)</td>
<td>T††; 3.2 mg; D; 6/12; n = 26</td>
<td>Spine (DPA)</td>
<td>DPA: 3.6% loss</td>
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<td></td>
<td></td>
<td></td>
<td>Femur (DPA)</td>
<td>No loss at either site</td>
</tr>
</tbody>
</table>

* N, nafarelin. † SPA, single photon absorptiometry. § DPA, dual photon absorptiometry. ‡ D, depot injection. †† G, goserelin. ‡‡ T, triptorelin.
BONE LOSS IN OTHER CLINICAL SITUATIONS

In a study of the effect of endogenous E levels on bone loss, Genant et al. (27) included 37 women who had oophorectomy performed for nonmalignant reasons, 9 of whom received a placebo preparation. These women over a 2-year period lost 9.5% bone mass per year from the spine as measured by quantitative CT but only 3.12% per year from the distal radius as measured by single photon absorptiometry, and 1.45% cortical bone in the hand as measured by radiogrammetry. Oophorectomy is a surgically induced menopause and thus the above rates of loss are extreme but, nevertheless, are relevant when one is considering the degree of bone loss that may occur in other induced menopausal situations. Women runners who become amenorrheic and who are not treated lose, on average, 4% spinal bone per year as measured by quantitative CT (28, 29).

Cavanaugh and Cann (30) were interested in the possible protective effect of a progressive walking program in postmenopausal women (not successful) and included 9 control subjects in this study (mean age of 57 years, mean 6.5 years postmenopausal). The follow-up was 1 year, and these women had 4% annual loss of bone from the spine measured by quantitative CT. This is similar to another study (31) of normal postmenopausal women showing approximately 5% annual spinal loss by quantitative CT assessment, whereas that documented by single photon absorptiometry and dual photon absorptiometry measurement is 1% and 2% to 3% per year, respectively (32). It is therefore important to be aware that in situations in which bone loss is occurring there will be dramatic differences in rates of bone loss between various sites in the skeleton. A further example of this is provided by Ettinger et al. (33) who performed a retrospective study of E users (mean duration of use 14 years and mean dose 0.9 mg conjugated equine E) and case controls. Estrogen users showed an increase of 54.2% in skeletal mass as measured in the spine by quantitative CT but an increase of only 19.4% in the forearm as measured by single photon absorptiometry and an increase of 15.6% in cortical bone in the hand as measured by radiogrammetry.

In addition, there will also be marked differences in rates of bone loss even at a single site depending on which technique is used for measurement. As stated above, normal women in early postmenopausal years may be losing spinal bone at a rate of 4% to 5% when measured by quantitative CT compared with 2% to 3% when measured by dual photon absorptiometry.

Block et al. (34) reviewed their experience of quantitative CT measurements in the spine of 538 normal women between 20 and 80 years of age. It was found that the average loss in spinal density between these years was 60% (this compares with an approximate 30% loss as measured by dual energy x ray absorptiometry [35]). The amount of bone lost in the decades 40 to 49, 50 to 59, and 60 to 69 years was 21%, 14%, and 19%, respectively. It is of considerable interest, however, that for the earlier decade of 30 to 39 years, i.e., premenopausal women, there was significant bone loss of 7.1%. It should be recognized that there are extremely limited data with serial quantitative CT in premenopausal women, and the only group who have studied this is Prior et al. (36) who found 2% annual loss. The question of premenopausal bone loss is somewhat contentious, but it has also been documented in the spine using dual photon absorptiometry in both serial (1.32%/y [32] and cross-sectional studies (37, 38). It is also worth emphasizing that there is considerable variation in bone density values for normal women.

The relationship between E2 levels and bone mass has been investigated by Sowers et al. (39) who recently carried out a study of normal women 20 to 40 years of age and found that those who had the lowest bone density had lower E2 levels when compared with controls. The data are preliminary, but it is suggested that the results may indicate that lower E2 levels are contributing to significant differences in bone mass, even among healthy women, at the time of maximal bone accumulation.

If a normal range is defined by mean ± 2 SD, for dual photon absorptiometry this is ±20% (32) and for quantitative CT it is ±30% (29); in other words, for dual photon absorptiometry there may be a 40% and for quantitative CT a 60% spread around the mean. The implication of this is that in situations in which bone loss occurs, e.g., after the menopause, a woman's bone mass will be determined for very many years thereafter by the amount of bone that is already present as well as by the rate of loss.

CLINICAL RELEVANCE OF BONE CHANGES WITH GnRH-a THERAPY

Although there is some variance between the results of the various GnRH-a studies, it is apparent that the magnitude of change depends on the skeletal site selected for study and the technique used for

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measurement (Table 1). Where measurements of cortical bone have been obtained, e.g., in the meta-
carpals of the hand, no significant loss of bone has been documented with a 6-month course of treat-
ment. In the distal forearm, where some trabecular bone is present, bone loss has been demonstrated ranging between 2% and 4.6%, but the largest changes have been found in the spine. The amount of bone loss from the spine has varied between 2% and 11.8% and is generally twice as great when tra-
becular bone is measured using quantitative CT compared with dual photon absorptiometry, which measures the total vertebra. It should be remem-
bered that trabecular bone only constitutes 23% of the total bone mass of a vertebra (40), and it has been shown that the breaking strength of a vertebra is more closely related to its total mass than to the trabecular content (41).

The degree of bone loss with GnRH-a is com-
parable with that found after oophorectomy, i.e., a surgical menopause. The situation is, however, dif-
ferent from the menopause in as much as the state of hypoestrogenism does not persist indefinitely but is limited to the duration of treatment, which is generally 6 months. The stimulus to bone loss is then withdrawn, and the bulk of the evidence to date sug-
gests that the loss is partially or completely revers-
able, although the completeness of this reversibility has varied in the reported series.

It is worthwhile commenting that few of the pub-
lished studies included normal controls. It would appear that from cross-sectional data (37, 38) and the prospective data of Riggs et al. (32) and Prior et al. (36) that premenopausal women lose bone. It may, therefore, not be possible for women receiving a 6-month course of GnRH-a, together with 6 months or 1 year's follow-up, to completely return to their original bone mass because of normal age-
related bone loss (perhaps mediated by relative E deficiency). It is also worth emphasizing that in any normal female population there is a large interin-
dividual variation in bone density values. As dis-
cussed above, this may vary by 40% for dual photon absorptiometry measurements and by 60% with quantitative CT. With quantitative CT measure-
ments, normal women may expect to lose, on aver-
age, 60% of their spinal trabecular bone mass be-
tween the ages of 20 and 80 years. In this context, a worst possible case of persistent bone loss of ap-
proximately 4% to 5% is unlikely to be clinically relevant, although in practice the amount of residual bone loss is likely to be less. It is not apparent whether, with longer follow-up, there will be con-
tinued improvement or, indeed, complete resolution of bone loss. However, the magnitude of any persist-
ent residual bone loss is unlikely to be of clinical relevance. Further, such possible loss is small in ab-
solute terms when compared with the wide variation in the values for bone density that exist between normal women. It could, of course, be argued that those who start off with the lowest values can least afford to lose any additional bone. If this is consid-
ered to be a valid argument, a solution could be to monitor bone density in women receiving GnRH-a for extended periods, i.e., longer than 6 months or in those undergoing retreatment with GnRH-a.

Because many of the studies using GnRH-a have been in patients with endometriosis, it should be noted that Comite et al. (42) have found reduced bone density in women with endometriosis. They studied 41 women (mean age of 30 years) with endo-
metriosis and 35 controls (mean age of 32 years) using quantitative CT of the distal forearm to eval-
uate both trabecular and cortical bone. At both sites, there was significantly lower bone density when compared with controls. In the context of GnRH-a therapy, these findings, if substantiated, would be of importance, for the implication is that women with endometriosis may be losing bone at an acceler-
ated rate. However, it should also be noted that several other authors have been unable to find any significant difference in bone density in patients with endometriosis when compared with controls (12, 13, 15, 22, 43). These latter studies assessed bone density in the spine, whereas Comite et al. (42) studied the distal forearm; it is possible that radial osteopenia may occur in the absence of vertebral bone loss.

CONCLUSIONS

The great majority of GnRH-a studies were pri-
marily instigated to evaluate clinical response in conditions such as endometriosis or leiomyoma rather than to assess skeletal response. This is un-
derstandable because initially it is important to demonstrate efficacy, but, in a situation in which hypoestrogenism is induced, one could predict that some statistically significant bone loss that may or may not be clinically significant may occur. It is thus surprising that the bone issue seems to have been an afterthought in most cases. The end result is that a wide variety of technologies have been used to measure bone density and, in some cases, different technologies within the same study. In many cases, incomplete data are present with bone density mea-
The effect of repeated courses. There is the possibility of preventing bone loss. This topic requires further research. Perhaps those with positive risk factors for bone loss, although there is no reason to suspect that the femoral neck is behaving differently from any other skeletal sites.

It remains unclear whether some individuals, perhaps those with positive risk factors for bone loss, might be at greater risk upon GnRH-a exposure. However, if there is an established clinical indication for use of GnRH-a, this should not be withheld on the basis of a possible deleterious effect on the skeleton. There are no data regarding the effect of the skeleton of more prolonged courses of GnRH-a or the effect of repeated courses. There is the possibility that in such situations, greater amounts of bone loss could occur. It is probable that the GnRH-a will eventually be used in combination with drugs that prevent bone loss. This topic requires further research.

REFERENCES