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Dockets Management Branch (HFA-305)
Food and Drug Administration
Department of Health and Human Services
Room 1061
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CITIZEN PETITION

A. Action Requested

This Citizen Petition is submitted under Section 505 of the Food, Drug, and Cosmetic Act ("FDCA" or "the Act") and Section 10.30 of the Food and Drug Administration's ("FDA") implementing regulations. It requests that FDA deny approval of any New Drug Application ("NDA") for recombinant salmon calcitonin ("rsCT") nasal spray, such as Unigene's Fortical, for prevention or treatment of osteoporosis that contains as "proof" of efficacy only bone mineral density data or other markers of bone cell activity but lacks clinical data demonstrating the efficacy of the specific rsCT product for which approval is sought in preventing or treating bone fractures.

Unigene has received an approvable letter for its Fortical NDA, stating that the company must submit additional information and data.¹ It is imperative that the Unigene NDA not be approved without the fracture data discussed in this Citizen Petition. FDA should therefore immediately review this petition and take it fully into account before proceeding to approve the Fortical or any similar NDA.

B. Statement of Grounds

The Unigene NDA

On May 5, 2003, Unigene Laboratories, Inc., announced that FDA had filed (i.e., agreed to review) its NDA for Fortical®, a nasal spray calcitonin product for osteoporosis.²

1. Press Release, Unigene, Unigene Receives FDA Approvable Letter for Its Nasal Calcitonin Osteoporosis Product (Jan. 8, 2004), available at http://www.unigene.com/ireye/ir_site.zhtml?ticker=ugne&script=410&layout=7&item_id=482754 (copy attached).

2. Press Release, Unigene, Unigene's U.S. NDA for FORTICAL-R-, Its Nasal Osteoporosis Product, Accepted for Review; \$3 Million Milestone Achieved in Upsher-Smith Agreement (May 5, 2003), available at http://www.unigene.com/ireye/ir_site.zhtml?ticker=ugne&script=400&layout=7 (copy attached).

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The calcitonin in Fortical is “recombinant salmon calcitonin produced using a direct expression technology in *E. coli*.”³

The ASBMR abstract described a study in which Fortical was compared to a commercially available calcitonin nasal spray product in 134 osteoporotic women for 6 months. Women in both arms of the study also received calcium and Vitamin D supplementation. There was no placebo nasal spray group in this study. The endpoints of the study were “pharmacodynamic” measures, including bone mineral density (“BMD”) at spine and hip, and plasma levels of beta-CTx, NTx, urinary DPD, osteocalcin, and BSAP. Fortical resulted in a “modest but statistically significant increase in BMD of 1.3% compared to baseline at the AP spine and 1.1% at the hip,” both at 6 months. There were no statistically significant differences between Fortical and the positive control in bone markers or BMD.⁴ Published studies of osteoporotic women receiving calcium and vitamin D supplementation demonstrate increases in BMD without calcitonin administration of 2.12% in the spine,⁵ an improvement greater than shown in the Fortical study.

Neither the abstract nor any other publicly available study assesses Fortical’s effect on bone mineral density or any other markers of bone cell activity for a period longer than 6 months. There are no publicly available studies of Fortical’s efficacy in preventing or treating bone fractures. Nevertheless, the abstract asserts that Fortical “achieves equivalent clinical results” to that of a currently marketed salmon calcitonin nasal spray product.

The only approved nasal spray containing calcitonin for osteoporosis is Novartis Miacalcin (calcitonin-salmon).⁶ The active ingredient in Miacalcin nasal spray is a synthetic version of calcitonin.⁷

3. N. Mehta et al., Hip and Spine BMD Increases Following Six Months of Daily Treatment with Fortical® Salmon Calcitonin Nasal Spray (hereinafter “ASBMR abstract”), available at <http://www.abstractsonline.com/viewer/viewAbstractPrintFriendly.asp?CKey={7B07DEAA-0E09-4EA1-AC6F-4E58BB62ABE0}&SKey={773A0159-5081-48A1-99DE-0CFC3EF6DBF}&MKey={231F6D2C-6C94-4A1C-8C62-10CC89E46254}&AKey={DOC01D4F-E23B-45E2-ACD4-0AF8AC866B8B}> (last visited Jan. 9, 2004) (copy attached).

4. Id.

5. B. Dawson-Hughes et al., Effect of Calcium and Vitamin D Supplementation on Bone Density in Men and Women, 65 Years of Age or Older, 337 N. Eng. J. Med. 670, 672 (1997) (copy attached).

6. FDA, Approved Drug Products with Therapeutic Equivalence Evaluations (“The Orange Book”) 3-56 (2003).

7. Miacalcin Nasal Spray Package Insert, Description, 1, available at <http://www.miacalcin.com/info/pi.jsp> (hereinafter “Miacalcin Package Insert”).

Summary of Argument

The Unigene NDA appears to have been submitted as a 505(b)(2) application that rests heavily on data in the previously-approved NDA for Miacalcin. The fact that it is a 505(b)(2) application does not mean, however, that the standards for approval are relaxed. To the contrary, the standard for approval of 505(b)(2) applications is the same as the standard for approval of 505(b)(1) applications, as FDA has repeatedly observed.⁸

Because it is now clear that improvements in bone mineral density do not necessarily correlate with improvements in fracture rates in women afflicted with osteoporosis, FDA no longer approves non-estrogenic products intended to prevent or treat osteoporosis on the basis of clinical trials demonstrating an effect only on bone mineral density and other biomarkers. Rather, the agency has consistently required fracture data, typically three year fracture data, as proof of efficacy for an osteoporosis treatment indication. In light of the importance of fracture data as the only reliable measure of the efficacy of osteoporosis drugs, a 505(b)(2) application which relates back to the 505(b)(1) NDA for Miacalcin nasal spray must also contain both bone mineral density data of the same duration (two years) and at least the minimal fracture data FDA required for Miacalcin.

Fracture data is especially imperative in the case of Fortical because its active ingredient, recombinant salmon calcitonin, is not identical to the Miacalcin active ingredient, which is a synthetic salmon calcitonin. It cannot be assumed that the properties of recombinant calcitonin are identical to those of the synthetic substance, and it is therefore not necessarily the case that what is so for Miacalcin is also so for Fortical. Thus, neither Unigene nor FDA can assume that Fortical's purported comparability to Miacalcin nasal spray on BMD necessarily predicts comparability of the two products with respect to fracture rates, nor, indeed, that it predicts any benefit at all with respect to fracture rates. Without corroboration of BMD data with fracture data on Fortical itself, the Fortical NDA cannot be approved.

Applicable Legal Standards

Approval of a new drug under Section 505(b) of the Act requires, *inter alia*, substantial evidence of effectiveness, that is, evidence of adequate and well-controlled investigations on the basis of which it could fairly and responsibly be concluded that the drug will have the effect it purports or is represented to have in the labeling.⁹ The studies must demonstrate that the drug provides a therapeutic benefit; it is not enough merely to establish that the drug affects some factor which is not necessarily correlated with therapeutic benefit.¹⁰

8. *E.g.*, FDA, Draft Guidance for Industry: Applications Covered by Section 505(b)(2), 7, available at <http://www.fda.gov/OHRMS/DOCKETS/98fr/994809gd.pdf> (hereinafter "505(b)(2) Draft Guidance"); Letter from Janet Woodcock, M.D., Director, Center for Drug Evaluation and Research to Katherine M. Sanzo, Esq. et al., 3 (October 14, 2003) (hereinafter "Woodcock letter") available at <http://www.fda.gov/cder/ogd/505b2-CPResponse.pdf> (last visited Jan. 8, 2004).

9. Section 505(d); *Weinberger v. Hynson, Westcott & Dunning, Inc.*, 412 U.S. 609, 613 (1973).

10. *Warner-Lambert v. Heckler*, 787 F.2d 147, 155 (3rd Cir. 1986).

Depending on whether the studies it contains were conducted by or for the applicant, an NDA can be either a 505(b)(1) application or a 505(b)(2) application. A 505(b)(1) application contains full reports of safety and effectiveness that were conducted by or for the applicant or for which the applicant has a right of reference. But “where at least some of the information required for approval comes from studies not conducted by or for the applicant and for which the applicant has not obtained a right of reference,” the application is a 505(b)(2) application rather than a 505(b)(1) application.¹¹

By definition, the drug which is the subject of a 505(b)(2) application is not a duplicate of - is not identical to - an approved drug, for if it were, the application would, under FDA’s regulations, have to be submitted and reviewed under 505(j) rather than 505(b).¹² The 505(b)(2) drug must be different in some way from the previously approved drug. It might, for example, have a different active ingredient, or a different route of administration, or be manufactured by a different process. “To the extent the products [i.e., the drug previously approved under 505(b) and the drug which is the subject of the 505(b)(2) application] are different, the 505(b)(2) application, like a stand alone NDA, must include sufficient data to demonstrate that the product with those different aspects meets the statutory approval standard for safety and effectiveness.”¹³

How much a 505(b)(2) applicant can rely on FDA’s findings that a somewhat similar product is safe and effective and how much data it will have to supply on its own, different drug, is a factual question that will vary from case to case. As is the case with all NDAs, the 505(b)(2) applicant has the burden of proof with respect to every requirement for approval, including efficacy and safety.¹⁴ That means that the 505(b)(2) applicant must demonstrate that its product will produce the same therapeutic benefits as the previously-approved product.

Osteoporosis

Osteoporosis is a disease characterized by low bone mass and architectural deterioration of bone tissue leading to enhanced bone fragility and consequent increase in fracture risk.¹⁵

11. Woodcock letter, supra note 8, at 2.

12. 21 C.F.R. 314.101(d)(9). Section 505(b)(2) does not provide “an appropriate approval pathway for a duplicate eligible for approval under Section 505(j).” Woodcock letter, supra note 8, at 17 n.18. An application for a duplicate of a listed drug and eligible for approval under Section 505(j) cannot be submitted as a 505(b)(2) application. 21 C.F.R. § 314.101(d)(9); 505(b)(2) Draft Guidance, supra note 8, at 6.

13. Woodcock letter, supra note 8, at 3.

14. Edison Pharm. Co. v. FDA, 513 F. 2d 1063, 1065 (D.C. Cir. 1975).

15. NIH, Osteoporosis Prevention, Diagnosis and Therapy, 285 JAMA 785, 786 (2000) (hereinafter “NIH-Osteoporosis”) (copy attached); Miacalcin Package Insert, supra note 7, at 2; FDA, Guidelines for Preclinical and Clinical Evaluation of Agents Used in the Prevention or Treatment of Postmenopausal Osteoporosis, 6 (1994), (hereinafter “Osteoporosis Guidelines”) available at <http://www.fda.gov/cder/guidance/osteo.pdf> (last visited Jan. 8, 2004).

Treating or preventing osteoporosis means providing the therapeutic benefit of reducing the risk of fracture.¹⁶

For many years, it was thought that drugs which had beneficial effects on bone mass (also called bone mineral density) and/or other biomarkers such as total body calcium in osteoporosis patients would necessarily also reduce the risk of fracture. That did in fact prove to be the case with certain drugs. But for other drugs, it is now clear that there is no necessary correlation between improvements in factors such as BMD and reduction in risk of fracture.¹⁷

One key signal that improvements in BMD and reductions in fracture risk are not necessarily correlated came with the finding that although fluoride produced significant increases (35%) in BMD, it had no effect on the rates of vertebral fracture and produced a statistically significant increase in non-vertebral fractures.¹⁸ The results of clinical trials of etidronate further fueled concern about assuming that improved BMD meant improved fracture rates. One pivotal trial on this drug showed that at the end of 3 years etidronate improved spinal bone mass, but had no effect on the fracture rate.¹⁹ Moreover, although pooled data from US studies showed similar improvements in vertebral bone mass at both 2 and 3 years, the etidronate subjects had an increase in vertebral fractures during the third year.²⁰

Another important warning that BMD data do not necessarily augur an improvement (i.e., decrease) in fracture rates arose from the regulatory history of synthetic calcitonin. The first NDA for calcitonin, for an injectable form of the drug, was based on data showing improvement of total body calcium - but no fracture data. An advisory committee to which the NDA was referred voted narrowly in favor of approval on those data, but urged that the sponsor conduct additional trials. FDA approved injectable calcitonin in 1984 and the fracture study began in 1985. It was never completed, however, and data are therefore still lacking on

16. NIH-Osteoporosis, supra note 15, at 785 (“Fracture prevention is the primary treatment goal for patients with osteoporosis”).

17. Osteoporosis Guidelines, supra note 15, at 7 (“...[A] treatment related increase in BMD cannot be assumed to result in reduced risk of fracture”). A likely reason for the lack of a direct correlation between BMD and fracture rates is the fact that the causes of osteoporosis and consequent fractures appear to be multifactorial. Bone quality is a function of the architecture, the mass, and the strength of bone. Id. at 2. Affecting any one of these factors may not suffice to affect the fracture rate. M. Bouxsein, Biomechanics of Osteoporotic Fractures, in NIH, NIH Consensus Development and Conference, 20-21 (2000) available at http://consensus.nih.gov/cons/111/osteo_abstract.pdf (last visited Jan. 8, 2004) (copy attached).

18. B.L. Riggs et al., Effect of fluoride treatment on the fracture rate in postmenopausal osteoporosis, 322 N. Eng. J. Med. 802-809 (1990).

19. E. Colman, The Food and Drug Administration’s Osteoporosis Guidance Document: Past, Present, and Future, 18 J. of Bone and Mineral Research 1125, 1126-27 (2003) (copy attached).

20. Id. at 1127.

fracture rates in women taking injectable synthetic calcitonin, as another advisory committee concluded. That committee again called for proof that calcitonin affects fracture rates:

The committee was unanimous in saying that there was no evidence that calcitonin prevents fractures and that there is evidence that it prevents bone loss. The committee recommended that ... a satisfactory fracture study be conducted to establish the efficacy on injected salmon-calcitonin in prevention of osteoporotic fracture.²¹

Meanwhile, an NDA for calcitonin in a nasal spray formulation had been submitted. The BMD data in the NDA were accompanied by data from the first two years of a five year study known as the PROOF (Prevent Recurrence of Osteoporotic Fractures) trial. A 1994 Advisory Committee considered these PROOF data, which showed that this calcitonin drug significantly increased bone mineral density of the lumbar spine and that the first two years of study showed favorable trends in fracture rate, although not statistical significance. With fracture data to confirm the BMD data to some extent, FDA approved the NDA for nasal spray calcitonin.

As it turned out, however, the PROOF was not in the pudding, for the final results of the trial were “disappointing.”²² Although the 200 IU dose of calcitonin nasal spray reduced the risk of fractures, neither the 100 IU nor the 400 IU dose did so.²³ Even more puzzling, the 400 IU dose was the only one that resulted in an increase in bone mass density; neither the 100 IU or the 200 IU did so. Yet because the 400 IU group fracture rate was not different from placebo group rate, this massive study, involving an initial patient population of 1255 and conducted over five years, demonstrates clearly that an increase in bone mineral density (as was seen at 400 IU per day) cannot be a surrogate for fracture rate. Moreover, measures of the biochemical markers of bone metabolism were also “inconsistent.”²⁴ As one article characterized the results, “after 30 years of clinical experience, calcitonin’s effect on fracture risk is uncertain.”²⁵

Indeed, the fact that the bone mineral density data and fracture risk trends did not correlate in this study is consistent either with

21. This history recounted by FDA’s Gloria Troendle, M.D., at a meeting of the Endocrinologic and Metabolic Drugs Advisory Committee, Transcript Nov. 18, 1994 Meeting, 73 (1994).

22. E. Colman et al., A Brief History of Calcitonin, 359 *The Lancet* 885, 886 (2002). (hereinafter “Brief History”) (copy attached).

23. Id.; C.H. Chestnut, III et al., A Randomized Trial of Nasal Spray Salmon Calcitonin in Postmenopausal Women with Established Osteoporosis: the Prevention Recurrence of Osteoporotic Fractures Study, 109 *Am. J. of Med.* 267, 272-73 (2000) (hereinafter “Chestnut”) (copy attached).

24. Brief History, supra note 22, at 886; Chestnut supra note 23, at 272-73.

25. Brief History, supra note 22, at 886.

a true absence of efficacy of nasal calcitonin to reduce fracture risk or with a conclusion that bone mineral density is not a valid surrogate for bone quality and fracture risk for this agent. Either way, the data are puzzling.²⁶

In sum, based on the results of clinical trials of fluoride, etidronate, injectable calcitonin, and nasal spray calcitonin, it is now clear that for non-estrogen drugs, improvements in bone mineral density do not necessarily predict a beneficial effect on fracture rates.²⁷ Because BMD data alone - uncorroborated by fracture data - do not provide adequate evidence of efficacy to support approval of an NDA under Section 505(b),²⁸ approvals of osteoporosis drugs rest on fracture data, not just BMD data. Accordingly, the sponsors for Fosamax (alendronate), Actonel (risendronate), and Evista (raloxifen) all presented compelling data that their products both improved bone mineral density and reduced the rate of bone fractures.²⁹

Assessing the Fortical NDA

The Fortical NDA is apparently a 505(b)(2) application which contains one study on Fortical itself and otherwise relies on FDA's previous determinations with respect to Miacalcin nasal spray. Such a 505(b)(2) application for this osteoporosis drug cannot be approved.

A 505(b)(2) application must demonstrate that the drug is safe and effective, and must meet the same standards as a 505(b)(1) application. A 505(b)(2) applicant can rely to some degree on what FDA has previously decided with respect to another drug, but it has the burden of showing that it is scientifically permissible to reach the same conclusions for its drug as FDA previously reached for the first drug, and also the burden of showing that, despite differences between its drug and the first drug, its drug is nevertheless safe and effective.³⁰ The single study on Fortical is inadequate to satisfy either burden.

The data reported in the ASBMR abstract are inadequate to show that Fortical is comparable in efficacy to Miacalcin nasal spray. As discussed above, in light of the scientific consensus that BMD data do not necessarily correlate with or predict fracture rates, a showing that an osteoporosis drug has a positive effect on fracture rates is an essential part of the

26. Id.

27. Similarly, while biochemical markers may be of use for certain purposes in research studies, marker levels do not predict bone mass or fracture risk and are only weakly associated with changes in bone mass. NIH-Osteoporosis, supra note 15, at 790.

28. Osteoporosis Guidelines, supra note 15, at 7, 9.

29. Actonel Package Insert, Clinical Studies, 5-6, available at <http://www.pgpharma.com/pi/US-Actonel.pdf> (last visited Jan. 8, 2004); Fosamax Package Insert, Clinical Pharmacology, 4-5, available at http://www.fosamax.com/fosamax/shared/product_info/pi/pi.pdf (last visited Jan. 8, 2004); Evista Package Insert, Clinical Studies, 6-8, available at <http://pi.lilly.com/us/evista-pi.pdf> (last visited Jan. 8, 2004).

30. Supra, pp. 3 to 4.

demonstration of effectiveness of an osteoporosis product. That standard was applied to Miacalcin nasal spray. There, although the evidence of Miacalcin's efficacy was based primarily on studies conducted over two years showing a statistically significant increase in bone mineral density data in a treated patient group compared to a placebo controlled patient group, those data did not stand alone. Rather, the agency (and the advisory committee which reviewed the Miacalcin NDA) closely scrutinized results of the first two years of the PROOF trial showing a trend toward improvement of fracture rates after two years. That the BMD data on Miacalcin nasal spray were essentially confirmed by the PROOF data on fracture played an essential part in the approval process.

By contrast, there are no fracture data at all on Fortical. All that is known is that after 6 months, the product produces BMD effects "comparable" to Miacalcin nasal spray.³¹ Thus, the Fortical data package is not comparable to the Miacalcin nasal spray data package, and does not, therefore, provide proof of efficacy.

FDA should also take careful note of the fact that although the BMD studies conducted on Miacalcin were two year studies, the Fortical study was only a six month study. So FDA cannot know whether Fortical would even be comparable to Miacalcin nasal spray with respect to BMD at 2 years.

Allowing Fortical to slide by without 2 year BMD studies and especially without any evidence of a positive effect on fracture rates would be particularly problematic in light of the fact that its active ingredient, recombinant salmon calcitonin, is not the same as Miacalcin nasal spray's active ingredient, synthetic salmon calcitonin.³² Use of a different active ingredient, recombinant calcitonin instead of a synthetic product, raises myriad questions not only about whether the recombinant product is effective but also about whether it is safe. It is the applicant which has the burden of proving that it is both. Neither burden can be discharged by reference to data on the synthetic product, because those data are not necessarily probative of the effects of the recombinant product.

31. This finding of "comparability" is itself suspect because the trial does not appear to have been designed as a non-inferiority trial and may therefore have lacked sufficient assay sensitivity to rule out differences between Fortical and Miacalcin nasal spray as to BMD. See R. Temple and S. Ellenberg, Placebo-Controlled Trials and Active-Control Trials in the Evaluation of New Treatments, 133 *Annals of Internal Med.* 455, 456-57 (2000) (copy attached); Draft Guidance, International Conference on Harmonisation; Choice of Control Group in Clinical Trials, 64 Fed. Reg. 51767, 51770 (Sept. 24, 1999).

32. Unigene's submitting an NDA rather than an ANDA for Fortical is a tacit admission that the active ingredients in Fortical and Miacalcin are not the same, for if they were, an ANDA would have been available, indeed required. Supra, note 12.

As a general matter, FDA has repeatedly recognized that two recombinant products may have different safety and efficacy profiles.³³ The situation is the same with a recombinant and a synthetic product; they will not necessarily have the same safety and efficacy profiles.

This issue is of particular importance for calcitonin drugs intended for treatment of osteoporosis, for two reasons. First, how calcitonin works in osteoporosis is not known; the package insert for Miacalcin nasal spray advises that “[t]he actions of calcitonin on bone and its role in normal human bone physiology are still not completely elucidated . . .”³⁴ Without a clear understanding of how and why calcitonin works, there is no way to know even in theory whether two different calcitonins, one synthetic and one recombinant, will act the same. For example, because the recombinant product requires enzymatic alpha amidation for full activity, even small amounts of non-amidated peptide could not fit the same receptors as the synthetic product. Or the recombinant product may fit different receptors or more receptors (e.g. calcitonin gene-related peptide receptors of the nervous system). Such differences could make the recombinant product different from the synthetic product with respect to efficacy, safety, or both. The efficacy issues can only be resolved by a demonstration through an appropriate clinical trial that recombinant calcitonin does what calcitonin is supposed to do, i.e., have a therapeutic effect on the fracture rate, and the safety issues must also be solved through appropriate animal and human studies.

Second, synthetic calcitonin is known to be immunogenic, and there is some thought that the immunogenicity affects efficacy of the drug. In one study about 20% of patients produced antibodies that neutralized the effects of exogenously administered calcitonin.³⁵ It seems likely that a recombinant calcitonin will have a pattern of immunogenicity different from that of the synthetic product, and may therefore be not only different from the synthetic in efficacy but also different in safety. Thus, immunogenicity differences could significantly alter the benefit-risk profile of recombinant calcitonin versus synthetic calcitonin, whether by changing the benefits, by changing the risks, or both. Animal and human data on Fortical itself, not unsupported assumptions about its similarity to Miacalcin nasal spray, are essential to resolve these issues of safety and efficacy.

33. E.g., Guidance Concerning Demonstration of Comparability of Human Biological Products; Availability, 61 Fed. Reg. 18612 (Apr. 26, 1996) (“Manufacturing process . . . changes have the potential to alter a product and affect its safety, identity, purity, and potency”); See also BIO Citizen Petition, Apr. 23, 2003, at 31 n.56 available at <http://www.fda.gov/ohrms/dockets/dailys/03/Apr03/042503/03p-0176-cp00001-01-vol1.pdf> (last visited Jan. 8, 2004).

34. Miacalcin Package Insert, *supra* note 7, at 2.

35. F. Singer et al., Abstract of Clinical Efficacy of Salmon Calcitonin in Paget's Disease of Bone, 49 *Calcified Tissue Int. S7-8* (Suppl. 2 1991) (copy attached); See also A. Grauer et al., Clinical Significance of Antibodies Against Calcitonin, 103 *Experimental and Clinical Endocrinology and Diabetes* 345-51 (1995) (copy attached).

Conclusion

Like any other 505(b)(2) applicant, Unigene must support any differences between the Fortical applications and the Miacalcin application with appropriate safety and effectiveness information. That support has not been provided here, so the Fortical NDA cannot be approved.

C. Environmental Impact

The relief requested by this petition would result in the refusal to approve an NDA, thus not altering the status quo. Because the grant of the petition would not have an effect on the environment, no environmental assessment is required. 21 C.F.R. §§ 25.31(a) (62 Fed. Reg. 40570, 40594 (July 29, 1997)).

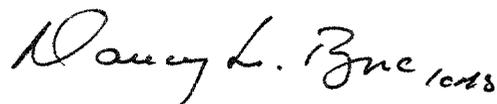
D. Economic Impact

Information on the economic impact of the action requested by this petition will be submitted if requested by the Commissioner.

E. Certification

The undersigned certify that, to the best of their knowledge and belief, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to us which are unfavorable to the petition.

Respectfully submitted,

A handwritten signature in cursive script that reads "Nancy L. Buc". To the right of the signature, the date "10/18" is written in a smaller, less legible hand.

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Unigene Laboratories, Inc. (ticker: UGNE, exchange: OTC Bulletin Board) News Release - 8-Jan-2004

Unigene Receives FDA Approvable Letter for Its Nasal Calcitonin Osteoporosis Product

FAIRFIELD, N.J.--(BUSINESS WIRE)--Jan. 8, 2004--Unigene Laboratories, Inc. (OTCBB: UGNE) has received an approvable letter from the U.S. Food and Drug Administration (FDA) for Fortical(R), its calcitonin nasal spray for the treatment of osteoporosis.

The letter is an official communication from the FDA indicating that the agency prepared to approve the New Drug Application for Fortical upon the finalization of the labeling and the resolution of specific remaining issues, including the submission of additional information and data. Upon approval, the product will be marketed in the U.S. by Upsher-Smith Laboratories.

"The FDA's action validates our confidence in the quality of Unigene's program and its Fortical product," said Mark Evenstad, President of Upsher-Smith Laboratories. "We are very enthusiastic about Fortical's potential for success in this growing osteoporosis market and we look forward to its launch."

"We are extremely pleased that our product has reached this crucial regulatory milestone," noted Dr. Ronald S. Levy, Executive Vice President of Unigene. "Fortical, which would be our first product approved in the U.S., would offer patients an important new option for the treatment of osteoporosis and we plan to work closely with the agency to ensure that the remaining issues are expeditiously addressed."

About Unigene

Unigene Laboratories, Inc. is a biopharmaceutical company focusing on the oral and nasal delivery of large-market peptide drugs. Due to the size of the worldwide osteoporosis market, Unigene is targeting its initial efforts on developing calcitonin and PTH-based therapies. Unigene has licensed the U.S. rights for its nasal calcitonin product to Upsher-Smith Laboratories and the worldwide rights for its oral PTH technology to GlaxoSmithKline. Unigene's patented oral delivery technology has successfully delivered, in preclinical and/or clinical trials, various peptides including calcitonin, PTH and insulin. Unigene's patented manufacturing

technology is designed to cost-effectively produce peptides in quantities sufficient to support their worldwide commercialization as oral or nasal therapeutics.

Safe Harbor statements under the Private Securities Litigation Reform Act of 1995: This press release contains forward-looking statements as defined in Section 27A of the Securities Act of 1933, as amended, and Section 21E of the Securities Exchange Act of 1934, as amended. Such forward-looking statements are based upon Unigene Laboratories, Inc.'s management's current expectations, estimates, beliefs, assumptions, and projections about Unigene's business and industry. Words such as "anticipates," "expects," "intends," "plans," "predicts," "believes," "seeks," "estimates," "may," "will," "should," "would," "potential," "continue," and variations of these words (or negatives of these words) or similar expressions, are intended to identify forward-looking statements. In addition, any statements that refer to expectations, projections, or other characterizations of future events or circumstances, including any underlying assumptions, are forward-looking statements. These forward-looking statements are not guarantees of future performance and are subject to certain risks, uncertainties, and assumptions that are difficult to predict. Therefore, our actual results could differ materially and adversely from those expressed in any forward-looking statements as a result of various risk factors. These risks and uncertainties include the risks associated with the effect of changing economic conditions, trends in the products markets, variations in Unigene's cash flow, market acceptance risks, technical development risks and other risk factors detailed in Unigene's Securities and Exchange Commission filings.

CONTACT: The Investor Relations Group
Investor Contact:
Damian McIntosh/Dian Griesel, Ph.D., 212-825-3210

SOURCE: Unigene Laboratories, Inc.





**Investor
Overview**

Unigene Laboratories, Inc. (ticker: UGNE, exchange: OTC Bulletin Board) News Release - 5-May-2003

**Corporate
Governance**

Unigene's U.S. NDA for FORTICAL-R-, Its Nasal Osteoporosis Product, Accepted for Review; \$3 Million Milestone Achieved in Upsher-Smith Agreement

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FAIRFIELD, N.J.--(BUSINESS WIRE)--May 5, 2003--Unigene Laboratories, Inc.'s (OTCBB:UGNE) New Drug Application ("NDA") for FORTICAL(R), its nasal calcitonin product for treating osteoporosis, has been accepted for review by the U. S. Food and Drug Administration ("FDA").

This event triggers a \$3 million milestone payment from Upsher-Smith Laboratories, the Company's exclusive U.S. licensing partner.

"We expect our current manufacturing operation for bulk calcitonin to meet the needs of Upsher-Smith in the U.S. as well as the anticipated demand for the nasal calcitonin product from prospective markets outside of the U.S.," commented D Warren P. Levy, President and CEO of Unigene. "We are committed to being in position to support product launch as soon as approval is granted, and we are taking the necessary steps to accomplish this goal. Our considerable manufacturing experience with calcitonin and the valuable input and assistance we are receiving from Upsher-Smith will hopefully enable us to receive regulatory approval in a timely fashion."

About Unigene

Unigene Laboratories, Inc. is a biopharmaceutical company focusing on the oral and nasal delivery of large-market peptide drugs. Due to the size of the worldwide osteoporosis market, Unigene is targeting its initial efforts on developing calcitonin and PTH-based therapies. In addition to the Upsher-Smith collaboration, Unigene has licensed to GlaxoSmithKline the worldwide rights to its oral PTH product. Unigene's patented oral delivery technology has successfully delivered, preclinical and/or clinical trials, various peptides including calcitonin, PTH and insulin. Unigene's patented manufacturing technology is designed to cost-effectively produce peptides in quantities sufficient to support their worldwide commercialization as oral or nasal therapeutics.

Safe Harbor statements under the Private Securities Litigation Reform Act of

1995: This press release contains forward-looking statements as defined in Section 27A of the Securities Act of 1933, as amended, and Section 21E of the Securities Exchange Act of 1934, as amended. Such forward-looking statements are based upon Unigene Laboratories, Inc.'s management's current expectations, estimates, beliefs, assumptions, and projections about Unigene's business and industry. Words such as "anticipates," "expects," "intends," "plans," "predicts," "believes," "seeks," "estimates," "may," "will," "should," "would," "potential," "continue," and variations of these words (or negatives of these words) or similar expressions, are intended to identify forward-looking statements. In addition, any statements that refer to expectations, projections, or other characterizations of future events or circumstances, including any underlying assumptions, are forward-looking statements. These forward-looking statements are not guarantees of future performance and are subject to certain risks, uncertainties, and assumptions that are difficult to predict. Therefore, our actual results could differ materially and adversely from those expressed in any forward-looking statements as a result of various risk factors. These risks and uncertainties include the risks associated with the effect of changing economic conditions, trends in the products markets, variations in Unigene's cash flow, market acceptance risks, technical development risks and other risk factors detailed in Unigene's Securities and Exchange Commission filings.

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Hip and Spine BMD Increases Following Six Months of Daily Treatment with Fortical® Salmon Calcitonin Nasal Spray

N. Mehta, W. Stern*, A. Sturmer*, A. Malootian*, S. Philip*, S. Mitta*, J. P. Gilligan. Unigene Laboratories Inc, Fairfield, NJ, USA.

Presentation Number: SA362

A novel nasal spray formulation (Fortical®) has been developed that contains recombinant sCT (rsCT) produced using a direct expression technology in *E. coli*. The pharmacodynamic response of Fortical® was determined in a multi-dose, double blind, parallel design tolerability and pharmacology study using a commercially available nasal spray product as a positive control. One hundred and thirty four osteoporotic women received 6 months of daily dosing of 200 IU per day of Fortical® nasal spray or the positive control, with calcium and vitamin D supplementation. Several markers of bone resorption and bone formation were measured throughout the first 3 months of the study. Spine and hip BMD were measured at baseline and at the end of the six-month dosing period. The key findings from the study were as follows: 1) Fortical® treatment resulted in a modest but statistically significant increase in BMD of 1.3 % at the AP spine and 1.1% at the hip at 6 months, compared to baseline. 2) Plasma levels of the primary end-point β -CTx, were decreased by approximately 40% after the first month, and this decrease persisted through 3 months of Fortical® treatment. 3) Statistically significant decreases in NTx and urinary DPD were also seen throughout the 3 months of measurement. 4) Fortical® significantly decreased the bone formation markers osteocalcin and BSAP at the 3 month time-point compared to baseline. Overall, there was no statistically significant difference in bone markers or BMD between Fortical® and the positive control. Fortical® nasal spray is an alternate sCT nasal spray therapy that achieves equivalent clinical results and has a comparable systemic safety profile to that of a currently marketed sCT nasal spray product, with a formulation that does not contain benzalkonium chloride.

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EFFECT OF CALCIUM AND VITAMIN D SUPPLEMENTATION ON BONE DENSITY IN MEN AND WOMEN 65 YEARS OF AGE OR OLDER

BESS DAWSON-HUGHES, M.D., SUSAN S. HARRIS, D.Sc., ELIZABETH A. KRALL, Ph.D., AND GERARD E. DALLAL, Ph.D.

ABSTRACT

Background Inadequate dietary intake of calcium and vitamin D may contribute to the high prevalence of osteoporosis among older persons.

Methods We studied the effects of three years of dietary supplementation with calcium and vitamin D on bone mineral density, biochemical measures of bone metabolism, and the incidence of nonvertebral fractures in 176 men and 213 women 65 years of age or older who were living at home. They received either 500 mg of calcium plus 700 IU of vitamin D₃ (cholecalciferol) per day or placebo. Bone mineral density was measured by dual-energy x-ray absorptiometry, blood and urine were analyzed every six months, and cases of nonvertebral fracture were ascertained by means of interviews and verified with use of hospital records.

Results The mean (\pm SD) changes in bone mineral density in the calcium-vitamin D and placebo groups were as follows: femoral neck, $+0.50\pm 4.80$ and -0.70 ± 5.03 percent, respectively ($P=0.02$); spine, $+2.12\pm 4.06$ and $+1.22\pm 4.25$ percent ($P=0.04$); and total body, $+0.06\pm 1.83$ and -1.09 ± 1.71 percent ($P<0.001$). The difference between the calcium-vitamin D and placebo groups was significant at all skeletal sites after one year, but it was significant only for total-body bone mineral density in the second and third years. Of 37 subjects who had nonvertebral fractures, 26 were in the placebo group and 11 were in the calcium-vitamin D group ($P=0.02$).

Conclusions In men and women 65 years of age or older who are living in the community, dietary supplementation with calcium and vitamin D moderately reduced bone loss measured in the femoral neck, spine, and total body over the three-year study period and reduced the incidence of nonvertebral fractures. (N Engl J Med 1997;337:670-6.)

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INADEQUATE intake of calcium and vitamin D leads to reduced calcium absorption, increased serum parathyroid hormone concentrations, and bone loss. Low bone mass is a strong predictor of fracture.¹ Supplemental calcium reduces bone loss in middle-aged, postmenopausal women²⁻⁸ and lowers rates of vertebral fracture in women with previous vertebral fractures.⁹ Supplementation with vitamin D alone reduced bone loss from the femoral neck in postmenopausal women,^{10,11} but it did not reduce the rate of hip fracture among elderly Dutch men and women.¹² Annual intramuscular injections

of vitamin D did, however, reduce rates of arm fracture among elderly Finnish subjects.¹³

There is a rationale for supplementing the diets of elderly subjects with a combination of calcium and vitamin D. Absorption of calcium¹⁴ and possibly of vitamin D¹⁵ and production of vitamin D¹⁶ by the skin decline with aging. Diets that are deficient in calcium tend also to be deficient in vitamin D because a single food, milk, is the principal dietary source of both these nutrients. Combined calcium and vitamin D supplementation has reduced rates of nonvertebral fracture among elderly women living in retirement homes.¹⁷ In the one available study of men (mean age, 58 years) who lived at home, calcium and vitamin D together did not reduce bone loss.¹⁸ The role of combined supplements in elderly men and women living at home is unknown. We examined the effects of combined calcium and vitamin D supplementation on bone loss, biochemical measures of bone metabolism, and the incidence of nonvertebral fractures in men and women 65 years of age or older who were living in the community.

METHODS**Subjects**

We studied only healthy, ambulatory men and women 65 years of age or older who were recruited through direct mailings and presentations in the community. The criteria for exclusion included current cancer or hyperparathyroidism; a kidney stone in the past five years; renal disease; bilateral hip surgery; therapy with a bisphosphonate, calcitonin, estrogen, tamoxifen, or testosterone in the past six months or fluoride in the past two years; femoral-neck bone mineral density more than 2 SD below the mean for subjects of the same age and sex; dietary calcium intake exceeding 1500 mg per day; and laboratory evidence of kidney or liver disease.

We prescreened 848 subjects by means of a questionnaire and invited 545 for screening. Of these, 51 were found to be ineligible, 49 were potentially eligible but were not enrolled, and 445 (199 men and 246 women) were enrolled. There were 430 whites, 11 blacks, and 4 Asians. The protocol was approved by the Human Investigation Review Committee at Tufts University, and written informed consent was obtained from each subject.

Study Design and Supplements

In this three-year, double-blind, placebo-controlled trial, the subjects were randomly assigned to either the placebo or the calcium-vitamin D group with stratification according to sex, race, and decade of age. At study entry, we performed physical examinations and assessed the subjects' medical history, diet, and phys-

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ical-activity level; analyzed blood and urine; and measured bone mineral density. The subjects were advised to maintain their usual diets and to avoid taking supplemental calcium and vitamin D on their own for two months before and throughout the study. At bedtime, the subjects took separate pills containing 500 mg of elemental calcium in the form of calcium citrate malate¹⁹ and 700 IU of cholecalciferol or separate placebo tablets containing microcrystalline cellulose.

Calcium citrate malate (Procter & Gamble, Cincinnati) was prepared in two batches; assays confirmed that the contents were as expected. The vitamin D tablets used initially contained 707 IU; two years later, the tablets were found to contain 563 IU (80 percent) of the planned dose of 700 IU; a second lot initially containing 768 IU was used during the second half of the study. The tablets were stored in opaque bottles at room temperature.

Status of Subjects and Compliance

During the trial, 127 subjects discontinued treatment; 4 died, 40 stopped for personal reasons (e.g., they lost interest or moved away), 46 withdrew because of illness, 17 started estrogen or glucocorticoid therapy, and 20 withdrew because of problems with the medication. The majority of subjects who discontinued treatment did so in the first year. These subjects were encouraged to return for all subsequent follow-up evaluations. At the last visit, 389 subjects (87 percent of the 445 enrolled) were evaluated and were included in the main intention-to-treat analyses. The 318 subjects who remained in the two study groups (i.e., those who took the supplements throughout the study period) were included in the analyses of subjects who completed the study according to the protocol.

The mean (\pm SD) rate of compliance with treatment, assessed on the basis of pill counts, was 92 ± 10 percent for the calcium or placebo tablets and 93 ± 10 percent for the vitamin D or placebo tablets among the 318 subjects who completed the study.

Measurements

The subjects came to the center every six months for measurements of bone mineral density, biochemical assays, and other measurements. Their calcium and vitamin D intake was estimated on the basis of a food-frequency questionnaire.²⁰ During the study, 44 of the subjects who completed the study treatment (23 in the placebo group and 21 in the calcium-vitamin D group) reported taking products that contained some calcium or vitamin D. They were asked to stop taking these products, and the intake from supplements was added to their dietary intake during the relevant period. Leisure, household, and occupational activity was estimated with use of the Physical Activity Scale for the Elderly questionnaire.²¹ Tobacco use was determined by questionnaire. Height was measured with a stadiometer, and weight with a digital scale.

The subjects were asked to send in a postcard after any fall. When such a postcard was received, a staff member called the subject to verify the circumstances. Subjects reported any additional falls at each follow-up visit. Nonvertebral fractures were identified during interviews at the same visits. The principal investigator, who was unaware of the subjects' study-group assignments, classified the fractures as nonosteoporotic (resulting from severe trauma) or osteoporotic (resulting from moderate-to-minor trauma — i.e., a fall from standing height or less). All but one nonvertebral fracture (a presumed toe fracture that was not treated) were verified by review of x-ray reports or hospital records.

Analytic Methods

Bone mineral density in the hip, spine, and total body was measured by dual-energy x-ray absorptiometry with use of a DPX-L scanner (Lunar Radiation, Madison, Wis.). Scanner software versions 1.2 and 1.3y were used for data acquisition and analysis, respectively. The coefficients of variation for the measurements were 2.0 percent (femoral neck), 1.0 percent (spine), and 0.6 percent (total body). The scans of the hip were performed in duplicate,

with repositioning between scans, and the values were averaged. A phantom consisting of bone ash embedded in a 12-cm block was scanned every other week as a control; the bone mineral density of the phantom was stable throughout the study.

Blood was drawn between 7:00 and 9:30 a.m. after the subjects had fasted for at least eight hours. Urine measurements were made in 24-hour collections. Plasma 25-hydroxyvitamin D was measured by the method of Preece et al.,²² plasma 1,25-dihydroxyvitamin D by a competitive protein-binding method,²³ serum parathyroid hormone by immunometric assay (Nichols Institute, San Juan Capistrano, Calif.), serum osteocalcin by immunoradiometric assay (Nichols Institute), urinary *N*-telopeptide cross-links by enzyme-linked immunosorbent assay (Ostex International, Seattle), and serum ionized calcium and urinary calcium and creatinine as reported previously.²⁰ The coefficients of variation for these assays ranged from 5.6 percent to 7.7 percent. Analyses were performed as the samples were collected, except for the plasma 1,25-dihydroxyvitamin D and urinary *N*-telopeptide assays, for which initial and final samples were analyzed at the same time.

Statistical Analysis

Comparisons between the study groups were made with two-sample *t*-tests and, when adjustments were required, with analysis of covariance. Terms for the interaction of sex and study group in analysis-of-variance models of the change in bone mineral density were statistically significant only at the femoral neck in the subjects in the intention-to-treat analysis; this term did not remain significant after adjustment for the duration of treatment. The relative risks of fracture among the subjects in the calcium-vitamin D and placebo groups were compared by means of the chi-square test. Analyses were conducted with SPSS (SPSS Inc., Chicago) and SAS (SAS Institute, Cary, N.C.) software. All *P* values are two-sided. Intention-to-treat analyses were conducted according to the principles described by Newell²⁴; selected secondary analyses were restricted to subjects who completed the study.

RESULTS

The base-line characteristics of the 389 subjects are shown in Table 1. As compared with placebo, supplementation with calcium and vitamin D had a significant positive effect on the change over three years in bone mineral density measured at the femoral neck, spine, and total body in all subjects together and in the men (Table 2). The women in the calcium-vitamin D group had significantly less total-body bone loss than those in the placebo group; the differences in the changes at the femoral neck and spine were smaller and not statistically significant. Adjustment for differences between the study groups in base-line bone mineral density and calcium intake did not alter the results.

The time course of the response to treatment was examined in the 318 subjects who completed the study. Their clinical characteristics and bone mineral density at base line did not differ significantly from those of subjects who discontinued the study treatment, except that smoking was more prevalent in the latter group (10 percent, as compared with 4 percent among those who completed the study; *P* = 0.02). During the first year there was significantly less bone loss at the hip, spine, and total body in the calcium-vitamin D group; during the second and third years, however, there was significantly less loss only in the total body (Table 3).

TABLE 1. BASE-LINE CHARACTERISTICS OF THE 389 STUDY SUBJECTS.*

CHARACTERISTIC	MEN		WOMEN	
	PLACEBO GROUP (N=90)	CALCIUM-VITAMIN D GROUP (N=86)	PLACEBO GROUP (N=112)	CALCIUM-VITAMIN D GROUP (N=101)
Age (yr)	71±5	70±4	72±5	71±4
Height (cm)	173.8±6.9	174.3±6.2	159.5±6.6	159.2±6.4
Weight (kg)	81.5±12.8	82.4±11.3	68.1±12.4	67.6±12.1
Dietary calcium intake (mg/day)	673±349	748±391	798±366	689±286
Dietary vitamin D intake (IU/day)	197±117	202±104	184±110	174±90
Smoker (%)	4.4	7.0	5.4	5.9
Physical-activity score	127±56 (89)	124±60 (85)	108±54	105±48
Bone mineral density (g/cm ²)				
Femoral neck	0.95±0.12	0.99±0.14	0.81±0.11	0.80±0.11
Spine	1.27±0.20 (89)	1.32±0.21	1.05±0.20 (109)	1.03±0.18 (97)
Total body	1.19±0.09 (89)	1.22±0.09	1.02±0.09	1.02±0.10

*Plus-minus values are means ±SD. When there were missing data, the number of subjects for whom data were available is shown in parentheses.

TABLE 2. CHANGE IN BONE MINERAL DENSITY OVER THREE YEARS IN ALL SUBJECTS AND IN SUBJECTS WHO COMPLETED THE STUDY *

SUBJECTS AND SITE	ALL SUBJECTS (N=389)			SUBJECTS COMPLETING STUDY (N=318)		
	PLACEBO GROUP (N=202)	CALCIUM-VITAMIN D GROUP (N=187)	P VALUE	PLACEBO GROUP (N=170)	CALCIUM-VITAMIN D GROUP (N=148)	P VALUE
	percent change			percent change		
All subjects						
Femoral neck	-0.70±5.03 (201)	+0.50±4.80 (185)	0.02	-0.45±5.07 (170)	+0.81±4.44 (148)	0.02
Spine (L2-L4)	+1.22±4.25 (197)	+2.12±4.06 (180)	0.04	+1.27±4.31 (166)	+2.56±3.93 (145)	0.006
Total body	-1.09±1.71 (199)	+0.06±1.83 (186)	<0.001	-1.04±1.71 (168)	+0.30±1.58 (148)	<0.001
Men						
Femoral neck	-1.35±4.70 (90)	+0.95±4.07 (85)	<0.001	-0.88±4.59 (77)	+0.91±3.92 (71)	0.01
Spine (L2-L4)	+1.74±3.85 (89)	+2.93±3.42 (84)	0.03	+2.03±3.69 (76)	+3.34±3.33 (70)	0.03
Total body	-0.85±1.53 (88)	+0.34±1.40 (86)	<0.001	-0.67±1.47 (75)	+0.48±1.34 (71)	<0.001
Women						
Femoral neck	-0.17±5.25 (111)	+0.11±5.34 (100)	0.70	-0.09±5.43 (93)	+0.71±4.90 (77)	0.31
Spine (L2-L4)	+0.78±4.54 (108)	+1.41±4.45 (96)	0.32	+0.63±4.71 (90)	+1.85±4.32 (75)	0.09
Total body	-1.29±1.82 (111)	-0.17±2.11 (100)	<0.001	-1.34±1.84 (93)	+0.14±1.76 (77)	<0.001

*Plus-minus values are means ±SD. The number of subjects for whom data were available is shown in parentheses. An interaction of sex with study group was statistically significant only at the femoral neck in all subjects (P=0.05), the P value for this interaction in subjects who completed the study was 0.36.

Among the 318 subjects who completed the study, those treated with calcium and vitamin D had significantly greater changes in a number of biochemical measures of bone metabolism (Table 4). Serum osteocalcin concentrations and urinary excretion of N-telopeptide were significantly lower in the men than in the women throughout the study (P=0.005).

Among the 389 study subjects, 37 (5 men and 32 women) had at least one nonvertebral fracture during the study period. The cumulative incidence of a first fracture at three years was 5.9 percent in the cal-

cium-vitamin D group and 12.9 percent in the placebo group (relative risk, 0.5; 95 percent confidence interval, 0.2 to 0.9; P=0.02) (Table 5 and Fig. 1). Among the women in the placebo group, the incidence of fractures at three years was 19.6 percent. Twenty-eight subjects (76 percent) had fractures classified as osteoporotic; the three-year cumulative incidence of a first osteoporotic fracture in the calcium-vitamin D group was lower than that in the placebo group (relative risk, 0.4; 95 percent confidence interval, 0.2 to 0.8; P=0.01). Only two men, both

EFFECT OF CALCIUM AND VITAMIN D SUPPLEMENTATION ON BONE DENSITY IN OLDER PERSONS

TABLE 3. RATES OF CHANGE IN BONE MINERAL DENSITY IN 318 SUBJECTS WHO COMPLETED THE STUDY, ACCORDING TO THE DURATION OF TREATMENT.*

SUBJECTS AND SITE	YEAR 1			YEARS 2 AND 3		
	PLACEBO GROUP	CALCIUM-VITAMIN D GROUP	P VALUE	PLACEBO GROUP	CALCIUM-VITAMIN D GROUP	P VALUE
	percent change/year			percent change/year		
All						
Femoral neck	-0.22±3.65 (168)	+0.64±3.96 (145)	0.05	-0.08±2.42 (168)	+0.18±1.90 (145)	0.30
Spine (L2-L4)	-0.29±2.92 (165)	+1.09±2.59 (145)	<0.001	+0.79±1.90 (166)	+0.73±1.50 (144)	0.75
Total body	-0.76±1.28 (168)	-0.16±1.11 (146)	<0.001	-0.14±0.68 (168)	+0.23±0.70 (146)	<0.001
Men						
Femoral neck	-0.55±3.61 (76)	+0.56±3.36 (69)	0.06	-0.12±2.22 (76)	+0.36±1.72 (69)	0.15
Spine (L2-L4)	+0.31±2.83 (76)	+1.29±1.95 (71)	0.02	+0.87±1.59 (76)	+1.00±1.54 (70)	0.61
Total body	-0.33±1.11 (76)	-0.10±1.14 (70)	0.22	-0.17±0.65 (76)	+0.30±0.59 (70)	<0.001
Women						
Femoral neck	+0.05±3.68 (92)	+0.72±4.46 (76)	0.30	-0.04±2.60 (92)	+0.01±2.04 (76)	0.88
Spine (L2-L4)	-0.80±2.91 (89)	+0.90±3.08 (74)	<0.001	+0.72±2.13 (90)	+0.46±1.43 (74)	0.36
Total body	-1.11±1.30 (92)	-0.22±1.08 (76)	<0.001	-0.11±0.71 (92)	+0.18±0.79 (76)	0.02

*Plus-minus values are means ±SD. The number of subjects for whom data were available is shown in parentheses.

TABLE 4. INITIAL LABORATORY VALUES AND CHANGES AT THREE YEARS IN 313 SUBJECTS WHO COMPLETED THE STUDY, ACCORDING TO STUDY GROUP.*

INDEX AND STUDY GROUP	MEN (N=146)		WOMEN (N=167)	
	INITIAL VALUE	CHANGE	INITIAL VALUE	CHANGE
Serum ionized calcium (mg/dl)				
Placebo	5.0±0.2	+0.0±0.1	5.0±0.2	+0.0±0.2
Calcium-vitamin D	5.0±0.2	+0.1±0.2†	5.1±0.2	+0.1±0.1
Plasma 25-hydroxyvitamin D (ng/ml)				
Placebo	33.6±12.7	-2.68±10.2	24.5±10.3	+0.7±8.1
Calcium-vitamin D	33.0±16.3	+11.8±11.6†	28.7±13.3‡	+16.1±14.3‡
Plasma 1,25-dihydroxyvitamin D (pg/ml)§				
Placebo	33.3±6.7	-4.8±8.7	37.3±8.0	-6.7±8.7
Calcium-vitamin D	33.6±7.0	-6.3±11.0	36.5±7.3	-5.8±9.5
Serum parathyroid hormone (pg/ml)				
Placebo	34.8±13.6	+6.2±11.2	42.6±18.9	+5.7±15.0
Calcium-vitamin D	38.0±19.1	-7.0±12.9†	37.4±15.3‡	-5.5±13.2‡
Serum osteocalcin (ng/ml)				
Placebo	5.7±1.9	+0.2±1.6	7.0±2.4	+0.0±2.1
Calcium-vitamin D	5.3±1.3	-0.5±1.4†	6.9±2.5	-0.9±1.9†
24-hr urinary calcium:creatinine ratio (mg/g)				
Placebo	98±46	-4±44	119±55	+9±62
Calcium-vitamin D	98±50	+35±51†	113±64	+67±64†
24-hr urinary N-telopeptide:creatinine ratio (nmol/mmol)				
Placebo	32±16	+1±10	48±30	-2±32
Calcium-vitamin D	29±9	-2±12	45±17	-2±16

*Plus-minus values are means ±SD. To convert values for calcium to millimoles per liter, multiply by 0.25; to convert values for 25-hydroxyvitamin D to nanomoles per liter, multiply by 2.50; to convert values for 1,25-dihydroxyvitamin D to picomoles per liter, multiply by 2.40; to convert values for parathyroid hormone to picomoles per liter, multiply by 0.106; to convert values for osteocalcin to nanomoles per liter, multiply by 0.172; to convert values for the 24-hour urinary calcium:creatinine ratio to millimoles per mole, multiply by 2.82. Initial or final laboratory values were missing for five subjects.

†P<0.005 for the comparison between the study groups.

‡P≤0.05 for the comparison between the study groups.

§Final measurements were made at 18 months.

TABLE 5. NUMBER OF FIRST NONVERTEBRAL FRACTURES AMONG ALL SUBJECTS, ACCORDING TO SKELETAL SITE.

SITE OF FRACTURE	PLACEBO GROUP (N=202)	CALCIUM-VITAMIN D GROUP (N=187)
Face	1	1
Shoulder, humerus, or clavicle	4	3
Radius or ulna	5	1
Hand	1	1
Ribs	2	2
Pelvis	2	0
Hip	1	0
Tibia or fibula	1	1
Ankle or foot	7	2
Multiple sites	2	0
Total	26	11

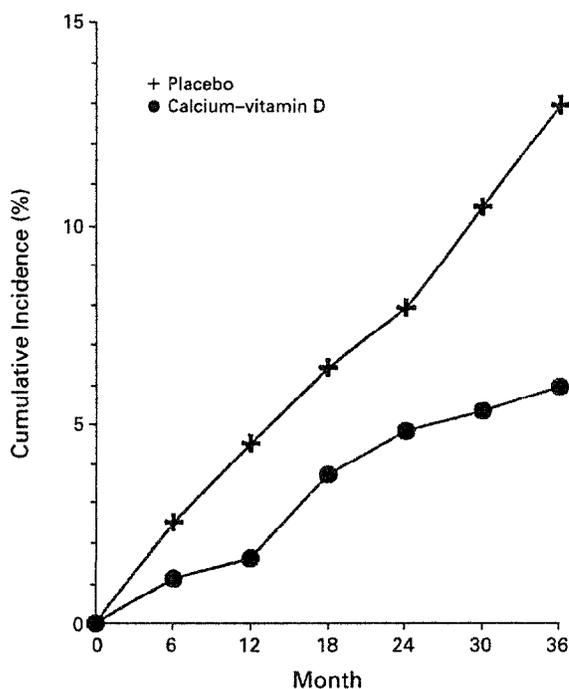


Figure 1. Cumulative Percentage of All 389 Subjects with a First Nonvertebral Fracture, According to Study Group.

By 36 months, 26 of 202 subjects in the placebo group and 11 of 187 subjects in the calcium-vitamin D group had had a fracture ($P=0.02$).

in the placebo group, had osteoporotic fractures, and the best predictor of osteoporotic fracture was female sex ($P<0.001$). Among the 318 subjects who completed the study, the relative risk of any first nonvertebral fracture in the calcium-vitamin D group as compared with the placebo group was 0.4 (95 percent confidence interval, 0.2 to 1.0; $P=0.03$), and that for fractures classified as osteoporotic was 0.4 (95 percent confidence interval, 0.2 to 1.1; $P=0.06$). There was no significant difference between the treatment groups in the percentage of subjects who fell; among women, the number of falls per subject who fell was somewhat higher in the calcium-vitamin D group than in the placebo group (data not shown). Two women (one in each study group) had a second osteoporotic fracture during the study.

The supplements were generally well tolerated, but 11 subjects discontinued treatment because of difficulty swallowing the pills and 9 discontinued because of other side effects (in the placebo group: 2 because of epigastric distress and 1 because of flank pain; in the calcium-vitamin D group: 3 because of constipation, 1 because of epigastric distress, 1 because of sweating, and 1 because of hypercalciuria).

DISCUSSION

In this study, dietary supplementation with calcium and vitamin D reduced bone loss moderately in men and women 65 years of age or older who were living in the community. Among the men, there was a significant effect of treatment at the hip, spine, and total body. In an earlier study by Orwoll et al., a similar regimen of calcium and vitamin D had no effect, perhaps because the men in that study were younger and had a higher mean calcium intake than the men we studied (1160 vs. about 700 mg per day).¹⁸ The reduction in total-body bone loss in women in this study was similar to that in other trials of calcium supplementation alone.^{3,4} The estimated differences in bone mineral density at the femoral neck and spine among the women in the two study groups were similar to those found in other studies,^{2,4,6,10,11,25} although the differences did not reach statistical significance in our study. The effect of supplementation in all subjects was similar to that in the subjects who completed the study, as would be expected, given the high degree of overlap between the two groups. Treatment caused few symptoms or side effects.

In both men and women, calcium-vitamin D supplementation reduced total-body bone loss not only in the first year (an effect that could be ascribed to the closure of bone-remodeling space²⁶), but also in the second and third years, suggesting long-term effectiveness of supplementation in terms of the skeleton as a whole. The initial effects of supplementation at the hip and spine during year 1 were maintained but not increased during the ensuing two years of the

study. Others have reported a cumulative benefit in terms of total-body^{3,4} and femoral-neck³ bone density with the use of higher doses of calcium in younger postmenopausal women. Spinal bone mineral density increased in both study groups, probably because of increases in osteoarthritis and aortic calcification.^{27,28}

After three years of calcium-vitamin D supplementation, serum osteocalcin concentrations were 9 percent lower in the men and 14 percent lower in the women than at base line, indicating that supplementation led to a sustained reduction in the rate of bone remodeling. The lack of change in urinary N-telopeptide excretion may reflect the variability of this measurement. Our study confirms previous observations that the rate of bone turnover, as measured by urinary excretion of pyridinoline cross-links²⁹ and serum osteocalcin concentrations,³⁰ is lower in men than in women.

The reduction in the incidence of nonvertebral fractures in the calcium-vitamin D group should be interpreted with some caution, because of the small number of study subjects. Nonetheless, the magnitude of the reduction in the risk of fracture was similar to that reported in a study of more than 3400 elderly French women treated with 1200 mg of calcium plus 800 IU of vitamin D or placebo each day.¹⁷ In a study of 2600 elderly Dutch men and women, there was no reduction in the incidence of fractures among those given 400 IU of vitamin D daily (without calcium), as compared with those given placebo.¹² Our results differ from those of the Dutch study, possibly by chance (we studied fewer subjects) or because the treatments differed. When comparing the three-year rates of nonvertebral fractures among women assigned to placebo in several recent trials, we found that the 19.6 percent rate in this study was intermediate between the 9 percent reported for women who were, on average, 7 years younger than our subjects³¹ and the 27 percent reported for women who were 13 years older.¹⁷ We do not know the individual contributions of calcium or vitamin D to the results in our study.

The limited effect of calcium and vitamin D on bone mineral density, which was evident primarily in year 1, seems unlikely to account for the constant decline in the rate of nonvertebral fractures during the three-year study. A treatment-induced reduction in the incidence of falls does not appear to account for the reduction in the rate of fractures, since the number of falls was similar in the two groups. The reduction in the rate of bone turnover may have influenced the fracture rate by reducing the potential for trabecular perforation and reducing cortical porosity.

In conclusion, calcium and vitamin D supplementation leads to a moderate reduction in bone loss and may substantially reduce the risk of nonvertebral fractures among men and women 65 years of age or older who live in the community.

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Osteoporosis Prevention, Diagnosis, and Therapy

NIH Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy

OSTEOPOROSIS IS A MAJOR health threat. In the United States alone, 10 million persons already have osteoporosis, and 18 million more have low bone mass, placing them at increased risk for this disorder. Once thought to be a natural part of aging among women, osteoporosis is no longer considered age- or sex-dependent. It is largely preventable due to the remarkable progress in the scientific understanding of its causes, diagnosis, and treatment. Optimization of bone health is a process that must occur throughout life in both men and women. Factors that influence bone health at all ages are essential to prevent osteoporosis and its devastating consequences.

Consensus Process

The National Institutes of Health organized this 2½-day conference to clarify the factors associated with prevention, diagnosis, and treatment of osteoporosis, and to present the latest information about this disease. After 1½ days of presentations and audience discussion, an independent, nonfederal, 13-member consensus panel chaired by Anne Klibanski, MD, from Harvard Medical School, weighed the scientific evidence and drafted a statement presented to the audience on the third day. Candidates for the panel and speakers were nominated by the planning committee. Panel members' research was in areas adjacent to conference issues and was not used to answer conference questions. The panel represented the fields of internal medicine, family and community medi-

Objectives To clarify the factors associated with prevention, diagnosis, and treatment of osteoporosis, and to present the most recent information available in these areas.

Participants From March 27-29, 2000, a nonfederal, nonadvocate, 13-member panel was convened, representing the fields of internal medicine, family and community medicine, endocrinology, epidemiology, orthopedic surgery, gerontology, rheumatology, obstetrics and gynecology, preventive medicine, and cell biology. Thirty-two experts from these fields presented data to the panel and an audience of 699. Primary sponsors were the National Institute of Arthritis and Musculoskeletal and Skin Diseases and the National Institutes of Health Office of Medical Applications of Research.

Evidence MEDLINE was searched for January 1995 through December 1999, and a bibliography of 2449 references provided to the panel. Experts prepared abstracts for presentations with relevant literature citations. Scientific evidence was given precedence over anecdotal experience.

Consensus Process The panel, answering predefined questions, developed conclusions based on evidence presented in open forum and the literature. The panel composed a draft statement, which was read and circulated to the experts and the audience for public discussion. The panel resolved conflicts and released a revised statement at the end of the conference. The draft statement was posted on the Web on March 30, 2000, and updated with the panel's final revisions within a few weeks.

Conclusions Though prevalent in white postmenopausal women, osteoporosis occurs in all populations and at all ages and has significant physical, psychosocial, and financial consequences. Risks for osteoporosis (reflected by low bone mineral density [BMD]) and for fracture overlap but are not identical. More attention should be paid to skeletal health in persons with conditions associated with secondary osteoporosis. Clinical risk factors have an important but poorly validated role in determining who should have BMD measurement, in assessing fracture risk, and in determining who should be treated. Adequate calcium and vitamin D intake is crucial to develop optimal peak bone mass and to preserve bone mass throughout life. Supplementation with these 2 nutrients may be necessary in persons not achieving recommended dietary intake. Gonadal steroids are important determinants of peak and lifetime bone mass in men, women, and children. Regular exercise, especially resistance and high-impact activities, contributes to development of high peak bone mass and may reduce risk of falls in older persons. Assessment of bone mass, identification of fracture risk, and determination of who should be treated are the optimal goals when evaluating patients for osteoporosis. Fracture prevention is the primary treatment goal for patients with osteoporosis. Several treatments have been shown to reduce the risk of osteoporotic fractures, including those that enhance bone mass and reduce the risk or consequences of falls. Adults with vertebral, rib, hip, or distal forearm fractures should be evaluated for osteoporosis and given appropriate therapy.

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cine, endocrinology, epidemiology, orthopedic surgery, gerontology, rheumatology, obstetrics and gynecology, preventive medicine, and cell biology. In addition, 32 experts from these same fields presented data to the panel and to a conference audience of 699. Speakers were chosen for research per-

A list of the members of the Consensus Conference Panel appears at the end of this article. A listing of speakers and conference sponsors can be found on the Consensus Development Program Web site at <http://consensus.nih.gov>.

This NIH Consensus Statement, State of the Science Statements, and related materials are available from the NIH Consensus Program Information Center, PO Box 2577, Kensington, MD 20891; (888) 644-2667; or the NIH Consensus Development Program home page at <http://consensus.nih.gov>.

formed in specific areas of concern regarding conference issues.

The literature from the period January 1995 through December 1999 was searched using MEDLINE, and an extensive bibliography of 2449 references was provided to the panel. Experts prepared abstracts for their conference presentations with relevant citations from the literature. Scientific evidence was given precedence over clinical anecdotal experience.

The panel, answering predefined questions, developed its conclusions based on the scientific evidence presented during the open forum and in the scientific literature. The panel composed a draft statement that was read in its entirety and circulated to the experts and the audience for comment. Thereafter, the panel resolved conflicting recommendations and released a revised statement. The final consensus statement included supporting references and the conclusions of the consensus panel, and addressed 5 key questions:

1. What is osteoporosis and what are its consequences?
2. How do risks vary among different segments of the population?
3. What factors are involved in building and maintaining skeletal health throughout life?
4. What is the optimal evaluation and treatment of osteoporosis and fractures?
5. What are the directions for future research?

1. What Is Osteoporosis and What Are Its Consequences?

Osteoporosis is defined as a skeletal disorder characterized by compromised bone strength predisposing a person to an increased risk of fracture. Bone strength primarily reflects the integration of bone density and bone quality. Bone density is expressed as grams of mineral per area or volume, and in any given individual is determined by peak bone mass and amount of bone loss. Bone quality refers to architecture, turnover, damage accumulation (eg, microfractures), and mineralization. A frac-

ture occurs when a failure-inducing force such as trauma is applied to osteoporotic bone. Thus, osteoporosis is a significant risk factor for fracture, and a distinction between risk factors that affect bone metabolism and risk factors for fracture must be made.

It is important to acknowledge a common misconception that osteoporosis is always the result of bone loss. Bone loss commonly occurs as men and women age; however, an individual who does not reach optimal (ie, peak) bone mass during childhood and adolescence may develop osteoporosis without the occurrence of accelerated bone loss. Hence, suboptimal bone growth in childhood and adolescence is as important as later bone loss in the development of osteoporosis.

Currently there is no accurate measure of overall bone strength. Bone mineral density (BMD) is frequently used as a proxy measure and accounts for approximately 70% of bone strength. The World Health Organization (WHO) operationally defines osteoporosis as bone density 2.5 SDs below the mean for young white adult women. It is not clear how to apply this diagnostic criterion to men and children, or across ethnic groups. Because of the difficulty of accurate measurement and standardization between instruments and sites, controversy exists among experts regarding the continued use of this diagnostic criterion.

Osteoporosis can be further characterized as either primary or secondary. Primary osteoporosis can occur in both sexes at all ages, but often follows menopause in women and occurs later in life in men. In contrast, secondary osteoporosis is a result of medications (eg, glucocorticoids), other conditions (eg, hypogonadism), or diseases (eg, celiac disease).

Osteoporosis has financial, physical, and psychosocial consequences, all of which significantly affect the individual, the family, and the community. An osteoporotic fracture is an outcome of trauma to bone of compromised strength, and its incidence is increased by various other risk factors. Trau-

matic events can range from normal lifting and bending to high-impact falls. The incidence of fracture is high in persons with osteoporosis and increases with age. The probability that a 50-year-old will have a hip fracture during his or her lifetime is 14% for a white woman and 5% to 6% for a white man. The risk for African Americans is much lower (6% and 3% for 50-year-old women and men, respectively).

Osteoporotic fractures, particularly vertebral fractures, can be associated with chronic disabling pain. Nearly one third of patients with hip fractures are discharged to nursing homes within the year following a fracture. Notably, 1 in 5 patients is no longer living 1 year after sustaining an osteoporotic hip fracture. Hip and vertebral fractures are a problem for women in their late 70s and 80s, wrist fractures are a problem for women in their late 50s to early 70s, and all other fractures (eg, pelvis and rib) are a problem throughout the postmenopausal years. Investigators acknowledge the impact of osteoporosis on other systems (eg, gastrointestinal, respiratory, genitourinary, and craniofacial), but reliable prevalence rates are unknown.

Hip fracture has a profound impact on quality of life, as evidenced by findings that 80% of women older than 75 years preferred death to a bad hip fracture resulting in their placement in a nursing home. However, little data exist on the relationship between fractures and psychological and social well-being. Other quality-of-life issues include adverse effects on physical health (eg, skeletal deformity) and on financial resources. An osteoporotic fracture is associated with increased difficulty with the activities of daily life, as only one third of fracture patients regain their prefracture level of function and one third require placement in a nursing home. Fear, anxiety, and depression are frequently reported in women with established osteoporosis, and such consequences are likely under-addressed when considering the overall impact of this condition.

Direct financial expenditures for treatment of osteoporotic fracture in the United States are estimated at \$10 billion to \$15 billion annually. A majority of these estimated costs are due to inpatient care but do not include the costs of treatment for persons without a history of fractures, nor do they include the indirect costs of lost wages or productivity of either the patient or the caregiver. Consequently, these figures significantly underestimate the true costs of osteoporosis. More needs to be learned about these indirect costs, which are considerable.

2. How Do Risks Vary Among Different Segments of the Population?

Sex/Ethnicity

The prevalence of osteoporosis and the incidence of fracture vary by sex and race/ethnicity. White postmenopausal women experience almost three quarters of all hip fractures and have the highest age-adjusted incidence of fracture. Most of the information regarding diagnosis and treatment is derived from research on this population. However, women of other ages, races, and ethnicities, as well as men and children, are also affected. Much of the difference in fracture rates among these groups appears to be explained by differences in peak bone mass and rate of bone loss; however, differences in bone geometry, frequency of falls, and prevalence of other risk factors appear to play a role as well.

Both men and women experience an age-related decline in BMD starting in midlife. Women experience more rapid bone loss in the early years following menopause, which places them at earlier risk for fractures. In men, hypogonadism is also an important risk factor. Men and perimenopausal women with osteoporosis more commonly have secondary causes for the bone loss than do postmenopausal women.

African American women have higher BMD than white non-Hispanic women throughout life, and experience lower rates of hip fracture. For reasons not

fully understood, some Japanese women have lower peak BMDs than white non-Hispanic women, but have lower rates of hip fracture. Mexican-American women have BMDs between those of white non-Hispanic women and African American women. Limited available information for Native American women suggests they have lower BMDs than white non-Hispanic women.

Risk Factors

Risks associated with low BMD are supported by evidence that includes large prospective studies. Predictors of low bone mass include female sex, increased age, estrogen deficiency, white race, low weight and body mass index (BMI), family history of osteoporosis, smoking, and history of prior fracture. Use of alcohol and caffeine-containing beverages is inconsistently associated with decreased bone mass. In contrast, some measures of physical function and activity have been associated with increased bone mass, including grip strength and current exercise. Levels of exercise in childhood and adolescence have an inconsistent relationship to BMD later in life. Late menarche, early menopause, and low endogenous estrogen levels are also associated with low BMD in several studies.

Although low BMD has been established as an important predictor of future fracture risk, the results of many studies indicate that clinical risk factors related to risk of fall also serve as important predictors of fracture. Fracture risk has been consistently associated with a history of falls, low physical function such as slow gait speed and decreased quadriceps strength, impaired cognition, impaired vision, and the presence of environmental hazards (eg, throw rugs). The risk of a fracture occurring with a fall is increased in tall persons and in falls to the side, and may be influenced by attributes of bone geometry such as hip axis and femur length. Some risks for fracture (eg, advanced age, a low BMI, and low levels of physical activity) probably af-

fect fracture incidence through their effects on bone density, propensity to fall, and inability to absorb impact.

Results of studies of persons with osteoporotic fractures have led to the development of models of risk prediction, which incorporate clinical risk factors along with BMD measurements. Results from the Study of Osteoporotic Fractures, a large longitudinal study of postmenopausal, white, non-Hispanic women, suggest that clinical risk factors can contribute greatly to assessment of fracture risk. In this study, 14 clinical risk factors predictive of fracture were identified. The presence of 5 or more of these factors increased the rate of hip fracture for women in the highest tertile of BMD from 1.1 per 1000 woman-years to 9.9 per 1000 woman-years. Women in the lowest tertile of BMD with no other risk factors had a hip fracture rate of 2.6 per 1000 woman-years, compared with 27.3 per 1000 woman-years among women with 5 or more risk factors. A second model, derived from the Rotterdam study, predicted hip fractures using a smaller number of variables including sex, age, height, weight, use of a walking aid, and current smoking. However, these models have not been validated in a population different from that in which they were derived.

Secondary Osteoporosis

A large number of medical disorders are associated with osteoporosis and increased risk of fracture. These can be organized into several categories: genetic disorders, hypogonadal states, endocrine disorders, gastrointestinal diseases, hematologic disorders, connective tissue diseases, nutritional deficiencies, drugs, and a variety of other common serious chronic systemic disorders such as congestive heart failure, end-stage renal disease, and alcoholism.

The distribution of the most common causes appears to differ by demographic group. Among men, 30% to 60% of osteoporosis cases are associated with secondary causes, the most common of which are hypogonadism,

use of glucocorticoids, and alcoholism. In perimenopausal women, more than 50% of cases are associated with secondary causes, the most common of which are hypoestrogenemia, use of glucocorticoids, thyroid hormone excess, and anticonvulsant therapy. In postmenopausal women, the prevalence of secondary conditions is thought to be much lower, but the actual proportion is not known. In 1 study, hypercalciuria, hyperparathyroidism, and malabsorption were identified in a group of white postmenopausal women with osteoporosis who had no history of conditions that cause bone loss. These data suggest that additional testing of such women may be indicated, but an appropriate or cost-effective evaluation strategy has not been determined.

Glucocorticoid use causes the most common form of drug-related osteoporosis, and the long-term administration of glucocorticoids for disorders such as rheumatoid arthritis and chronic obstructive pulmonary disease is associated with a high rate of fracture. For example, in 1 study, a group of patients treated with 10 mg/d of prednisone for 20 weeks experienced an 8% loss of BMD in the spine. Some experts suggest that any patient who receives prednisone or other orally administered glucocorticoids in a dose of 5 mg/d or more for longer than 2 months is at high risk for excessive bone loss.

People who have undergone organ transplantation are at high risk for osteoporosis due to a variety of factors, including pretransplant organ failure and use of glucocorticoids after transplantation.

Hyperthyroidism is a well-described risk factor for osteoporosis. In addition, some studies have suggested that women receiving thyroid replacement therapy may also be at increased risk for excessive bone loss, suggesting that careful regulation of thyroid replacement is important.

Children and Adolescents

Several groups of children and adolescents may be at risk for compromised

bone health. Premature and low-birth-weight infants have lower-than-expected bone mass in the first few months of life, but the long-term implications of this are unknown.

Glucocorticoids are now commonly used for the treatment of a variety of common childhood inflammatory diseases, and the effects of this treatment on bone need to be considered when chronic use of steroids is required. The long-term effects on bone health of intermittent courses of systemic steroids or the chronic use of inhaled steroids, such as those used in asthma, are not well described.

Cystic fibrosis, celiac disease, and inflammatory bowel disease are examples of conditions associated with malabsorption and resultant osteopenia in some persons. The osteoporosis of cystic fibrosis is also related to the frequent need for corticosteroids as well as to other undefined factors.

Hypogonadal states, characterized clinically by delayed menarche, oligomenorrhea, or amenorrhea, are relatively common in adolescent girls and young women. These occur with strenuous athletic training, emotional stress, and low body weight. Failure to achieve peak bone mass, bone loss, and increased fracture rates have been shown in this group. Anorexia nervosa deserves special mention. Although hypogonadism is an important feature of the clinical picture, undernutrition and other nutrition-related factors are also critical. This latter point is evidenced, in part, by the failure of estrogen replacement to correct the bone loss.

Residents of Long-term Care Facilities

Residents of nursing homes and other long-term care facilities are at particularly high risk of fracture. Most have low BMD and a high prevalence of other risk factors for fracture, including advanced age, poor physical function, low muscle strength, poor nutrition, decreased cognition and high rates of dementia, and, often, use of multiple medications.

3. What Factors Are Involved in Building and Maintaining Skeletal Health Throughout Life?

Growth in bone size and strength occurs during childhood, but bone accumulation is not completed until the third decade of life, after the cessation of linear growth. The bone mass attained early in life is perhaps the most important determinant of lifelong skeletal health. Persons with the highest peak bone mass after adolescence have the greatest protective advantage when bone density declines as a result of aging, illness, and diminished sex-steroid production. Bone mass may be related not only to osteoporosis and fragility later in life but also to fractures in childhood and adolescence. Genetic factors exert a strong and perhaps predominant influence on peak bone mass, but physiological, environmental, and modifiable lifestyle factors can also play a significant role. Among these are adequate nutrition and body weight, exposure to sex hormones at puberty, and physical activity. Thus, maximizing bone mass early in life presents a critical opportunity to reduce the impact of bone loss related to aging. Childhood is also a critical time for the development of lifestyle habits conducive to maintaining good bone health throughout life. Cigarette smoking, which usually starts in adolescence, may have a deleterious effect on achieving bone mass.

Nutrition

Good nutrition is essential for normal growth. A balanced diet, adequate calories, and appropriate nutrients are the foundation for development of all tissues, including bone. Supplementation with calcium and vitamin D may be necessary. Adequate and appropriate nutrition is important for all persons, but not all follow a diet that is optimal for bone health. In particular, excessive pursuit of thinness may preclude adequate nutrition and affect the health of bone.

Calcium is the nutrient most important for attaining peak bone mass and for preventing and treating osteoporosis.

sis. Sufficient data exist to recommend specific dietary calcium intakes at various stages of life. Although the Institute of Medicine recommends calcium intakes of 800 mg/d for children aged 3 to 8 years and 1300 mg/d for children and adolescents aged 9 to 17 years, it is estimated that only about 25% of boys and 10% of girls aged 9 to 17 years meet these recommendations. Factors contributing to low calcium intakes are restriction of dairy products, a generally low consumption of fruits and vegetables, and a high intake of low-calcium beverages such as sodas. For older adults, calcium intake should be maintained at 1000 to 1500 mg/d, yet only about 50% to 60% of this population meets this recommendation.

Vitamin D is required for optimal calcium absorption and thus is also important for bone health. Most infants and young children in the United States have adequate vitamin D intake because of supplementation and fortification of milk. During adolescence, when consumption of dairy products decreases, vitamin D intake is less likely to be adequate, and this may adversely affect calcium absorption. A recommended vitamin D intake of 400 to 600 IU/d has been established for adults.

Other nutrients have been evaluated for their relation to bone health. High dietary protein, caffeine, phosphorus, and sodium can adversely affect calcium balance, but their effects appear not to be important in individuals with adequate calcium intakes.

Exercise

Regular physical activity has numerous health benefits for persons of all ages. The specific effects of physical activity on bone health have been investigated in randomized clinical trials (RCTs) and observational studies. There is strong evidence that physical activity early in life contributes to higher peak bone mass. Some evidence indicates that resistance and high-impact exercise are likely the most beneficial. Exercise during the middle years of life has numerous health benefits, but there

are few studies of the effects of exercise on BMD. Exercise during the later years, in the presence of adequate calcium and vitamin D intake, probably has a modest effect on slowing the decline in BMD. It is clear that exercise late in life, even beyond age 90 years, can increase muscle mass and strength 2-fold or more in frail persons. There is convincing evidence that exercise in elderly persons also improves function and delays loss of independence and thus contributes to quality of life.

Randomized clinical trials of exercise have been shown to reduce the risk of falls by approximately 25%, but there is no experimental evidence that exercise affects fracture rates. It also is possible that regular exercisers might fall differently and thereby reduce the risk of fracture due to falls, but this hypothesis requires testing.

Gonadal Steroids

Sex steroids secreted during puberty substantially increase BMD and peak bone mass. Gonadal steroids influence skeletal health throughout life in both women and men. In adolescents and young women, sustained production of estrogens is essential for the maintenance of bone mass. Reduction in estrogen production at menopause is the major cause of loss of BMD during later life. Timing of menarche, absent or infrequent menstrual cycles, and the timing of menopause influence both the attainment of peak bone mass and the preservation of BMD. Testosterone production in adolescent boys and men is similarly important in achieving and maintaining maximal bone mass. Estrogens have also been implicated in the growth and maturation of the male skeleton. Pathologic delay in the onset of puberty is a risk factor for diminished bone mass in men. Disorders involving hypogonadism in adult men result in osteoporosis.

Growth Hormone and Body Composition

Growth hormone and insulin-like growth factor I, which are maximally secreted during puberty, continue to play

a role in the acquisition and maintenance of bone mass and the determination of body composition into adulthood. Growth hormone deficiency is associated with a decrease in BMD. Children and youth with low BMI are likely to attain lower-than-average peak bone mass. Although there is a direct association between BMI and bone mass throughout the adult years, it is not known whether the association between body composition and bone mass is due to hormones, nutrition, higher impact during weight-bearing activities, or other factors. There are several observational studies of fractures in older persons that show an inverse relationship between fracture rates and BMI.

4. What Is the Optimal Evaluation and Treatment of Osteoporosis and Fractures?

The goals for the evaluation of patients at risk for osteoporosis are to establish the diagnosis of osteoporosis on the basis of assessment of bone mass, to establish the fracture risk, and to make decisions regarding the needs for instituting therapy. A history taking and physical examination are essential in evaluating fracture risks and should include assessment for loss of height and change in posture. Laboratory evaluation for secondary causes of osteoporosis should be considered when osteoporosis is diagnosed.

The measurement most commonly used to diagnose osteoporosis and predict fracture risk is based on assessment of BMD. Measurements of BMD have been shown to correlate strongly with load-bearing capacity of the hip and spine and with the risk of fracture. Several different techniques have been developed to assess BMD at multiple skeletal sites including the peripheral skeleton, hip, and spine. The WHO has selected BMD measurements to establish criteria for the diagnosis of osteoporosis. A T score is defined as the number of SDs above or below the average BMD value for young healthy white women. This should be distinguished from a Z score, which is defined as the number of SDs above or below the average BMD for age-

and sex-matched controls. According to the WHO definition, osteoporosis is present when the T score is at least -2.5 SDs. Although T scores were based originally on assessment of BMD at the hip by dual-energy x-ray absorptiometry (DXA), they have been applied to define diagnostic thresholds at other skeletal sites and for other technologies. Experts have expressed concern that this approach may not produce comparable data between sites and techniques. Of the various sampling sites, measurements of BMD made at the hip predict hip fracture better than measurements made at other sites while BMD measurement at the spine predicts spine fracture better than measures at other sites.

Newer measures of bone strength, such as ultrasound, have been introduced. Recent prospective studies using quantitative ultrasound (QUS) of the heel have predicted hip fracture and all nonvertebral fractures nearly as well as DXA at the femoral neck. Quantitative ultrasound and DXA at the femoral neck provide independent information about fracture risk, and both of these tests predict hip fracture risk better than DXA at the lumbar spine. In general, clinical trials of pharmacological therapies have used DXA, rather than QUS, for entry criterion for studies, and there is uncertainty regarding whether the results of these trials can be generalized to patients identified by QUS to have a high risk of fracture.

Over the past year, several professional organizations have been working on establishing a standard of comparability of different devices and sites for assessing fracture risk. With this approach, measurements derived from any device or site could be standardized to predict hip fracture risk. However, the values obtained from different instruments cannot be used to predict comparable levels in bone mass. Limitations in precision and low correlation among different techniques will require appropriate validation before this approach can be applied to different skeletal sites and to different age groups.

It has been suggested that the diagnosis and treatment of osteoporosis

should depend on risk-based assessment rather than solely on the assessment of a T score. Consideration of risk factors in conjunction with BMD will likely improve the ability to predict fracture risk. This approach needs to be validated in prospective studies and tested in appropriate RCTs.

In addition to the effects of bone mass, microarchitecture, and macrogeometry, bone strength is also affected by the rate of remodeling. Bone remodeling can be assessed by the measurement of surrogate markers of bone turnover in the blood or urine. These markers include indices of bone formation, such as bone-specific alkaline phosphatase and osteocalcin, and urine levels of pyridinolines and deoxypyridinolines, as well as indices of bone resorption such as serum and urine levels of type I collagen C- and N-telopeptides. The levels of these markers may identify changes in bone remodeling within a relatively short interval (several days to months) before changes in BMD can be detected. However, according to available data, marker levels do not predict bone mass or fracture risk and are only weakly associated with changes in bone mass. Therefore, they are of limited use in the clinical evaluation of individual patients. Despite these limitations, markers have been shown in research studies to correlate with changes in indices of bone remodeling and may provide insights into mechanisms of bone loss.

Who Should Be Evaluated?

The value of bone density in predicting fracture risk is established, and there is general consensus that measurement of BMD should be considered in patients receiving glucocorticoid therapy for 2 months or more and in patients with other conditions that place them at high risk for osteoporotic fracture. However, the value of universal screening, especially in perimenopausal women, has not been established. There are 2 unknown factors with this approach.

First, the number of women evaluated and treated would need to be high

to prevent a single fracture. For example, in white women aged 50 to 59 years, an estimated 750 BMD tests would be required to prevent just 1 hip or vertebral fracture over a 5-year period of treatment. Second, the value has not been established for the common practice of beginning preventive drug therapy in the perimenopausal period for the purpose of preventing fractures later in life.

Until there is good evidence to support the cost-effectiveness of routine screening, or the efficacy of early initiation of preventive drugs, an individualized approach is recommended. A measurement of BMD should be considered when it will help the patient decide whether to institute treatment to prevent osteoporotic fracture. In the future, a combination of risk factor evaluation and BMD measurements may increase the ability to predict fracture risk and help with treatment decisions. Until RCTs are conducted, individual decisions regarding screening could be informed by the preliminary evidence that the risk for fracture increases with age, and with an increased number of additional risk factors.

What Are the Effective Medical Treatments?

In the past 30 years, major strides have been made in the treatment of osteoporosis. Evidence-based reports systematically reviewing the data from RCTs, including meta-analyses for each of the major treatments, are available and permit conclusions regarding the role of each modality of osteoporosis therapy.

Calcium and vitamin D intake modulates age-related increases in parathyroid hormone (PTH) levels and bone resorption. Randomized clinical trials have demonstrated that adequate calcium intake from diet or supplements increases spinal BMD and reduces vertebral and nonvertebral fractures. Low levels of 25-hydroxyvitamin D are common in the aging population, and significant reductions in hip and other nonvertebral fractures have been observed in patients receiving calcium and

vitamin D₃ in prospective trials. The optimal effective dose of vitamin D is uncertain, but thought to be 400 to 1000 IU/d. There is consensus that adequate vitamin D and calcium intakes are required for bone health. The therapeutic effects of most of the clinical trials of various drug therapies for osteoporosis have been achieved in the presence of calcium and vitamin D supplementation among control and intervention groups. Optimal treatment of osteoporosis with any drug therapy also requires calcium and vitamin D intake meeting recommended levels. The preferred source of calcium is dietary. Calcium supplements need to be absorbable and should have United States Pharmacopeia designation.

Physical activity is necessary for bone acquisition and maintenance through adulthood. Complete bed rest and microgravity have devastating effects on bone. Trials of exercise intervention show most of the effect during skeletal growth and in very inactive adults. Effects beyond those directly on bone, such as improved muscular strength and balance, may be very significant in the reduction of fracture risk. Trials in older adults have successfully used various forms of exercise to reduce falls. High-impact exercise such as weight training stimulates accrual of bone mineral content in the skeleton. Lower-impact exercises, such as walking, have beneficial effects on other aspects of health and function, although their effects on BMD have proved minimal.

Placebo-controlled RCTs of cyclic etidronate, alendronate, and risedronate analyzed by a systematic review and meta-analysis have revealed that all of these bisphosphonates increase BMD at the spine and hip in a dose-dependent manner. They consistently reduce the risk of vertebral fractures by 30% to 50%. Alendronate and risedronate reduce the risk of subsequent nonvertebral fractures in women with osteoporosis and adults with glucocorticoid-induced osteoporosis. There is uncertainty about the effect of antiresorptive therapy in reducing nonvertebral fracture in women without osteoporosis. In RCTs, the rela-

tive risk of discontinuing medication due to an adverse event with each of the 3 bisphosphonates was not statistically significant. The safety and efficacy of this therapy in children and young adults has not been evaluated. Since subjects in clinical trials may not always be representative of the community-based population, an individual approach to treatment is warranted.

Hormone replacement therapy (HRT) is an established approach for osteoporosis treatment and prevention. Many short-term studies and some longer-term studies of HRT with BMD as the primary outcome have shown significant efficacy. Observational studies have indicated a significant reduction in the occurrence of hip fracture in cohorts of women who maintain HRT therapy; still, there is a paucity of trials with fractures as the end point. Trials of HRT have shown decreased risk of vertebral fractures, but there have been no trials of estrogen having hip fracture as the primary outcome.

The development of selective estrogen-receptor modulators (SERMs) has been an important new thrust in osteoporosis research. The goal of these agents is to maximize the beneficial effect of estrogen on bone and to minimize or antagonize the deleterious effects on the breast and endometrium. Raloxifene, a SERM approved by the Food and Drug Administration for the treatment and prevention of osteoporosis, has been shown to reduce the risks of vertebral fracture by 36% in large clinical trials. Tamoxifen, used in the treatment and prevention of breast cancer, can maintain bone mass in postmenopausal women. However, tamoxifen's effects on the risk of fracture are unclear.

There is a great deal of public interest in natural estrogens, particularly plant-derived phytoestrogens. These compounds have weak estrogen-like effects, and although some animal studies are promising, no reduction in risk of fracture in humans has been shown. Salmon calcitonin has demonstrated positive effects on BMD at the lumbar spine, but this effect is less clear at the hip. Other than a recently completed

RCT of nasal calcitonin, no analysis of fracture risk is available. The Prevent Recurrence of Osteoporotic Fractures (PROOF) study revealed a significant reduction in vertebral fracture risk at the 200 IU daily dose but not at the 100 IU or 400 IU daily doses. The absence of dose response, a 60% dropout rate, and the lack of strong supporting data from BMD and markers decrease confidence in the fracture risk data from this trial. Nonpharmacological interventions directed at preventing falls and reducing their effect on fractures have been promising. These include improving strength and balance in the elderly, as well as using hip protectors to absorb or deflect the impact of a fall.

Multifactorial approaches to preventing falls, as well as improving bone mass through combinations of interventions, suggest promising new directions.

Should the Response to Treatment Be Monitored?

Several approaches have been introduced for the monitoring of patients receiving therapies for osteoporosis. The goals of monitoring are to increase adherence to treatment regimens and determine treatment responses. Many persons do not continue prescribed therapy or do not adhere to a treatment protocol, even when enrolled in formal clinical trials. Monitoring by densitometry or measurements of bone markers have not been effective in improving compliance, and more research is needed to determine how to improve adherence to treatment protocols.

The best tests for monitoring treatment response would reflect the largest changes with the least error, and these assessment tools are not readily available. The Fracture Intervention Trial (FIT) reveals an additional problem with monitoring, namely, the statistical phenomenon of regression to the mean. In the FIT study, the larger the bone loss in the first year the greater the gain the next year, for both the placebo and active treatment groups. Therefore, physicians should not stop or change therapies with demonstrated efficacy solely

because of modest loss of bone density or adverse trends in markers of bone turnover.

Orthopedic Management of Osteoporotic Fractures

Proximal femur (hip) fractures comprise nearly 20% of all osteoporotic fractures. This injury is among the most devastating of all the osteoporotic fractures and is responsible for the greatest expenditure of health care resources. The 1-year mortality rate following hip fracture is about 1 in 5. As many as two thirds of hip fracture patients never regain their preoperative activity status. Early surgical management of hip fractures is associated with improved outcomes and decreased perioperative morbidity.

The adverse effects of vertebral fractures on health, function, and quality of life are commonly underestimated; such fractures are also associated with increased mortality. The occurrence of a single vertebral fracture substantially increases the likelihood of future fractures and progressive kyphotic deformity. Due to the challenges of reconstructing osteoporotic bone, open surgical management is reserved only for those rare cases involving neurologic deficits or an unstable spine. Recently, there has been a burgeoning interest in 2 minimally invasive procedures for management of acute vertebral fractures. These procedures, vertebroplasty and kyphoplasty, involve the injection of polymethylmethacrylate bone cement into the fractured vertebra. Anecdotal reports of both techniques frequently claim relief of acute pain; however, neither technique has been subjected to a controlled trial to demonstrate the benefits over traditional medical management. Furthermore, the long-term effect of 1 or more reinforced rigid vertebrae on the risk of fracture of adjacent vertebrae is unknown for both of these procedures.

Several issues are critically important to the management of acute osteoporotic fractures. It is most important to avoid the misconception that the only treatment required for an osteoporotic

fracture is management of the acute fracture itself. Management during the peri-fracture period must consider blood clot prevention (mechanical or pharmacological) in patients who will have delayed ambulation, the avoidance of substances that may inhibit fracture repair (eg, nicotine, corticosteroids), and the frequent need for supplemental caloric intake. Finally, since less than 5% of patients with osteoporotic fractures are referred for medical evaluation and treatment, more aggressive diagnostic and therapeutic intervention of this population represents an opportunity to prevent subsequent fractures. Physicians treating the acute fracture should initiate an outpatient evaluation of the patient for osteoporosis and a treatment program, if indicated, or refer the patient for an osteoporosis assessment.

5. What Are the Directions for Future Research?

The following questions, issues, and concerns should be addressed:

- Peak bone mass is an important factor in determining long-term fracture risk. Strategies to maximize peak bone mass in girls and boys are essential. These strategies include identifying and intervening in disorders that can impede the achievement of peak bone mass in ethnically diverse populations, and determining how long these interventions should last. More research regarding the risks for fracture in chronic diseases affecting children is needed. What is the impact of calcium deficiency and vitamin D deficiency in childhood, and can it be reversed? How does gonadal steroid insufficiency, pubertal delay, or undernourishment impact bone mass? What is known about the use of bisphosphonates or other agents in the treatment of children with osteoporosis?

- Genetic factors leading to osteoporosis are being identified. These factors may relate to bone mass acquisition, bone remodeling, or bone structure. Pharmacogenetic approaches for identifying and targeting specific genetic factors predisposing to osteoporosis need to be developed.

- Glucocorticoid use is a common cause of secondary osteoporosis and associated fractures. What is the impact of glucocorticoid-induced osteoporosis in adults and children? What are the mechanisms of disease? What novel approaches can be taken to stimulate bone formation in this condition? Development of glucocorticoids having fewer adverse effects on the skeleton are needed.

- Secondary causes of osteoporosis are prevalent. A number of risk factors have been identified, including specific disease states and medication use. How should patients be identified for diagnosis and treatment of osteoporosis? What is known about the use of bisphosphonates or other agents in young adults with secondary osteoporosis? What is known about the causes of osteoporosis in perimenopausal women? How should they be monitored for treatment response? Are therapies for improving bone mass in postmenopausal women effective in secondary causes?

- There is a need for prospective studies of sex, age, and ethnic diversity to provide data permitting more accurate fracture risk identification in these categories. Fracture risk is a combination of bone-dependent and bone-independent factors. Bone-independent factors include muscle function and cognition, which also contribute to falls leading to fractures. A comprehensive assessment of bone-dependent and bone-independent factors should be included. There is a need for a comprehensive evaluation of a validated risk assessment tool. What is the best way to identify patients in need of treatment for osteoporosis? An algorithm should be constructed that incorporates risk factors for fracture in addition to assessment of bone density. What is the best use of surrogate markers of bone turnover to determine osteoporosis, and how does this impact on fracture risks?

- Quality of life is significantly impaired by osteoporosis. Future research should characterize and validate quality-of-life tools in patients across sex, age, and race/ethnicity cat-

egories. It will be important to identify effects of fracture risk and intervention on quality of life. Quality of life should be incorporated as an outcome in clinical trials evaluating fracture risk and therapy. In addition, the psychosocial and financial effects of osteoporosis on caregivers and on family dynamics should be considered.

- Data should be obtained suggesting which asymptomatic patients should have screening bone-density tests done or when screening is justified.

- Neuropsychiatric disorders may cause or be the result of osteoporosis. Specific psychiatric disorders, including depression and anorexia nervosa, are associated with osteoporosis or clinical fractures. Medications used to treat psychiatric or neurologic disorders may cause osteoporosis, and the diagnosis of osteoporosis may have psychological implications. Research efforts into these relationships should be strongly encouraged.

- There is an urgent need for RCTs of combination therapy, which includes pharmacological, dietary, and lifestyle interventions (including muscle strengthening, balance training, management of multiple drug use, smoking cessation, psychological counseling, and dietary interventions). Primary outcomes would be fractures, and secondary outcomes would include quality of life and functional capability. Cost-effectiveness evaluations should also be considered.

- What is the optimal paradigm for the evaluation and management of fractures? What are the long-term consequences of osteoporosis and clinical fractures on nonskeletal body systems? What measures can be taken to prevent subsequent fractures?

- Anabolic agents that stimulate bone formation, such as PTH and fluoride, have been evaluated. Meta-analysis of fluoride therapy revealed no protective effects on fracture risk. Parathyroid hormone peptides are the most promising but are still in clinical trials. Other factors, including growth hormones, are under investigation. There is a critical need to develop and assess

anabolic agents that stimulate bone formation.

- Ensure accessibility to treatment regardless of income and geography.

- There is a need to determine the most effective method of educating health care professionals and the public about the prevention, diagnosis, and treatment of osteoporosis.

- There is a need to improve the reporting of BMD and fracture risk so it is understandable to medical specialists and can be explained to patients.

- Study is needed to determine the efficacy and safety of long-term administration of various drug interventions in maintaining BMD and preventing fractures.

- Trials of dietary supplements are needed.

- Study is needed to understand the influence of nutrition on micronutrients and nonpatentable medical interventions.

- Study is needed to understand cost-effectiveness and effectiveness of programs encouraging bone health.

- Study of interventions examining the long-term effects of fractures on health, function, and quality of life is needed.

NIH Consensus Development and State of the Science Conferences are convened to evaluate available scientific information and resolve safety and efficacy issues related to biomedical technology. The resultant statements are intended to advance understanding of the technology or issue in question and to be useful to health professionals and the public. **This statement is an independent report of the panel and is not a policy statement of the NIH or the federal government.**

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Division of Pediatric Endocrinology, Vanderbilt University Medical Center, Nashville, Tenn. The abstract is prepared by the conference organizers and added to the consensus conference panel's statement as a service for JAMA readers.

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The consensus conference speakers identified the following key references in developing their presentations for the consensus conference. A more complete bibliography prepared by the National Library of Medicine, along with the references below, was provided to the technology assessment panel for their consideration. The full bibliography is available at: <http://www.nlm.nih.gov/pubs/cbm/osteoporosis.html>.

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Biomechanics of Osteoporotic Fractures

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Bone plays a vital role as a mineral reservoir and source of hematopoietic cells. However, its major functions are structural: to protect vital internal organs and to provide a framework that allows movement and locomotion. Bone is unique with respect to other structural materials in that it can undergo self-repair and can adapt its composition and structure in response to hormonal and mechanical stimuli.

From a mechanical viewpoint, osteoporotic fractures represent a structural failure of the skeleton wherein the load applied to a bone exceeds its ability to support that load. The load-bearing capacity of a bone depends primarily on the intrinsic *material* properties of the tissue that comprises the bone, the *structure* of the bone (the size, shape, and bone mass), and the specific *loading* conditions. Thus it is clear that factors related both to the loads applied to the bone and to its load-bearing capacity are important determinants of fracture risk (Figure 1).

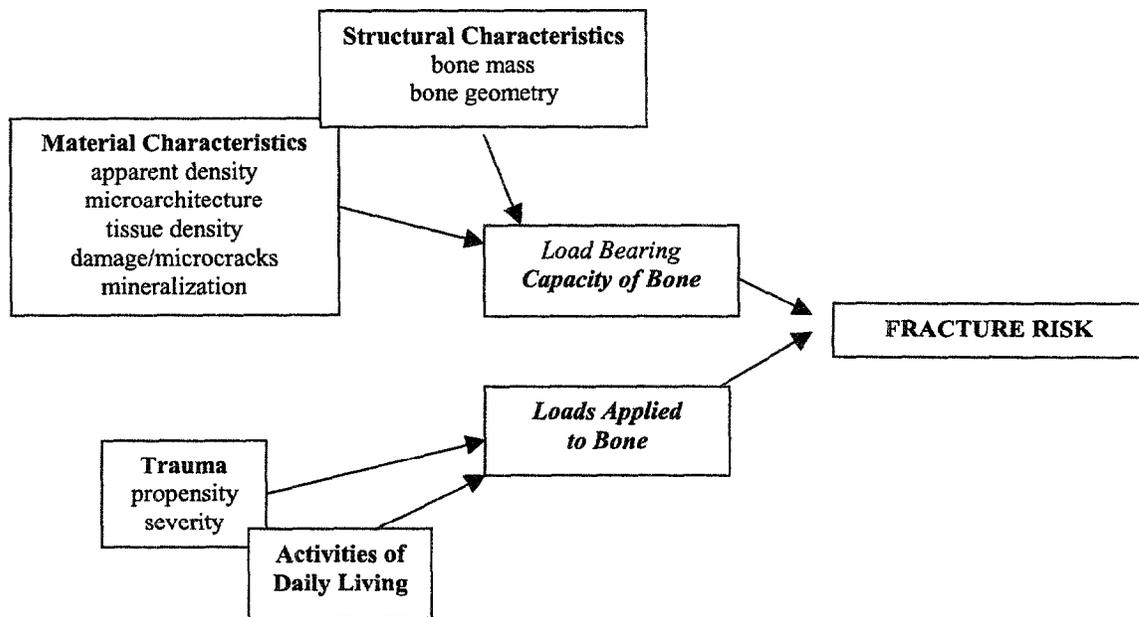


Figure 1. Determinants of fracture risk.

The intrinsic mechanical properties of both cortical and trabecular bone decrease dramatically with increasing age in men and women. These decreases in mechanical competence are due predominantly to age-related reductions in the apparent density (bone mass per unit volume) of cortical and trabecular bone, as 60 to 90 percent of the variability in trabecular and cortical bone strength is explained by apparent density. Moreover, the relationship between apparent density and trabecular bone strength is nonlinear (Carter, Hayes, 1977; Rice, Cowin, Bowman, 1988), whereby a decrease in the apparent density of trabecular bone leads to a

disproportionately larger reduction in bone strength. However, since 10 to 40 percent of the variability in bone strength remains unexplained by density, it is likely that other factors influence skeletal fragility. These factors may involve changes in trabecular architecture and in the bone tissue matrix itself. Changes in trabecular architecture, such as a decrease in the thickness and number of trabecular elements and the degree to which they are interconnected, accompany age-related declines in bone density. In the vertebral body, for example, preferential thinning and perforation of horizontally aligned trabecular elements substantially reduce the ability of the remaining vertical trabecular elements to support loads. Whereas these architectural features of trabecular bone are strongly correlated to bone density in “normal” nonpathologic bone (Compston, 1994; Goldstein, Goulet, McCubbrey, 1993), much less is known about the relationships among bone density, architecture, and bone strength in osteoporotic bone. Additional age-related changes in the properties of the bone tissue that may also contribute to increased skeletal fragility include alterations in the patterns of deposition or mineralization of bone matrix itself, an increase in osteonal remodeling, or an accumulation of microdamage. Bone microdamage, in the form of microcracks, accumulates with increasing age and appears to be greater in women than men (Mori, Harruf, Ambrosius, et al., 1997; Norman, Wang, 1997). However, the portion of the age-associated increase in fracture risk attributable to microdamage accumulation remains controversial (Burr, Forwood, Fyhrie, et al., 1997). These age-related decrements in bone density and mechanical properties may be partially offset by geometric rearrangements of the bone tissue, particularly in the long bones, that help to preserve the bone’s ability to resist bending and torsional loads.

Arguably the most widely used measurement to diagnose osteoporosis and predict fracture risk is areal bone mineral density (BMD) by dual-energy X-ray absorptiometry. Although BMD measurements correlate strongly with the load-bearing capacity of the hip and spine, they are potentially limited in that they cannot measure trabecular and cortical bone compartments separately. Furthermore, they do not reflect trabecular architecture or other properties of the bone matrix that may be predictive of fracture risk. Thus, it may be useful to investigate new methodologies capable of assessing bone strength more accurately and precisely than the bone densitometry techniques that are used currently.

It is clear that bone strength plays an important role in fracture risk; therefore, investigations have focused primarily on methods to prevent bone loss and to restore bone to the osteopenic skeleton. However, alternative approaches for fracture prevention that are directed at reducing the loads applied to the skeleton may prove to be both effective and cost-efficient. Although much is known about the contribution of falls to hip fracture risk, little is known about the interactions between spinal loading and skeletal fragility in the etiology of vertebral fractures. In contrast to previously held beliefs that vertebral fractures are caused primarily by bending and lifting activities, there is increasing evidence that falls may also play a significant role in the etiology of vertebral fractures (Myers, Wilson, 1997). Thus, fracture prevention strategies should include prevention of falls, decreasing the severity of falls, and avoiding activities that generate high loads on skeletal sites at risk for fracture. For example, trochanteric padding systems designed to reduce the load applied to the hip during a fall have shown great potential for reducing fracture risk (Lauritzen, Peterson, Lund, 1993). Ultimately, fracture prevention may be best achieved by an educational program designed to limit high-risk activities in conjunction with interventions targeted at increasing bone strength and reducing loads applied to the skeleton.

Directions for Future Research

- Determine the relationships among bone density, architecture, microdamage, and turnover in normal and osteoporotic bone, and determine how these characteristics contribute to skeletal fragility.
- Improve existing and develop new noninvasive techniques for assessing skeletal fragility and for measuring the effects of therapeutic agents on skeletal fragility.
- Improve our understanding of the relative roles of skeletal fragility and skeletal loading in determination of fracture risk.

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The Food and Drug Administration's Osteoporosis Guidance Document: Past, Present, and Future

ERIC G COLMAN

ABSTRACT

In December 1979, the Food and Drug Administration's (FDA) Division of Metabolic and Endocrine Drug Products issued its *Guidelines for the Clinical Evaluation of Drugs Used in the Treatment of Osteoporosis*. The Guidance Document recommended study designs, patient populations for study, and techniques for evaluating skeletal mass and fracture frequency that were considered central to showing the efficacy and safety of drugs used to treat and prevent postmenopausal osteoporosis (PMO). In this paper, I discuss the evolution of the Osteoporosis Guidance as it relates to the pharmaceutical industry's efforts to develop effective and safe anti-osteoporosis drugs. Current regulatory policy on osteoporosis drugs and thoughts on the future direction of the Osteoporosis Guidance are also provided. (J Bone Miner Res 2003;18:1125–1128)

THE ORIGINAL GUIDANCE

RESPONDING TO THE NEED for effective and safe drugs to treat osteoporosis, the FDA's Division of Metabolic and Endocrine Drug Products, with input from an ad hoc workshop and an Advisory Committee, published the first issue of its Osteoporosis Guidance in December 1979. This document, entitled, *Guidelines for the Clinical Evaluation of Drugs Used in the Treatment of Osteoporosis*, began with the acknowledgment that evaluating the clinical effectiveness of osteoporosis drugs posed special challenges because of the "difficulties in assessing the state of skeletal bone quantitatively in vivo, the relatively small changes that are usually encountered, and the duration of studies necessary to show significant effects."⁽¹⁾

These limitations in mind, the Guidance recommended that phase II studies of osteoporosis drugs be randomized, double-blind, placebo-controlled, and at least 24 months in duration. Phase III studies were expected to be continuations of the phase II trials—no minimal duration of study was suggested, however. Appropriate criteria for patient inclusion in the studies included objective evidence of disease (history of an osteoporosis-related fracture) and/or the somewhat subjective criterion (evidence of a decrease in bone mass as measured by any of a number of techniques).

The views expressed in this paper are those of the author and should not be construed as representing the official position of the FDA.

The author has no conflict of interest.

Six methods to measure skeletal mass—all with noted disadvantages—were provided in the Guidance, with single photon absorptiometry, radiogammetry, and total body neutron activation analysis considered the most applicable to drug development. It was expected that skeletal mass would be measured at baseline and every 6 months during the first 2 years of the trials, and annually thereafter.

In an attempt to balance the desire for definitive evidence of efficacy (i.e., fracture reduction) with the realities of conducting a large clinical trial, the first issue of the Osteoporosis Guidance left ample room for interpretation regarding the most appropriate primary efficacy variable for osteoporosis trials: skeletal mass or fracture. On the one hand, the Guidance said that the assessment of a drug's effect on the frequency of fracture was "highly desirable," yet on the other hand, the document conceded that fracture trials would "require a relatively large numbers of patients to provide statistically significant results." As a compromise the Guidance offered "where there is evidence that bone formed during therapy is normal, adequate and well-controlled studies showing a favorable effect on bone mass [will] provide reasonable evidence of effectiveness of the drug in the management of osteoporosis." This approach was not without risk, however, as the Guidance made clear that in the event that bone formed was not normal, a fracture study would be required in addition to studies on bone mass.

In 1984, injectable salmon calcitonin (Calcimar), which had been approved by the FDA in the late 1970s for the treatment of Paget's disease and hypercalcemia, won approval for the treatment of patients with osteoporosis.⁽²⁾

Market licensure was based primarily on the results from two 24-month studies of about 100 men and women, with total body calcium (TBC) measured by neutron activation analysis as the primary efficacy end-point. While there was little question of Calcimar's favorable effect on TBC (at least over a 1-year period), and hence skeletal mass, and no evidence that the drug adversely affected bone quality, some Advisory Committee members were hesitant to recommend approving a drug to treat osteoporosis in the absence of definitive fracture data. Nonetheless, because the minimum criteria for determining efficacy as set out in the Osteoporosis Guidance were satisfied by the Calcimar clinical data (i.e., increase or maintenance in bone mass and normal bone histology), and three of the five members of the Advisory Committee believed the data presented demonstrated adequate efficacy, the drug was approved.

The Advisory Committee's concerns about fracture efficacy did not fall on deaf ears, however, as the company agreed to conduct a 3-year, 300 patient, phase IV study to examine the effect of Calcimar on fracture frequency. Unfortunately, after 4 years of enrollment, it was obvious that the trial had significant problems (e.g., 50% dropout rate) that would hinder successful completion. Indeed, the study was eventually considered unsalvageable and terminated. While FDA officials were eager for data verifying that an increase in TBC was a valid surrogate for reduced fracture risk, they did not believe that the unsuccessful fracture trial justified withdrawal of the drug's osteoporosis indication, as some had suggested. For those who read the drug's labeling, it was clear that the osteoporosis indication was based on TBC data and that the Calcimar studies were not designed to detect differences in fracture rates.⁽²⁾

THE 1984 GUIDANCE

In the same year that calcitonin received its osteoporosis indication, the Division of Metabolic and Endocrine Drugs updated its Osteoporosis Guidance.⁽³⁾ The changes of note included suggestions for studies designed to secure an indication for the prevention of PMO and an upgrading of dual-energy photon absorptiometry from an investigational to a valid and reliable method for measuring trabecular bone mass of the spine, a recommendation to supplement all trial participants with calcium and vitamin D, and inclusion of the option to use an active versus a placebo control in trials of women with established osteoporosis. All but the last of these updates were embraced by industry.

The years 1980–1990 were critical to the approach to development and regulation of osteoporosis drugs. In 1982, Riggs et al. published results of a study that indicated that the combination of calcium fluoride, a stimulator of bone formation, and estrogen, an antiresorptive agent, had favorable effects on vertebral fracture risk.⁽⁴⁾ Encouraged by these findings, a randomized, double-blind, placebo-controlled 4-year trial of sodium fluoride was conducted in 202 postmenopausal women with osteoporosis, the results of which were published in a 1990 issue of the *New England Journal of Medicine*.⁽⁵⁾ Despite a massive 35% placebo-subtracted median increase in bone mineral density (BMD) of the lumbar spine, the rates of new vertebral fracture were

similar for the fluoride and placebo groups. More worrisome was the statistically significant increase in nonvertebral fractures in the active versus control-treated women. *Journal Watch General Medicine* headlined the findings, *Fluoride not helpful, and possibly harmful, in osteoporosis*.⁽⁶⁾ The implication of the discrepancy between bone density and fracture frequency was obvious; a pharmacologically induced increase in bone mass did not necessarily equate with reduced fracture risk. This dictum would find tangential support when the results of studies with the bisphosphonate etidronate were reviewed by the FDA and its Advisory Committee.

The March 8, 1991 Advisory Committee meeting held to discuss etidronate's effects on PMO began with the traditional Open Public Hearing.⁽⁷⁾ The sole speaker in this hearing, the president of the National Osteoporosis Foundation (NOF) and co-investigator of the fluoride studies mentioned above, spoke of accumulating evidence that bone mass predicted osteoporotic fracture as accurately as cholesterol levels predicted coronary artery disease. He urged members of the FDA and its advisory panel to rely on bone mass, not fracture, as the primary indicator of drug efficacy and approval. "When fractures are used as an end-point," he remarked, "extremely large groups and a long follow-up are required to eliminate type II errors." Such requirements, he believed, "would lead to very high costs and to poor patient compliance, therefore, sharply reducing the likelihood of approval of the effective new drugs for the treatment of osteoporosis which we badly need."

To allay fears brought about by the fluoride experience, the same speaker pointed out that fluoride was known to cause abnormal mineralization and altered structure of bone. . . . "So, clearly bone mass can predict fractures only when the bone is structurally normal, and these results are not relevant to most agents used to treat osteoporosis." The take home message was "when bone biopsy examination reveals normal histology, a drug-induced increase in bone mass is an adequate biomarker on which to approve a drug for the treatment of osteoporosis." Thus, it was clear that although the 1979 and 1984 versions of Osteoporosis Guidance indicated that favorable effects on bone mass coupled with normal bone quality *could* form the basis of drug approval, some believed that the FDA was too narrowly equating drug efficacy with reduction in fractures, to the exclusion of data on bone mass. The stage was set for discussion of the etidronate clinical trials.

Armed with the largest osteoporosis clinical trial program to date and one specifically designed to satisfy the efficacy and safety criteria of the Osteoporosis Guidance, the sponsoring company, Norwich-Eaton, and their clinical investigators, were confident that "etidronate [was] of definite benefit in treating osteoporosis—a public health problem of near epidemic proportions."⁽⁷⁾ The primary efficacy data came from one foreign 3-year study and two U.S. 2-year randomized, double-blind studies comparing intermittent cyclical etidronate to placebo. Although vertebral fracture data were collected, the change in lumbar spine bone mass, measured by dual photon absorptiometry, was, according to the company, the primary efficacy variable for the three trials. Compared with placebo, 3 years of intermittent treat-

ment with etidronate increased spinal bone mass by 8% and significantly reduced the vertebral deformity index, but not the rate of new vertebral fractures. Pooled data from the U.S. studies supported the findings from the 3-year trial, with one critical exception. At the end of the 2 years, patients were given the option of continuing for an additional year of double-blind treatment or changing to open-label calcium. Eighty-four percent of the subjects elected to receive an additional year of blinded treatment. The significant increase in vertebral bone mass was maintained during the third year; however, compared with placebo, there was an increase in new vertebral fractures during year 3 in patients who received etidronate—a complete reversal of the 2-year data. The company and its clinical investigators had a host of explanations for the unexpected third year fracture data, including small sample size, a short period of observation, and a belief that new vertebral fractures was a “relatively insensitive” method compared with the vertebral deformity index.

Cautiously optimistic that their explanations for the puzzling third-year fracture findings eased the committee's concern, the company turned the lectern over to the FDA medical officer responsible for review of the etidronate application. The Agency reviewer spoke for about 20 minutes, but it only took 60 s for him to deliver his opening and closing remarks, which were probably sufficient to end any hope the company had for their drug's approval.⁽⁷⁾ He began his presentation by pointing out to the committee that in preclinical testing, relatively low doses of etidronate caused osteomalacia, hyperosteoidosis, and increased the potential for fracture. He closed his talk with reference to the increased fracture rate noted in the third year of the U.S. studies and asked, rhetorically: “[Does] prolonged cyclical etidronate therapy have any deleterious effects on bone architecture that lead to an increased incidence of fracture?” Because there were no bone biopsy data from the third year of the studies in question, the company and its investigators could only sit in silence. With preclinical evidence of osteomalacia and clinical concerns about etidronate's long-term effect on fractures, favorable data on bone mass, the primary efficacy variable, were insufficient for drug approval.

THE 1994 GUIDANCE

Unlike the 1979 and 1984 versions of the Osteoporosis Guidance, which had little practical experience to draw from and hence were vague on the regulatory requirements for drug approval, the 1994 issue of the Guidance incorporated lessons learned from the fluoride and etidronate experiences and left no question as to what was required for licensure of a non-estrogenic drug indicated to treat PMO.⁽⁸⁾ These requirements included (1) normal bone quality in preclinical studies of two animal species, (2) normal bone quality in a subset of clinical trial participants, (3) a statistically and clinically significant increase in BMD, and (4) most importantly, at least a positive trend (i.e., $p < 0.2$) in 3-year fracture data.

The first non-estrogenic drug evaluated within the regulatory paradigm of the 1994 Guidance was the oral bisphos-

phonate, alendronate. Approved by the FDA in 1995 for the treatment of PMO, Merck and its clinical investigators provided phase III data from more than 900 women that left little doubt of alendronate's efficacy.⁽⁹⁾ Preclinical and clinical studies indicated that the drug increased bone mass by a statistically and clinically significant amount, maintained normal bone quality, and significantly reduced the risk for vertebral fracture over a 3-year treatment period. With normal bone quality and positive long-term fracture data in hand, as per the 1994 Guidance, alendronate secured an indication for the prevention of PMO based on 2-year BMD data. Using a very similar development program, risedronate was approved for the prevention and treatment of PMO in 1999.⁽¹⁰⁾

ESTROGENS AND SELECTIVE ESTROGEN RECEPTOR MODULATORS

Estrogen's regulatory history dates to 1942 when the FDA approved conjugated estrogens for menopausal symptoms. Three decades later, the National Academy of Sciences and the National Research Council took part in the Drug Evaluation study Implementation (DESI) process, whereby an assessment was made of estrogen's role in the treatment of osteoporosis. After reviewing the limited available data, the DESI panel half-heartedly endorsed estrogen's use, concluding that it was “probably effective” in select cases of osteoporosis.⁽¹¹⁾ This language formed the basis for estrogen's osteoporosis indication from about 1974 until 1986, when additional research was believed to support strengthening the osteoporosis indication to read “estrogen effective in the treatment of osteoporosis.”

As stated in the 1994 Osteoporosis Guidance, manufacturers of estrogens were not required to provide evidence of fracture efficacy to gain a treatment of PMO indication because “epidemiological studies have demonstrated that estrogen therapy reduces the risk of vertebral and nonvertebral fractures. Therefore, fracture evaluation for estrogen preparations is not required for the treatment study.”⁽⁸⁾ BMD was considered sufficient for both prevention and treatment of PMO indications.

The selective estrogen receptor modulator (SERM) raloxifene was approved for the prevention of PMO in 1997.⁽¹²⁾ Considered an estrogen from a regulatory perspective, raloxifene's initial approval was based on BMD data alone. While U.S. approval of raloxifene for the treatment of PMO would at that time have been possible based on BMD data, because of European regulatory requirements, a fracture trial of nearly 8000 women was conducted and provided the basis for raloxifene's approval for the treatment of PMO in 1999.

Since raloxifene's approval, and in contrast to the position articulated in the 1994 Guidance, it has been regulatory policy to require evidence of fracture efficacy from adequately powered prospective trials before approving an estrogen (ERT), an estrogen plus progestin (HRT), or a SERM for the treatment of PMO. Such evidence from the Women's Health Initiative has just been published, but the reduction in risk for osteoporotic fractures associated with the use of HRT came at the price of an increased risk for breast cancer

and cardiovascular disease, tipping the scale of risk–benefit in the wrong direction.⁽¹³⁾ It is unclear how these results will affect the regulatory status of HRT and ERT as therapeutic options for osteoporosis.

THE FUTURE OF THE GUIDANCE

While some have criticized the requirement to show fracture efficacy of an osteoporosis drug before approval as too stringent, this approach has provided drug regulators, pharmaceutical manufacturers, physicians, and patients with definitive evidence of drug efficacy, and in turn, permitted a more reliable benefit–risk assessment. The requirement for fracture data has also created a dilemma, however: with the availability of drugs that have been shown to reduce the risk for vertebral, and in some cases, nonvertebral fractures, is it appropriate to continue to conduct placebo-controlled fracture trials? This is, I believe, the most important question that regulators, companies, investigators, institutional review boards, and patients must now address as the field of clinical osteoporosis research moves forward.

Opponents to the continued use of placebos cite the Declaration of Helsinki, which states that it is unethical to use a placebo control if effective therapy exists and if the use of placebo will increase a patient's risk for serious or irreversible harm.⁽¹⁴⁾ There is no evidence that the drugs approved for the treatment of osteoporosis reduce mortality, but there is unquestionable evidence that alendronate, risedronate, and raloxifene reduce the risk for morphometric vertebral fracture, and in the case of the bisphosphonates, nonvertebral fractures. Do these events represent irreversible harm?

Proponents of the continued use of placebo-controlled fracture trials consider the frequently discussed alternative, active-control trials, to be at best, unfeasible, and at worst, unethical.⁽¹⁵⁾ Resurrecting the decade-old rationale used to argue against the regulatory requirement for fracture trials, today's placebo advocates believe that the sample sizes required to show fracture equivalence or non-inferiority would be prohibitively large. In this scenario, research and development of new osteoporosis drugs would decline, to the detriment of patients. Furthermore, some placebo advocates believe that because equivalence or non-inferiority trials, by definition, lack internal validity (i.e., there is no assurance that the reference treatment was actually effective relative to placebo), a new drug could be deemed equivalent or non-inferior to an approved drug, when in fact, the new drug is no better than placebo. In this case, an ineffective osteoporosis drug would be approved for widespread use, itself an unethical proposition. Since its inception, the Osteoporosis Guidance has reflected a joint effort among FDA,

industry, and academia. To be sure, continued collaboration will bring changes to the Guidance, and patients with osteoporosis should be assured that these changes will not forsake their needs.

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Viewpoint

A brief history of calcitonin

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In the mid-1990s, after lengthy consultation with experts in bone biology and osteoporosis, the US Food and Drug Administration's (FDA) Division of Metabolic and Endocrine Drug Products issued an updated version¹ of its guidance for preclinical and clinical evaluation of drugs used in prevention or treatment of osteoporosis. Although much the same as previous editions, the 1994 edition differed from its predecessors in that it took into account studies of fluoride and etidronate, in which increases in bone mineral density failed to predict reduction in risk of fractures. The 1994 guidance emphasised the importance of documenting the efficacy of the drug in reducing fractures before it is approved for treatment of osteoporosis. Since 1995, the FDA has approved three drugs under this guidance—Fosamax (alendronate), Evista (raloxifene), and Actonel (risedronate). All approvals were based on data from large, randomised, placebo-controlled 3-year trials, in which active treatment was shown to significantly decrease risk of vertebral fractures that had been radiographically identified.²

Calcitonin began development as a drug to treat osteoporosis long before the 1994 guidance. As a result, its history is unlike that of the three drugs mentioned here. In the early 1960s, Copp and colleagues³ noted that a hormone from the parathyroids regulated the "tone" of calcium in body fluids, and named the 32-aminoacid peptide calcitonin. Soon after, the hormone's ability to lower serum calcium concentrations was associated with its inhibition of osteoclast activity.⁴ Calcitonin's potential as a treatment for osteoporosis—a disorder characterised by increased osteoclast activity—was quickly realised. The transition from animal to human studies was rapid, and reports of calcitonin's bone-sparing effect began to be published in the early 1970s,^{5,6} with investigations sponsored by industry in full swing by the middle of that decade.

By the late 1970s, the industry-sponsored studies were completed and a new drug application was submitted to the FDA, seeking approval of injectable calcitonin (Calcimar) for treatment of postmenopausal osteoporosis. The submission included data for total body calcium and bone mineral content from studies⁷ of about 120 men and women, but the investigators were not masked and controls did not receive placebo injections. The initial review of the clinical data was not favourable, and the drug was not approved.⁸ Although some submitted data suggested that daily subcutaneous or intramuscular injections of 100 IU of Calcimar increased total body calcium compared with no treatment, that the drug had no effect on bone mineral content in the radius was of concern.

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With the agency and the company in disagreement, the data were presented to the FDA's Endocrinologic and Metabolic Drugs Advisory Committee. In the autumn of 1981, the committee of seven academics met with members of the FDA and representatives from the sponsoring company to review the Calcimar data.⁸ While reporters, consumer advocates, and company allies and adversaries looked on, the investigators of the pivotal studies presented their results, giving particular emphasis to the data for bone mineral content and total body calcium. In keeping with the FDA's original concerns, much of the ensuing dialogue focused on Calcimar's failure to increase bone mineral content in the radius. After lengthy discussion, however, the drug's failure to increase bone mineral content of the radius was judged not to be unexpected since Calcimar's antiresorptive effect was most pronounced in trabecular bone (ie, vertebrae), and the distal radius was known to be composed largely of cortical bone. The committee thereby dismissed any potential clinical relevance of this negative finding.

With a consensus on interpretation of the bone mineral content data, the committee shifted its attention to the results for total body calcium. Although total body calcium was generally agreed to be a more appropriate endpoint than bone mineral content of the forearm, concern was expressed about the decreased rate of accrual of total body calcium noted during the second year of treatment. Additionally, several members of the committee were concerned about absence of fracture data, and questioned the validity of total body calcium as a surrogate for fracture risk.

As the meeting neared closure and the vote on approvability, a spokesman for the company asked the FDA if the advisory committee could suggest that approval be contingent on the company agreeing to do a phase-4 (or postapproval) study. Although this option was not rejected outright, a senior FDA official reminded the committee that recommendations for approval should be based on available data. Phase-4 studies were not intended to be used to "clarify substantial points of safety and effectiveness".⁹

With that said, the committee was asked to vote on whether they believed the data supported approval of Calcimar. A day of spirited debate ended with half of the committee voting yes and half no. Through the efforts of the chairman, however, the committee soon learned that a member who left the meeting early was in favour of approval. Although close, the majority now believed that Calcimar's benefit-to-risk ratio was favourable.

As a result of the discussions at the advisory committee meeting, the FDA reversed its original stance on Calcimar and in 1984 approved it for treatment of postmenopausal osteoporosis contingent on a phase-4 study.⁷ Within a year, a phase-4 fracture study had begun. But, recruitment was slow; after 4 years, only 151 of the proposed 300 women had been enrolled, and 77 of those enrolled had dropped out of the study. Furthermore, an interim analysis showed a substantial imbalance in the

mean number of vertebral fractures at baseline between the Calcimar and control groups.⁹ The results from this study were ultimately judged unreliable, and calcitonin's efficacy in reducing fracture remained unknown.

After the failed fracture study, the company cited competition for patients and investigators, non-compliance with daily injections, and the questionable ethics of giving some patients placebo for 3 years, as reasons against attempting a second fracture study.⁹ Use of Calcimar has since declined.

However, calcitonin lived on in a formulation more amenable to patient compliance. By the early 1990s, a nasally administered calcitonin (Miacalcin nasal spray, Novartis, East Hanover, NJ, USA) was in the late stages of development—under the stewardship of a different company. In fact, a large, randomised, double-blind 5-year study comparing the effects of 100 IU, 200 IU, and 400 IU of Miacalcin nasal spray daily with placebo on incidence of vertebral fractures was underway. The study was known as the Prevent Reoccurrence of Osteoporotic Fractures, or PROOF trial.⁹

In 1994, another FDA advisory committee convened to discuss results from studies of Miacalcin nasal spray.⁹ By this time, measurement of bone mineral density with dual photon X-ray absorptiometry was widely available. Increases in bone mineral density, as measured by dual photon X-ray absorptiometry, were deemed by many to be a reasonable surrogate for reduced risk of osteoporotic fracture. Data from five randomised, placebo-controlled trials lasting 1–2 years and including about 550 patients were presented to the committee. The company concluded, and the committee agreed, that the drug significantly increased bone mineral density of the lumbar spine compared with placebo. Because of the favourable fracture trends from the bone mineral density studies and of the fact that the PROOF trial was continuing, the advisory committee concluded that the potential benefits of Miacalcin nasal spray outweighed the potential risks and recommended its approval. The FDA subsequently approved Miacalcin nasal spray for treatment of postmenopausal osteoporosis in women who were more than 5 years postmenopausal.¹⁰ The drug's label explicitly stated that “the evidence of efficacy [was] based on increases in spinal bone mineral density”, not fracture data.

While physicians and patients waited for definitive evidence of calcitonin's efficacy in reduction of risk of fractures, reports from small studies began to be published. Although at least one study reported an increased risk of fracture in patients receiving calcitonin, others claimed beneficial effects.^{11–15} Then, after 20 years of waiting for conclusive evidence that calcitonin reduces risk of fracture, the results of the PROOF trial were published in late 2000.¹⁶

As pointed out in the editorial¹⁷ that accompanied the report, the data were disappointing. Whereas the 200 IU dose of Miacalcin nasal spray was reported to significantly decrease risk of new vertebral fractures, no fracture efficacy was shown for the 100 IU or 400 IU doses. And, the 400 IU dose was the only dose associated with a significant increase in spinal bone mineral density. Data for biochemical markers of bone turnover were also inconsistent. With opinions close to those of Cummings and Chapurlat,¹⁷ a US National Institutes of Health osteoporosis consensus panel summarised the results of the PROOF trial as follows: “The absence of dose response, a 60% dropout rate, and the lack of strong supporting data from BMD [bone mineral density] and markers decrease confidence in the fracture risk data.”¹⁸

Indeed, the fact that the bone mineral density data and fracture risk trends did not correlate in this study is consistent either with a true absence of efficacy of nasal calcitonin to reduce fracture risk or with a conclusion that bone mineral density is not a valid surrogate for bone quality and fracture risk for this agent. Either way, the data are puzzling.

As attested to by the estimated 4 million prescriptions dispensed for Miacalcin nasal spray in the USA last year, calcitonin is a widely used drug.¹⁹ Its ease of use and favourable side-effect profile might be enough for patients, and its claimed effect on bone mineral density might be sufficient for clinicians to keep prescription rates stable. Time will tell. But for now, after 30 years of clinical experience, calcitonin's effect on fracture risk is uncertain. As the 40th anniversary of calcitonin's discovery approaches, perhaps it is time for all interested parties to reassess this drug's role in treatment of patients with osteoporosis.

Conflict of interest statement

None declared.

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CLINICAL STUDIES

A Randomized Trial of Nasal Spray Salmon Calcitonin in Postmenopausal Women with Established Osteoporosis: the Prevent Recurrence of Osteoporotic Fractures Study

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PURPOSE: We conducted a 5-year, double-blind, randomized, placebo-controlled study to determine whether salmon calcitonin nasal spray reduced the risk of new vertebral fractures in postmenopausal women with osteoporosis.

SUBJECTS AND METHODS: A total of 1,255 postmenopausal women with established osteoporosis were randomly assigned to receive salmon calcitonin nasal spray (100, 200, or 400 IU) or placebo daily. All participants received elemental calcium (1,000 mg) and vitamin D (400 IU) daily. Vertebral fractures were assessed with lateral radiographs of the spine. The primary efficacy endpoint was the risk of new vertebral fractures in the salmon calcitonin nasal spray 200-IU group compared with the placebo group.

RESULTS: During 5 years, 1,108 participants had at least one follow-up radiograph. A total of 783 women completed 3 years of treatment, and 511 completed 5 years. The 200-IU dose of salmon calcitonin nasal spray significantly reduced the risk of new vertebral fractures by 33% compared with placebo [200 IU:

51 of 287, placebo: 70 of 270, relative risk (RR) = 0.67, 95% confidence interval (CI): 0.47– to 0.97, $P = 0.03$]. In the 817 women with one to five prevalent vertebral fractures at enrollment, the risk was reduced by 36% (RR = 0.64, 95% CI: 0.43– to 0.96, $P = 0.03$). The reductions in vertebral fractures in the 100-IU (RR = 0.85, 95% CI: 0.60– to 1.21) and the 400-IU (RR = 0.84, 95% CI: 0.59– to 1.18) groups were not significantly different from placebo. Lumbar spine bone mineral density increased significantly from baseline (1% to 1.5%, $P < 0.01$) in all active treatment groups. Bone turnover was inhibited, as shown by suppression of serum type-I collagen cross-linked telopeptide (C-telopeptide) by 12% in the 200-IU group ($P < 0.01$) and by 14% in the 400-IU group ($P < 0.01$) as compared with placebo.

CONCLUSION: Salmon calcitonin nasal spray at a dose of 200 IU daily significantly reduces the risk of new vertebral fractures in postmenopausal women with osteoporosis. *Am J Med.* 2000;109:267–276. ©2000 by Excerpta Medica, Inc.

Calcitonin, a physiologic endogenous inhibitor of bone resorption, decreases osteoclast formation (1,2), osteoclast attachment (2,3), and bone resorption in organ culture and animal models (1,4,5).

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Thus, treatment with calcitonin may be beneficial in diseases associated with increased bone resorption, such as postmenopausal osteoporosis (6). Several studies (7–21) have suggested that salmon calcitonin, administered as an injection or a nasal spray, is safe and can stabilize or increase bone mineral density. However, although bone appears to be of normal quality after salmon calcitonin treatment—in terms of mechanical performance, material density, and patterns of collagen birefringence (22–26)—the efficacy of salmon calcitonin in reducing fractures remains to be determined in a large randomized, controlled trial. Previous studies indicating fracture reduction at the spine and hip have been retrospective (27) or, if prospective, involved small numbers of participants (13–15,17–20). Therefore, we conducted a 5-year, multicenter clinical trial [the Prevent Recurrence of Osteoporotic Fractures (PROOF) study] to determine the long-term efficacy and safety of salmon calcitonin nasal spray in the prevention of vertebral fractures in postmenopausal women with osteoporosis.

MATERIAL AND METHODS

This double-blind, placebo-controlled trial was conducted in 42 centers in the United States and five centers in the United Kingdom. A total of 1,255 women were enrolled between February 1991 and July 1993.

Study Participants

White, Asian, or Hispanic women were eligible to participate if they were postmenopausal for at least 1 year and had one to five prevalent thoracic or lumbar vertebral compression fractures as evaluated at the study center, lumbar spine bone mineral density at least 2 SD below normal for normal women age 30 years, and no history of hip fracture. Women with a history of diseases, conditions, or chronic usage of medications (eg, corticosteroids) that could affect bone metabolism or bone mass measurements were excluded, as were those who had been treated with calcitonin, estrogens, or fluorides within 3 months of study entry, continuous bisphosphonates for at least 3 months within 24 months, or cyclical bisphosphonates within 18 months. The study was performed in accordance with the US Code of Federal Regulations dealing with clinical studies and the Declaration of Helsinki concerning medical research in humans. Women provided informed consent before any study-specific procedure was performed. Institutional Review Boards/Ethics Committees approved the protocol at each center.

Treatment Protocols/Follow-up Studies

Participants were assigned to receive salmon calcitonin nasal spray at a dose of 100, 200, or 400 IU (Miacalcin Nasal Spray; Novartis Pharmaceuticals, East Hanover, New Jersey) or placebo nasal spray, using a computer-generated randomization list. The randomization code was stratified by center using a permuted block design with a block size of eight. The nasal spray containers looked identical and had similar labels. All participants received two 500-mg OS-CAL tablets (1,000 mg oral calcium) and one Centrum tablet daily (400 IU vitamin D) to ensure a minimum daily intake of 1,500 mg of calcium and adequate vitamin D daily intake. Evaluations were performed at months 1, 3, 6, 9, 12, and every 6 months thereafter up to month 60 or in case of participant discontinuation. Adherence was estimated by counting used and unused bottles of study medication. Spinal radiographs; lumbar spine and hip bone mineral density; serum type-I collagen cross-linked C-telopeptide, bone-specific alkaline phosphatase, and osteocalcin levels; urinary type-1 collagen cross-linked N-telopeptide levels; and calcitonin binding antibodies were assessed every year. Participants were monitored closely for medication safety and tolerability throughout the study.

Analytical Procedures

Lateral thoracic and lumbar radiographs were evaluated qualitatively at each study center before enrollment, and 1,255 women were enrolled based on the initial radiograph report at the study site. Subsequently, all baseline and follow-up lateral thoracic and lumbar radiographs were analyzed at the University of California, San Francisco, using a combined quantitative and semiquantitative method (28,29). Based on this review, 269 women who were initially determined by the study site principal investigator to meet the criteria of one to five vertebral fractures were found to have only a mild compression fracture that did not meet the enrollment criteria. An additional 65 women were found to have more than five vertebral fractures. However, all enrolled participants were allowed to continue in the study. Prevalent fractures were defined as a 3 or greater SD reduction in any height ratio (vs normative data) by quantitative morphometry and a fracture grade 1 or greater (where grade 0 is "no fracture" and grade 3 is "severe fracture") using a semiquantitative evaluation. Two independent radiologists made the evaluation, with adjudication by a third radiologist in the event of discrepant quantitative and semiquantitative results. Incident fractures were defined as a 20% or greater and greater than 4-mm decrease in any vertebral height (vs previous radiograph) by quantitative morphometry, as well as a change in the fracture grade from 0 to 1 or greater by semiquantitative evaluation, with adjudication in discrepant cases as outlined above (28,29). Nonvertebral fractures were recorded and verified by hospital records. Participants were not withdrawn from the study when they had a fracture.

Bone mineral density at the lumbar spine and hip (femoral neck, greater trochanter, and Ward's triangle) was evaluated by dual x-ray absorptiometry (DXA) using Hologic (QDR 1000, 1500, 2000; Waltham, Massachusetts), Lunar (DPXL-DPXIQ; Madison, Wisconsin), or Norland (XR26-XR36; White Plains, New York) densitometers. Lumbar vertebrae with prevalent or incident fractures at L1 to L4 were not included in the bone mineral density measurements. A quality-control procedure to enable pooling of the data from the different centers and densitometers (including scanning of a phantom by all centers) was conducted at the University of California, San Francisco (30,31). The longitudinal in vitro precision error for lumbar spine bone mineral density measurements ranged from 0.3% to 2.0% over 5 years. Investigators were not blinded to the bone mineral density measurements.

Serum samples for C-telopeptide, bone-specific alkaline phosphatase, and osteocalcin levels were obtained primarily in the morning hours and assessed centrally at the Jerry L. Pettis Veterans Affairs (VA) Medical Center (Loma Linda, California). Samples were frozen at -70°C

after collection. Bone-specific alkaline phosphatase was assessed by the method of Farley et al (32) using a heat-inactivation assay with an interassay variation of 6.3%. Osteocalcin was assessed with the n-terminus, mid-molecule assay (33,34); the interassay variation was 7.7%. For C-telopeptide (CrossLaps; Osteometer Biotech, Herlev, Denmark), samples were batch-assayed at the end of the study to ensure that samples from any given participant were assayed together to minimize interassay variation. The analytical interassay precision was $\pm 8.1\%$.

The urinary N-telopeptide/creatinine ratio was also assessed centrally at the Jerry L. Pettis VA Medical Center. Urine samples were frozen at -20°C . The urinary N-telopeptide samples were analyzed in multiple batches, and it was discovered that there was a decrease in recovery of urinary creatinine over time, perhaps resulting from the relatively high storage temperature; thus, the N-telopeptide results are not reported.

Salmon calcitonin antibody titers were determined centrally by radioimmunoassay (35) at the Cedars-Sinai Medical Center in California.

Statistical Analyses

The primary analysis for the incident vertebral fracture endpoint was an intention-to-treat analysis among all participants with at least one follow-up radiograph. Secondary analyses were performed among participants with one to five prevalent vertebral fractures at enrollment (as per protocol) and among those who received the study drug for at least 3 years or who had a fracture during the first 3 years of treatment (3-year valid completer analysis). The 3-year duration is the minimum length required by regulatory guidelines to demonstrate a therapeutic effect on vertebral fractures. The original study design was intended to compare the risk of new vertebral fractures between the placebo group and each of the active treatment groups. After the approval of salmon calcitonin nasal spray 200 IU in the United States for the treatment of osteoporosis, and the issuing of the new Food and Drug Administration (FDA) guidelines, the protocol was amended in 1996, such that the primary statistical assessment was changed to be the pairwise comparison of 200 IU versus placebo using statistical life-table methods. The study had a power of 80% to show a 50% reduction in the risk of new vertebral fractures, on the assumption that 20% of participants would have a fracture in the placebo group compared with 10% in the salmon calcitonin nasal spray 200-IU group. The study was not designed to have power to discriminate between doses. All reported *P* values are two-sided, and treatment contrasts are presented with their 95% confidence intervals (CI).

Descriptive statistics, one-way analysis of variance (ANOVA), *F* tests, and chi-squared tests were used to compare the treatment groups at baseline. Time to first new fracture or time to fracture after administration of

study drug was analyzed primarily by life-table methods using the proportional hazards model with treatment as a variable (36). Relative risks were estimated as hazard ratios. Kaplan-Meier estimates and plots provided descriptive measures of fracture rates. Data about multiple new fractures were analyzed using the Wilcoxon rank sum test (chi-squared approximation). The effects of treatment of the risk of developing two or more new vertebral fractures were estimated as odds ratios from logistic regression models. Life-table methods using proportional hazards models were also used for nonvertebral fractures.

For bone mineral density and markers of bone metabolism among women who withdrew from the trial prematurely, the last value was carried forward to subsequent visits. Descriptive statistics were calculated on percent change from baseline for bone mineral density and serum C-telopeptide and osteocalcin levels at each evaluable time point. Descriptive statistics for bone-specific alkaline phosphatase levels were calculated as change from baseline. Women who developed calcitonin antibodies above 1,000 at any time were tabulated.

ANOVA or chi-square tests were used to compare groups. Serum C-telopeptide levels were skewed, and nonparametric statistics were used to compare groups. The overall effect on serum C-telopeptide levels (baseline to year 5) was evaluated by comparing least square means of different groups by the Proc Mixed output procedure (37) (from the Statistical Analysis System, Cary, North Carolina), which provides a descriptive measure of treatment effect compared with placebo during the entire study period by using the observed correlations structures within the participants' longitudinal data (also known as "repeated measures" data).

RESULTS

More than 3,500 women were screened for study participation, of whom 1,255 were randomly assigned to either placebo ($n = 311$), salmon calcitonin nasal spray 100 IU ($n = 316$), 200 IU ($n = 316$), or 400 IU ($n = 312$) (Table 1). After adjudication of baseline spine radiographs, 910 women had one to five prevalent vertebral fractures (as specified by the protocol), 269 had no vertebral fractures, and 65 had more than five fractures. Spinal radiographs could not be evaluated in 11 women, who were excluded from all analyses.

Baseline characteristics of the participants, including age, years since menopause, body mass index, number of prevalent fractures, lumbar spine bone mineral density, calcium intake, smoking history, and serum C-telopeptide levels, were similar among the groups (Table 2). More than 90% of women were more than 75% adherent to treatment during the time they were in the trial. Fifty-nine percent of the participants (744 of the 1,255 who

Table 1. Participation and Reasons for Withdrawal, by Randomization Group

	Treatment Group			
	Placebo (n = 311)	Nasal Spray Salmon Calcitonin		
		100 IU (n = 316)	200 IU (n = 316)	400 IU (n = 312)
Completed 3 years	190	189	204	200
Completed study	128	124	132	127
Withdrawals	183	192	184	185
Drug-related adverse effect	21	21	19	31
Adverse effect or illness not related to study drug	56	50	51	57
Lack of cooperation	23	16	23	14
Protocol violation	10	11	14	12
Ineffective study drug	25	25	15	17
Other*	48	71	62	54

*Other reasons for discontinuation include lost to follow-up, consent withdrawn, and switched to another therapy. No statistically significant differences were observed for any reason for discontinuation between any of the treatment groups and placebo.

were enrolled) withdrew from the study prematurely. Rates of discontinuation were similar in all of the dosage groups (Table 1); for example, 4.4% of participants in the salmon calcitonin nasal spray groups and 3.3% of participants in the placebo group discontinued because of nasal events. To determine whether the relatively high rate of early discontinuation led to selection bias, the baseline characteristics of the participants still at risk of a first new vertebral fracture (at years 3 and 4) were compared

among groups; no statistically significant differences were observed. To determine if nonresponders had discontinued selectively in any treatment group, response to treatment (as lumbar spine bone mineral density and serum C-telopeptide levels) was compared among groups in participants who discontinued before years 3 and 4 and who were still at risk of first new vertebral fracture. Although there were no significant differences in suppression of serum C-telopeptide levels, participants who dis-

Table 2. Baseline Demographic Characteristics of Enrolled Women

	Treatment Group			
	Placebo (n = 311)	Nasal Spray Salmon Calcitonin		
		100 IU (n = 316)	200 IU (n = 316)	400 IU (n = 312)
	Number (Percent) or Mean \pm SD			
Age (years)				
<65	99 (32)	100 (32)	84 (27)	95 (30)
65–74	148 (48)	149 (47)	153 (48)	166 (53)
\geq 75	64 (21)	67 (21)	79 (25)	51 (16)
Age (years)	68.2 \pm 7.7	68.2 \pm 7.8	69.0 \pm 8.1	67.9 \pm 6.9
Years since menopause	22.0 \pm 9.4	22.2 \pm 9.2	23.0 \pm 10.0	21.9 \pm 8.4
Body mass index (kg/m ²)	24.7 \pm 3.9	24.7 \pm 3.8	25.0 \pm 3.7	24.9 \pm 3.6
Vertebral fractures at baseline*				
0	64 (21)	79 (25)	67 (21)	59 (19)
1–5	232 (75)	223 (71)	224 (71)	231 (74)
>5	13 (4)	10 (3)	21 (7)	21 (7)
Lumbar spine bone mineral density (g/cm ²)	0.85 \pm 0.12	0.84 \pm 0.11	0.85 \pm 0.11	0.84 \pm 0.12
Calcium intake (mg/day) [†]	979 \pm 592	907 \pm 563	911 \pm 452	874 \pm 480
Current smokers	47 (15)	51 (16)	44 (14)	37 (12)
Serum C-telopeptide (pM)	2,393 \pm 1,456	2,647 \pm 2,971	2,555 \pm 1,736	2,608 \pm 2,367

* Eleven participants had no evaluable spinal radiograph data.

[†] Data were collected through a calcium-intake questionnaire for 177 (placebo), 187 (100 IU), 207 (200 IU), and 203 (400 IU) participants.

Table 3. Summary of Vertebral Fracture Analyses for Entire Study Cohort, for Subgroup with One to Five Prevalent Vertebral Fractures, and for 3-Year Completers

	Treatment Groups			
	Placebo	Nasal Spray Salmon Calcitonin		
		100 IU	200 IU	400 IU
Entire study cohort	n = 270	n = 273	n = 287	n = 278
Participants with ≥1 new vertebral fractures [n (%)]	70 (26)	59 (22)	51 (18)	61 (22)
Relative risk (95% CI)		0.85 (0.60–1.21)	0.67 (0.47–0.97)*	0.84 (0.59–1.18)
Participants with ≥2 new vertebral fractures [n (%)]	33 (12)	34 (13)	24 (8)	30 (11)
Odds ratio (95% CI)		1.02 (0.64–1.88)	0.65 (0.38–1.14)	0.87 (0.41–1.30)
New vertebral fractures/1,000 participant radiograph years	131	129	78*	111
Participants with 1–5 prevalent fractures	n = 203	n = 201	n = 207	n = 206
Participants with ≥1 new vertebral fractures [n (%)]	60 (30)	52 (26)	40 (19)	48 (23)
Relative risk (95% CI)		0.94 (0.65–1.36)	0.64 (0.43–0.96)*	0.78 (0.53–1.14)
Participants with ≥2 new vertebral fractures [n (%)]	30 (15)	32 (16)	18 (9)	23 (11)
Odds ratio (95% CI)		1.09 (0.64–1.88)	0.55 (0.30–1.02)	0.73 (0.41–1.30)
Three-year completers	n = 162	n = 152	n = 157	n = 155
Participants with ≥1 new vertebral fractures [n (%)]	59 (36)	49 (32)	40 (26)	42 (27)
Relative risk (95% CI)		0.91 (0.62–1.33)	0.66 (0.44–0.99)*	0.71 (0.48–1.05)

*200-IU versus placebo $P < 0.05$.
CI = confidence interval.

continued prematurely in the placebo group had a significantly higher percentage decrease in lumbar spine bone mineral density compared with those who discontinued in the active-treatment groups.

Vertebral Fractures

Follow-up radiographs were obtained for 1,108 of the participants (270 in the placebo group, 273 in the 100-IU group, 287 in the 200-IU group, and 278 in the 400-IU group). There was a 33% reduction in the relative risk of

developing a new vertebral fracture in the salmon calcitonin nasal spray 200-IU group compared with placebo (RR = 0.67, 95% CI: 0.47 to 0.97, $P = 0.03$; Table 3 and Figure 1). The number of women with multiple new vertebral fractures (2 or more new vertebral fractures) was reduced by 35% ($P = 0.13$), and the number of new vertebral fractures per 1,000 participant radiograph years was reduced by 40% ($P = 0.02$) in the 200-IU group compared with the placebo group. Among women with one to five prevalent vertebral fractures at baseline, there was a 36% (RR = 0.64, 95% CI: 0.43– to 0.96, $P = 0.03$) reduction in the risk of developing a new vertebral fracture and a 45% ($P = 0.06$) reduction in the number with more than one new vertebral fracture (Table 3).

An analysis among participants who received the study drug for at least 3 years or who had a fracture during the first 3 years of treatment was performed to determine whether the high discontinuation rate had influenced the response to treatment. The results for the salmon calcitonin nasal spray 200-IU group were statistically and clinically significant and were similar to those observed in the main analysis (Table 3). In this “post hoc” analysis, based on the Kaplan-Meier survival curve, 11 women needed to be treated for 3 years with 200 IU salmon calcitonin nasal spray to prevent one vertebral fracture.

There were no significant differences in any of these

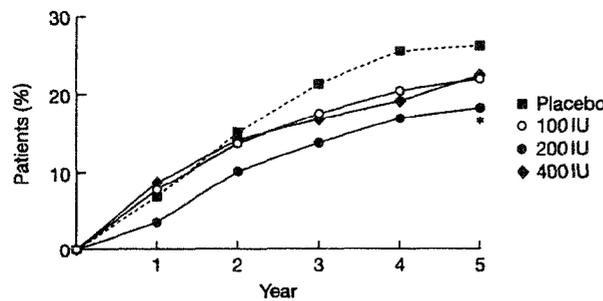


Figure 1. Cumulative percentage of participants with at least one new fracture per year. Number of participants with follow-up radiographs (placebo = 270, 100 IU = 273, 200 IU = 287, 400 IU = 278). The asterisk indicates $P < 0.05$ versus placebo.

Table 4. Summary of Nonvertebral Fracture Analyses

	Treatment Group			
	Placebo	Nasal Spray Salmon Calcitonin		
		100 IU	200 IU	400 IU
Number of participants at risk	(n = 305)	(n = 313)	(n = 315)	(n = 312)
All nonvertebral fractures				
Participants [n (%)]	48 (16)	32 (10)	46 (15)	41 (13)
Relative risk (95% CI)	—	0.64 (0.41–0.99)*	0.88 (0.59–1.32)	0.81 (0.53–1.23)
Hip or femoral fractures				
Participants [n (%)]	9 (3)	1 (0.3)	5 (2)	7 (2)
Relative risk (95% CI)	—	0.1 (0.01–0.9)*	0.5 (0.2–1.6)	0.8 (0.3–2.0)
Arm fractures [†]				
Participants [n (%)]	16 (5)	6 (2)	13 (4)	14 (5)
Relative risk (95% CI)	—	0.4 (0.1–0.9)*	0.75 (0.36–1.56)	0.84 (0.41–1.72)

* $P < 0.05$ versus placebo.[†] Fractures of the humerus, radius, ulna, or wrist.

CI = confidence interval.

outcomes when the 100-IU and 400-IU treatment groups were compared with the placebo group.

Nonvertebral Fractures

A total of 167 women had a nonvertebral fracture during the study (Table 4). Compared with placebo, the percentages of participants with nonvertebral fractures were significantly lower in the salmon calcitonin nasal spray 100-IU group ($P < 0.05$), but not in the 200-IU or 400-IU groups.

The small number of hip and femoral fractures precluded a meaningful statistical analysis. There was a non-significant reduction in the risk of hip fracture in the 200-IU group (RR = 0.5, 95% CI: 0.2– to 1.6). There was a significant reduction in hip fractures in the 100-IU group (RR = 0.1, 95% CI: 0.01– to 0.9, $P = 0.04$), but not in the 400-IU group.

The number of fractures of the arm (humerus, radius, ulna, wrist) was also small (Table 4). There was a significant 64% reduction in the risk of fractures of the arm in participants receiving 100 IU salmon calcitonin nasal spray (RR = 0.36, 95% CI: 0.1– to 0.9, $P = 0.03$), but the reductions in risk in the 200-IU and 400-IU groups were not statistically significant.

Bone Mineral Density

Lumbar spine bone mineral density did not change substantially in the placebo group during the study. At year 1 and year 2, there was a significant increase ($P < 0.05$) in lumbar spine bone mineral density in all calcitonin groups compared with placebo (Figure 2). At year 3, the increase in lumbar spine bone mineral density was statistically significantly different from placebo ($P = 0.01$) in only the 400-IU group. Lumbar spine bone mineral density in each salmon calcitonin nasal spray treatment group was increased significantly from baseline at each time point during the 5 years ($P < 0.01$). No clinically

significant effect of treatment on bone mineral density was apparent at the femoral neck or trochanter. At the Ward's triangle, there was a 1.5% to 2.0% increase compared with placebo over 5 years in the salmon calcitonin nasal spray 200-IU group, which was statistically significant at years 1 ($P < 0.01$) and 2 ($P < 0.05$).

Markers of Bone Metabolism

Serum C-telopeptide levels decreased significantly from baseline in the 200-IU and 400-IU salmon calcitonin nasal spray groups at all time points up to year 5 ($P < 0.05$; Figure 3). When the overall effect (average effect from baseline to year 5) was considered, the 200-IU and 400-IU doses produced statistically significant suppression compared with placebo (200 IU: -12% , $P = 0.01$; 400 IU: -14% , $P = 0.008$). Compared with placebo, serum bone-specific alkaline phosphatase levels decreased significantly in the 200-IU group at each time point ($P < 0.05$).

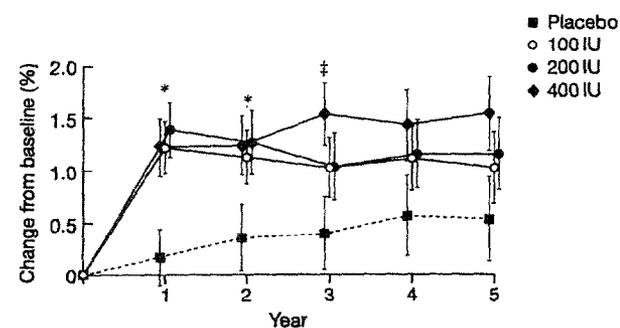


Figure 2. Lumbar spine bone mineral density, mean percentage change from baseline (\pm SEM). Number of participants with at least 1 postbaseline evaluation (placebo = 268, 100 IU = 273, 200 IU = 280, 400 IU = 274). A single asterisk indicates $P < 0.05$ versus placebo; a double asterisk indicates $P < 0.01$ versus placebo.

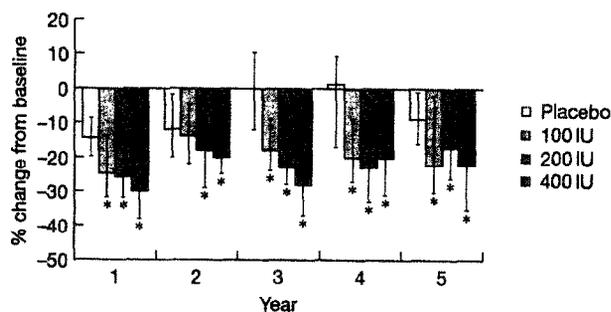


Figure 3. Serum C-telopeptide levels, median percentage change from baseline (\pm 95% confidence intervals). Number of participants with a least 1 postbaseline evaluation (placebo = 258, 100 IU = 262, 200 IU = 273, 400 IU = 262). A single asterisk indicates $P < 0.05$ change from baseline.

and in the 100-IU and 400-IU groups up to year 3 ($P < 0.01$). There were statistically significant decreases in serum osteocalcin levels in the active treatment groups as compared with baseline, but no significant differences were observed compared with placebo. Antibodies that bind salmon calcitonin at titers greater than 1,000 developed in 74 participants (26%) in the 100-IU group, 94 (29%) in the 200-IU group, and 94 (34%) in the 400-IU group. The presence of high titers of antibodies did not influence the effect of salmon calcitonin on the risk reduction of new vertebral fractures.

Adverse Effects

The distribution of adverse effects was similar among the salmon calcitonin nasal spray and placebo groups, except for a significant increase in rhinitis related to the study drug (defined as nasal congestion, nasal discharge, or sneezing), which occurred in 22% of active-treated participants compared with 15% of placebo participants ($P < 0.01$). Ninety-seven percent of nasal events in the calcitonin-treated groups and 91% of nasal events in the placebo group were of mild or moderate severity (calcitonin: 67% mild, 30% moderate; placebo: 64% mild, 27% moderate). Headache was reported less frequently in the salmon calcitonin nasal spray groups (4%) than in the placebo group (7%, $P = 0.03$).

DISCUSSION

The results of this 5-year clinical trial show that 200 IU of salmon calcitonin nasal spray per day significantly reduces the risk of new vertebral fractures by 33% to 36% in postmenopausal women with low bone mass or prevalent vertebral fractures. Among women with one to five vertebral fractures at baseline, 11 needed to be treated for 3 years to prevent a new vertebral fracture. The effect on vertebral fractures was accompanied by a modest increase in lumbar spine bone mineral density and a decrease in bone resorption.

Previous studies with parenteral or nasal salmon calcitonin, principally in participants with Paget's disease, have suggested that resistance may develop with continued use, potentially because of antibody formation, down-regulation of receptor sites, or counter-regulatory mechanisms (1,38–41). The results of this study, however, demonstrate a sustained effect in terms of reduction of fracture risk at the spine, maintenance of improved bone mineral density, and suppression of bone turnover during 5 years of observation.

Although vertebral fractures are the usual presenting manifestation of osteoporosis (42) and are associated with substantial morbidity (43), fractures of the hip have greater morbidity, mortality, and cost (43). Although definite conclusions on the risk of hip fracture cannot be drawn from our study, which was not designed to examine such effects, we did observe a nonsignificant 48% reduction in the risk of hip fracture in the salmon calcitonin nasal spray 200-IU group compared with the placebo group. The significant benefit observed in the 100-IU group may be the result of chance: the observed incidence (only one event, 0.3%) is about one-quarter of the incidence observed in active-treatment groups in other studies (44,45) as well as in the 200-IU group in this study. Further studies are indicated to determine the effect of salmon calcitonin nasal spray on the risk of hip fracture.

Salmon calcitonin nasal spray was well tolerated in these elderly women. The rate and reasons for discontinuation were distributed equally among treatment groups. Intolerance to the nasal spray did not contribute significantly to study discontinuation; less than 5% of participants discontinued for this reason.

Although there was a persistent benefit on spinal bone mineral density during the 5 years of the study in the 200-IU group, salmon calcitonin nasal spray reduced fracture risk without substantial effects on bone mineral density. Furthermore, only a modest effect was observed on serum C-telopeptide levels as a marker of bone resorption, although these levels were evaluated only at yearly intervals; the effects of salmon calcitonin nasal spray on bone resorption markers may occur within weeks to months (46). Although there was an association between reduced fracture risk and a 6% to 8% increase in bone mineral density and a 60% decrease in markers of bone resorption in women with vertebral fractures who were treated with alendronate (47–49), the results of this study and a study of raloxifene (45) show that approved osteoporosis therapies can reduce the risk of vertebral fractures without substantial improvement in bone mineral density or reduction in markers. How salmon calcitonin reduces the risk of fractures is not known; a decrease in bone turnover, particularly of the bone resorption component, may be as important a determinant of antifracture efficacy as an increase in bone mineral density (50–52). An improvement in bone mineralization (30,53)

may also matter. It is also possible that salmon calcitonin may improve bone quality and strength. These factors may act together to reduce the osteoclast activation frequency and trabecular erosion depth with a consequent reduction in trabecular perforations, microfractures, and subsequent macrofractures.

The high dropout rate in the study may have affected our results. The study was started in 1991 and was the first multicenter study to assess the effect of a new drug with vertebral fractures as the endpoint. The relatively high discontinuation rate should be considered in view of the 5-year treatment duration (approximately a 12% dropout rate per year). One reason for the dropout rate might have been that the investigators were not blinded to the bone mineral density results. When the trial was being planned, it was not considered ethical in a 5-year study to withhold the bone mineral density results from the investigator and the participant. The approval of two new osteoporosis treatments in the United States (salmon calcitonin nasal spray and alendronate) and the relatively modest increase in bone mineral density (which participants and investigators may have perceived as lack of efficacy) may have caused some participants to discontinue prematurely. However, the statistical methods that we used to analyze our results were intention-to-treat analyses that considered time to event. Analysis of the baseline characteristics of participants at risk for a new vertebral fracture at years 3 and 4 shows that the groups were still well matched at these times, suggesting that selection bias had not occurred. Finally, the estimate of the treatment effect could have been biased if poor responders had discontinued in the 200-IU group while continuing in the placebo group. However, participants who discontinued prematurely in the placebo group had a significantly higher percentage decrease in lumbar spine bone mineral density compared with those who discontinued in the active-treatment groups.

We did not observe a dose-response in the reductions in the risk of new vertebral fractures. Such a dose-response would have strengthened the conclusions of the study, but its absence does not invalidate the results showing statistically and clinically significant antifracture efficacy in the salmon calcitonin nasal spray 200-IU dose group. However, the lack of antifracture efficacy in the 400-IU group was unexpected, especially because we observed significant biologic effects of the 400-IU dose on lumbar spine bone mineral density and serum C-telopeptide levels. Why these effects did not lead to significant reductions in the rate of vertebral fractures is not clear.

In summary, the results of our study demonstrate that salmon calcitonin nasal spray at a dose of 200 IU is a safe and effective treatment for postmenopausal women with established spinal osteoporosis.

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Placebo-Controlled Trials and Active-Control Trials in the Evaluation of New Treatments

Part 1: Ethical and Scientific Issues

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In recent years, several authors have argued that placebo-controlled trials are invariably unethical when known effective therapy is available for the condition being studied, regardless of the condition or the consequences of deferring treatment. Some have also disputed the value of placebo-controlled trials in such a setting, asserting that the comparison of new treatment with old treatment is sufficient to establish efficacy and is all that should be of interest. This article considers the ethical concerns about use of placebo controls and describes the limited ability of active-control equivalence (also known as noninferiority) trials to establish efficacy of new therapies in many medical contexts. The authors conclude that placebo-controlled trials are not uniformly

unethical when known effective therapies are available; rather, their acceptability is determined by whether the patient will be harmed by deferral of therapy. If patients are not harmed, such trials can ethically be carried out. Furthermore, active-control trials, although valuable, informative, and appropriate in many circumstances, often cannot provide reliable evidence of the effectiveness of a new therapy.

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Placebo-controlled trials are used extensively in the development of new pharmaceuticals. They are sometimes challenged as unethical in settings in which patients could be treated with an existing therapy (1-7). The issues of when placebo controls are ethically acceptable and when they are scientifically necessary are important and worthy of discussion.

The Ethics of Placebo Controls

The Declaration of Helsinki

The Declaration of Helsinki (8) is an international document that describes ethical principles for clinical investigation. Those who contend that placebo controls are unethical whenever known effective therapy exists for a condition usually cite the following sentence in the Declaration as support for that position: "In any medical study, every patient—including those of a control group, if any—should be assured of the best proven diagnostic and therapeutic method."

We believe that an interpretation of this sentence as barring placebo controls whenever an effective treatment exists is untenable. First, the requirement that all patients receive the "best proven diagnostic and therapeutic method" would bar not only placebo-controlled trials but also active-control and historically controlled trials. When effective treatment exists, the patient receiving the investi-

gational treatment instead of the established therapy is clearly not getting the best proven treatment.

Second, it does not seem reasonable to consider as equivalent all failures to use known effective therapy. Historically, concerns about placebo use have usually arisen in the context of serious illness. There is universal agreement that use of placebo or otherwise untreated controls is almost always unethical when therapy shown to improve survival or decrease serious morbidity is available. But in cases in which the treatment does not affect the patient's long-term health, an ethical imperative to use existing therapy is not plausible. Can it be, for example, that because topical minoxidil or oral finasteride can grow hair, a placebo-controlled trial of a new remedy for baldness is unethical? Is it really unethical to use placebos in short-term studies of drugs for allergic rhinitis, insomnia, anxiety, dermatoses, heartburn, or headaches in fully informed patients? We do not believe that there is a reasonable basis for arguing that such studies and many other placebo-controlled studies of symptom relief are unethical and that an informed patient cannot properly be asked to participate in them.

Third, there is good reason to doubt that the cited phrase was intended to discourage placebo-controlled trials. The phrase under discussion was not part of the original 1964 Declaration but was added in 1975 to reinforce the idea that the physician-patient relationship "must be respected just as it would be in a purely therapeutic situa-

tion not involving research objectives" (8). In the explanation accompanying the 1975 change, the issue of placebo-controlled trials was not even mentioned (9). The American Medical Association (10), the World Health Organization (11), and the Council for International Organizations of Medical Sciences (12) have rejected the position that the Declaration uniformly bars placebo-controlled trials when proven therapy is available.

Informed Consent in Placebo-Controlled Trials

Patients asked to participate in a placebo-controlled trial must be informed of the existence of any effective therapy, must be able to explore the consequences of deferring such therapy with the investigator, and must provide fully informed consent. Concern about whether consent to participate in trials is as informed as we would like to believe is valid, but these concerns apply as much to the patient's decision to forgo known effective treatment and risk exposure to a potentially ineffective or even harmful new agent in an active-control trial as to a decision to accept possible persistence of symptoms in a placebo-controlled trial. Thus, this problem is not unique to placebo-controlled trials.

For the above reasons, we conclude that placebo-controlled trials may be ethically conducted even when effective therapy exists, as long as patients will not be harmed by participation and are fully informed about their alternatives. Although in many cases application of this standard will be fairly straightforward, in others it will not, and there may be debate about the consequences of deferring treatment (13).

Assessment of Effectiveness with Active-Control Trials

Clinical trials that, because of deficiencies in study design or conduct, are unlikely to provide scientifically valid and clinically meaningful results raise their own ethical concerns (12, 14). The remainder of this paper will address the inability of commonly proposed alternatives to placebo-controlled trials to evaluate the effectiveness of new treatments in many medical settings.

Active-Control Equivalence Trials (Noninferiority Trials)

The ability to conduct a placebo-controlled trial ethically in a given situation does not necessarily mean that

placebo-controlled trials should be carried out when effective therapy exists. Patients and physicians might still prefer a trial in which every participant is given an active treatment. What remains to be examined is why placebo-controlled trials (or, more generally, trials intended to show an advantage of one treatment over another) are frequently needed to demonstrate the effectiveness of new treatments and often cannot be replaced by active-control trials showing that a new drug is equivalent or noninferior to a known effective agent. The limitations of active-control equivalence trials (ACETs) that are intended to show the effectiveness of a new drug have long been recognized and are well described (15–33) but are perhaps not as widely appreciated as they should be. A recent proposed international guideline on choice of control group addresses this issue in detail (33).

The Fundamental Problem: Need for Assay Sensitivity

There are two distinct ways to show that a new therapy is effective. One can show that the new therapy is superior to a control treatment, or one can show that the new therapy is equivalent to or not worse by some defined amount than a known effective treatment. Each method can be valid, but each requires entirely different inferential approaches. A well-designed study that shows superiority of a treatment to a control (placebo or active therapy) provides strong evidence of the effectiveness of the new treatment, limited only by the statistical uncertainty of the result. No information external to the trial is needed to support the conclusion of effectiveness. In contrast, a study that successfully shows "equivalence"—that is, little difference between a new drug and known active treatment—does not by itself demonstrate that the new treatment is effective. "Equivalence" could mean that the treatments were both effective in the study, but it could also mean that both treatments were ineffective in the study. To conclude from an ACET that a new treatment is effective on the basis of its similarity to the active control, one must make the critical (and untestable within the study) assumption that the active control had an effect in that particular study. In other words, one must assume that if a placebo group had been included, the placebo would have been inferior to the active control (15–33). Support for this assumption must come from sources external to the trial. Although it might appear reasonable to expect a known

Table. Results of Six Trials Comparing Nomifensine, Imipramine, and Placebo*

Study	Common Baseline Score on the Hamilton Depression Scale	Four-Week Adjusted Score on the Hamilton Depression Scale (Number of Participants)			P Value†
		Nomifensine	Imipramine	Placebo	
R301	23.9	13.4 (33)	12.8 (33)	14.8 (36)	0.78
G305	26.0	13.0 (39)	13.4 (30)	13.9 (36)	0.86
C311(1)	28.1	19.4 (11)	20.3 (11)	18.9 (13)	0.8*
V311(2)	29.6	7.3 (7)	9.5 (8)	23.5 (7)	0.63‡
F313	37.6	21.9 (7)	21.9 (8)	22.0 (8)	1.0
K317	26.1	11.2 (37)	10.8 (32)	10.5 (36)	0.85

* Results shown are those reported in the review by Leber (18).

† Two-tailed P value for nomifensine versus imipramine.

‡ P = 0.001 for nomifensine versus placebo and imipramine versus placebo.

active agent to be superior to placebo in any given appropriately designed trial, experience has shown that this is not the case for many types of drugs.

The ability of a study to distinguish between active and inactive treatments is termed *assay sensitivity*. If assay sensitivity cannot be assumed, then even if the new and standard treatments appear virtually identical and the confidence interval for their comparison is exquisitely narrow, the study cannot demonstrate effectiveness of the new drug. (Note that in practice, ACETs are not designed simply to show lack of a statistically significant difference between treatments. Rather, such trials are designed to show noninferiority—that the new treatment is not inferior to the control by more than a specified margin. This approach is described in the Appendix.)

The best evidence that an active drug would have an effect superior to that of placebo in a given study would be a series of trials of similar design in which the active drug has reliably outperformed placebo. The ACET thus requires information external to the trial (the information about past placebo-controlled studies of the active control) to interpret the results. In this respect, an ACET is similar to a historically controlled trial. In some settings, such as highly responsive cancers, most infectious diseases, and some cardiovascular conditions, such external information is available and ACETs can and do provide a valid and reliable basis for evaluating new treatments. In many cases, however, the historically based assumption of assay sensitivity cannot be made; for many types of effective drugs, studies of apparently adequate size and design do not regularly distinguish drugs from placebo (16–18, 25, 34). More than 20 years ago, Lasagna (19) described this difficulty particularly well (reflecting long recognition of the problem among analgesiologists):

... a comparison between new drug and standard . . . is convincing only when the new remedy is superior to standard treatment. If it is inferior, or even indistinguishable from a standard remedy, the results are not readily interpretable. In the absence of placebo controls, one does not know if the "inferior" new medicine has any efficacy at all, and "equivalent" performance may reflect simply a patient population that cannot distinguish between two active treatments that differ considerably from each other, or between active drug and placebo. Certain clinical conditions, such as serious depressive states, are notoriously difficult to evaluate because of the delay in drug effects and the high rate of spontaneous improvement, and even known remedies are not readily distinguished from placebo in controlled trials.

The problem is well recognized in studies of antidepressant drugs (18, 32). In practice, many such studies include three arms—new drug, active control, and placebo—to provide clear evidence of effectiveness (new drug vs. placebo) and an internal standard (active control vs. placebo). This design allows a clear distinction (particularly valuable to a drug manufacturer) between a *drug* that does not work (the standard agent is superior to placebo but the new drug is not) and a *study* that does not work (neither the standard drug nor the new drug is superior to placebo).

The assay sensitivity problem was illustrated by Leber (18), who examined the results of all three-arm studies comparing nomifensine (an effective but toxic antidepressant), imipramine (a standard tricyclic antidepressant shown to be superior to placebo in dozens of clinical trials), and placebo. The results of the studies are shown in the Table. No study found a difference between nomifensine

and imipramine on the Hamilton depression scale (a standard measure of depression), but the changes from baseline with both drugs were substantial and seemed clinically meaningful. Examination of the placebo results, however, shows similar changes. Only one of the six studies—the smallest one—found any significant difference between either of the two active drugs and placebo. None of the other five studies showed even a trend favoring either drug. These five studies appear to have lacked assay sensitivity; they could not distinguish active from inactive treatments. Although some of these studies were small, three studies with 30 or more patients per group were typical of studies that often did show effectiveness of imipramine or other antidepressants.

Although we cannot be certain of the reason for these outcomes, the most likely explanation is that differences in study samples, study designs, or study conduct affected the response to these antidepressants and thus the ability of the studies to identify effective therapy. It does not seem to be merely a matter of study size, however; many studies with 10 to 30 patients per group (including one of the six shown) detect effects of antidepressant drug effects, and many much larger studies of essentially the same design do not show even a favorable trend. Similar patterns, although not as extreme, have been seen with many recently developed antidepressants, such as fluoxetine (34). Overall, in recent experience at the U.S. Food and Drug Administration, about one third to one half of modern antidepressant trials do not distinguish a known effective drug from placebo (Laughren T. Unpublished observations).

One might speculate that variable results of trials of antidepressants are simply the consequence of modest effect sizes coupled with samples too small to overcome the inherent variability of the condition studied. Results, however, are consistent with effect sizes that vary greatly and unpredictably from study to study. With current knowledge, one cannot specify a particular study population, treatment protocol, or sample size that will regularly identify active agents.

Antidepressants are only one of many classes of drugs with assay sensitivity problems. Analgesics (35), anxiolytics, antihypertensives, hypnotics, antianginal agents, angiotensin-converting enzyme inhibitors for heart failure, postinfarction β -blockers (36), antihistamines, nonsteroidal asthma prophylaxis, motility-modifying drugs for gastroesophageal reflux disease, and many other effective

agents are often indistinguishable from placebo in well-designed and -conducted trials.

A recently published overview by Tramer and coworkers (37) of studies of ondansetron, a widely used and very effective antiemetic, provides a further example of this phenomenon. Although the totality of data clearly supports the efficacy of this agent, many placebo-ondansetron comparisons show no effect of the drug. It is notable that the incidence of nausea and vomiting varied greatly among the trials and in some cases was so low that it precluded any demonstration of efficacy. In a placebo-controlled study of an antiemetic, a low rate of nausea and vomiting in the placebo group would lead to a negative outcome—the drug could not appear superior to placebo, and the trial could not provide evidence of effectiveness. In contrast, an ACET (new drug vs. ondansetron) with a low rate of nausea and vomiting in both arms would not be unambiguously interpretable. If one assumed that the low rate in the active-control group reflected the known ability of ondansetron to reduce a rate of nausea and vomiting that would have been high in the absence of treatment, one would conclude that the new drug was also effective. But the article by Tramer and coworkers shows that such an assumption cannot be supported in many situations. Clearly, if many placebo-controlled studies of ondansetron showed no effect, a trial showing “equivalence” of a new agent to ondansetron could not be considered reliable evidence that the new agent was effective, unless one could identify a treatment setting (for example, a setting defined by the chemotherapy administered) in which ondansetron was regularly distinguishable from placebo.

In the cases described, the effectiveness of drugs that sometimes (or even often) fail to be proven superior to placebo is not in doubt; even if a drug is statistically significantly superior to placebo in only 50% of well-designed and well-conducted studies, that proportion is still vastly greater than the small fraction that would be expected to occur by chance if the drugs were ineffective. The problem may be a generally small response that varies among populations, insufficient adherence to therapy or use of concomitant medication, study samples that improve spontaneously (leaving no room for drug-induced improvement) or that are unresponsive to the drug, or some other reason not yet recognized. What all of these influences have in common is that they reduce or eliminate the drug-placebo difference, so that a study design and size adequate to de-

test a larger effect will not detect the reduced effect. In each case, however, the problem is not identifiable a priori by examining the study; it is recognized only by the observed failure of the trial to distinguish the drug and placebo treatments.

Incentive To Minimize Errors Is Reduced in ACETs

Active-control equivalence trials present another problem that is difficult to quantitate or assess in any given study. Most imperfections in a clinical trial—patient non-adherence to treatment, use of concomitant therapy potentially affecting study outcome, inclusion of inappropriate patients (for example, those who lack the disease or those who experience spontaneous improvement), or administering the wrong treatments—tend to reduce observable differences between treatment groups, promoting the conclusion that the two treatments are indistinguishable. Study organizers seeking to demonstrate a difference between treatments have a powerful incentive to minimize such imperfections and to identify a population in which an effect could be demonstrated. This incentive is absent when the intent is to demonstrate *lack* of difference (17, 32). This is not to suggest that trial organizers deliberately make less of an effort to maintain study quality in ACETs than in placebo-controlled trials, any more than the practice of blinding investigators to treatment suggests that investigators are not to be trusted. It is important, however, to recognize the possible influence of the desired outcome on the conduct of clinical trials.

It is difficult in any given ACET to determine the extent to which the ability to show potential treatment differences has been diminished by deficiencies in study design and conduct. In such areas as treatment of depression, however, even placebo-controlled trials, in which the incentive to conduct an excellent study capable of showing a difference between treatments is maximal, often cannot distinguish effects of active drugs from those of placebo. Results of ACETs would be expected to be at least as variable as those of placebo-controlled trials in their ability to detect treatment differences. In considering how to conduct ACETs, this issue needs to be recognized. In addition, approaches to study interpretation usually thought of as conservative, such as intention-to-treat analyses, are no longer conservative when the objective of a trial is to show no difference between treatments (17, 24, 32).

Use of Active Controls

Active-control equivalence trials can be informative and have been used successfully and appropriately in many therapeutic areas in which assay sensitivity is not in doubt. These trials are often credible and have been widely used in such areas as treatment of cancer, infectious disease, and some cardiovascular conditions (for example, acute myocardial infarction treated with thrombolysis). In general, the larger the effect size, the less study-to-study variability in outcomes, and the fewer the instances of unexplained failure of the control agent to show superiority to placebo in well-controlled studies, the more persuasive is the case for using this design. Investigators who intend to perform an ACET will therefore need to review previous placebo-controlled trials of the control agent to see whether it can be persuasively shown that such information exists. The ACET should be as similar as possible to the past placebo-controlled trials with regard to patient selection, dose, end points, assessment procedures, use of concomitant therapy, and other pertinent study design characteristics (17, 20).

Given the inevitable residual uncertainty about the assay sensitivity of a trial that does not contain an internal standard, reliance on ACETs may also require more evidence of replicability than would be needed for trials intended to show differences. It should be appreciated, however, that even if assay sensitivity can be assumed, the effect that the active control can be presumed to have had under the study conditions will often be relatively small. In such cases, large sample sizes will be needed to provide the narrow confidence interval needed to ensure that the new drug is not inferior to the control by more than that amount. This issue is considered further in the Appendix.

Studying Relative Effectiveness

In some cases, a study may be intended to evaluate the comparative effectiveness of two known active treatments. In that case, too, the presence of assay sensitivity is essential to interpretation of the trial. If one cannot be confident that the trial could have distinguished active drug from placebo, one cannot be confident that it could have distinguished a more effective drug from a less effective drug. A three-arm study (new drug, placebo, and active control) is optimal because it can 1) assess assay sensitivity and, if assay sensitivity is confirmed, 2) measure the effect of the new drug and 3) compare the effects of the two active treatments.

Alternative Approaches

Not all placebo-controlled studies leave patients untreated. It is frequently possible to provide standard therapy while carrying out a superiority study—that is, a study intending to demonstrate an advantage of a treatment regimen over the control. Sometimes a new agent can be assessed by using an “add-on” study design in which all patients are given standard therapy and are randomly assigned to also receive either new agent or placebo. This design is common in trials of therapy for cancer, heart failure, and epilepsy, in which omitting standard therapy would generally be unacceptable. Such studies are not directly informative about a drug as monotherapy, but they do provide interpretable evidence of effectiveness in a well-defined setting and are particularly appropriate where clinical use of the new agent will largely be as added treatment. Moreover, if successful, they demonstrate the ability to provide benefit greater than the standard therapy alone, in contrast to the (usually) less clinically interesting demonstration that a new therapy is not worse than the standard. This design is not useful, however, if the new drug and standard therapy are pharmacologically similar.

Although we have argued that an informed patient may choose to accept pain or discomfort or to defer needed long-term therapy for a short time to participate in a placebo-controlled trial, we do not mean to suggest that indifference to patient discomfort is appropriate. Some study designs limit the duration of placebo exposure without compromising the rigor of the study. These include “early escape” designs and randomized withdrawal studies (31, 38). In an “early escape” study, patients are randomly assigned to receive new drug or placebo, but a well-defined treatment failure end point (such as persistence of symptoms or maintenance of elevated blood pressure at a specified time) is used as the basis for changing therapy in patients who are not benefiting from their initially assigned treatment. In a randomized withdrawal study, apparently responsive patients are given an investigational therapy for a period and are randomly assigned to receive placebo or to continue active therapy. The randomly assigned groups can be compared for a defined period or by using an “early escape” approach. This design was initially proposed by Amery (39) as a way of avoiding extended placebo treatment of patients with angina pectoris. A particular value of the randomized withdrawal study is that it demonstrates a persistent effect for durations that would be difficult to study in placebo-controlled trials.

Regulatory Status of Study Designs

Critics of placebo-controlled trials have often attributed their use to Food and Drug Administration practices that favor the smallest possible trials, seek to assess absolute efficacy, and ignore what they consider the more important clinical question of how a new drug compares with standard therapy (1–6). Although a broad range of trial designs can be used to demonstrate the effectiveness of a new drug (15), regulations describing adequate and well-controlled studies have since 1985 indicated concerns about the interpretation of ACETs, reflecting views expressed since the 1950s by numerous clinical and statistical researchers (15–33). Thus, where assay sensitivity cannot be established for an ACET, trials that show a difference between treatments (a placebo-controlled trial is only one such example) would be needed to demonstrate effectiveness. The basis for this requirement is not a preference for small trials (although efficiency is not a trivial matter) nor indifference to comparisons (although under law, a drug need not be superior to or even as good as other therapy to be approved), but rather the fundamental need for evidence of assay sensitivity to interpret an ACET as showing effectiveness of a new drug.

Conclusions

Placebo controls are clearly inappropriate for conditions in which delay or omission of available treatments would increase mortality or irreversible morbidity in the population to be studied. For conditions in which forgoing therapy imposes no important risk, however, the participation of patients in placebo-controlled trials seems appropriate and ethical, as long as patients are fully informed. Arguments to the contrary are not based on established ethical principles but rather rely on a literal reading of one passage in the Declaration of Helsinki that would also preclude the conduct of active-control trials, and even historically controlled trials, whenever effective treatment exists. It seems inconceivable that the authors of the 1975 revision intended such an outcome, and nothing in their explanation of the revision suggests they did (8). We therefore believe this interpretation is untenable.

If ACETs were always adequate substitutes for placebo-controlled trials, the ethical issue might not arise. Unfortunately, ACETs are often uninformative. They can neither demonstrate the effectiveness of a new agent nor provide a valid comparison to control therapy unless assay

sensitivity can be assured, which often cannot be accomplished without inclusion of a concurrent placebo group.

Appendix

Blackwelder (40) and others (20, 22, 24, 31) have pointed out that equivalence testing can be better described in most cases as a test of a one-sided hypothesis that the test drug is not inferior to the control by a defined amount, the "equivalence margin," also called the noninferiority margin. The null and alternate hypotheses H_0 and H_a then become:

$$H_0 = E_S - E_T \geq \Delta$$

$$H_1 = E_S - E_T \leq \Delta$$

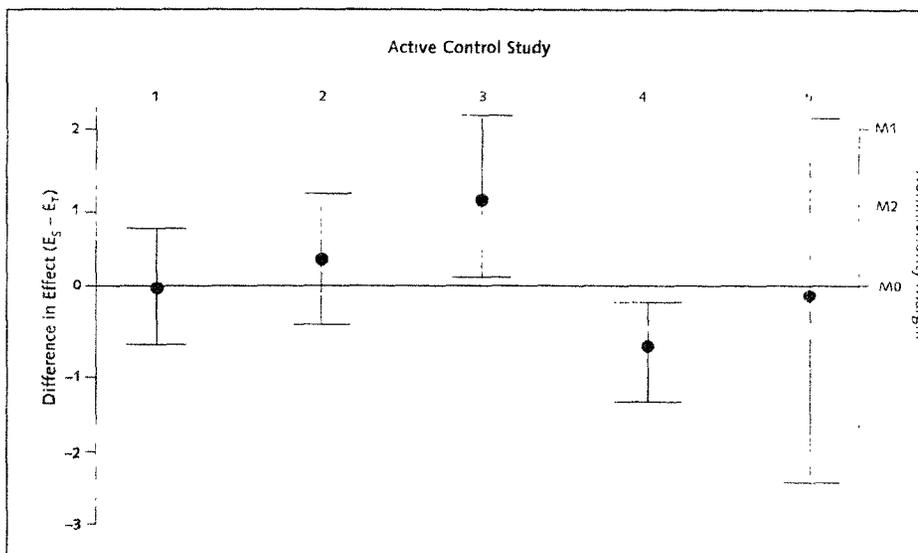
where E_S and E_T are the effects of the standard and test drugs, respectively, and Δ is the equivalence or noninferiority margin of interest. The null hypothesis is rejected if the upper bound of the confidence interval for the difference between the treatment being tested and control is smaller than the specified margin. In this case, the new agent is considered effective. A confidence interval that cannot exclude a difference greater than the margin would not permit rejection of the null hypothesis, and noninferiority would not be supported.

Choice of the margin is critical and depends on both knowledge of the effect of the control drug and clinical judgment. The margin chosen must be no larger than the smallest difference between control drug and placebo that could regularly be demonstrated in controlled trials. Exclusion of a difference greater than that margin would therefore mean that at least some part of

the effect of the control agent was preserved for the test drug and that the test drug therefore had at least some effect. If it were thought medically compelling to assure preservation of a specific fraction of the control drug effect, the specified margin would have to be made smaller than the largest possible noninferiority margin. If the control drug has not regularly shown superiority to placebo in trials of adequate size and design, the noninferiority margin must be set at zero: that is, only superiority to the control could be interpreted as evidence of effectiveness of the new drug. The ability to choose a margin representing the "guaranteed" effect of the control agent thus becomes functionally equivalent to saying that the trial has "assay sensitivity," an ability to distinguish active from inactive treatments.

The use of equivalence margins is shown in the Appendix Figure. The hypothetical results of five different active-control studies are presented. The result of each study is shown on the y-axis as the difference between treatments ($E_S - E_T$, the difference between the standard drug control and test drug), with a positive difference favoring the standard drug) and confidence intervals for these differences. Three possible noninferiority margins are shown. M1 is the smallest effect the standard drug can be presumed to have in the study compared to a placebo treatment. M2 is a fraction of M1, chosen because it is considered essential to assure that the new drug retains some substantial fraction of the effect of the standard drug. M0 is the margin that must be used when the standard drug is not regularly superior to placebo:

Appendix Figure. Interpretation of equivalence margins in active-control trials.



Hypothetical results of five studies are shown. The result of each study is shown on the y-axis as the difference between treatments ($E_S - E_T$), where E_S represents the control and E_T represents the test drug. A positive difference favors the standard drug. Error bars show hypothetical 95% CIs for these differences. Three possible noninferiority margins are shown (M0, M1, M2). For more explanation, see the Appendix.

that is, only superiority of the new drug is acceptable evidence of effectiveness.

The results of studies 1 through 5 (Appendix Figure) are summarized in the following paragraphs.

Study 1: Where an effectiveness margin M1 can be defined, effectiveness is shown because the confidence interval of the difference favoring the standard drug excludes inferiority greater than M1. Moreover, the study shows that more than 50% of the standard drug effect is preserved. If, however, assay sensitivity cannot be assumed (that is, there is no assurance that the standard drug had any effect in the study so that the noninferiority margin is M0), the study would not show effectiveness of the new drug.

Study 2: Effectiveness would be shown by noninferiority of the new drug based on the M1 margin but not if the more stringent M2 margin were used.

Study 3: Effectiveness is not demonstrated because noninferiority to the standard drug based on the effectiveness margin M1 is not demonstrated; the test drug may have no effect at all.

Study 4: Effectiveness of the test drug is demonstrated for any choice of margin by a showing of superiority of the test drug to the standard drug.

Study 5: Effectiveness is not demonstrated, despite the favorable point estimate of the effect of the test drug, because the wide confidence interval does not exclude inferiority to the standard drug greater than the M1 margin.

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Disclaimer: The views expressed in these papers are those of the authors. They are similar to the conclusions and principles published in a Food and Drug Administration draft guidance document (33) based on a guideline developed by the International Conference on Harmonization, a body representing regulators and industry from the United States, the European Union, and Japan. The inferential problems associated with use of equivalence designs to show effectiveness are reflected in regulations (15) and guidelines (41).

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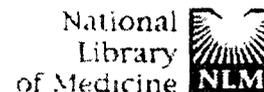
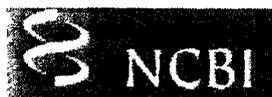
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Doubts and uncertainties suck my blood and poison my strength, and there are times when they implant despair—cold and terrible as death—in the soul. . . . Can you possibly restore my pure and powerful faith, unblemished by any shadow of doubt and despair!

Michael Bar-Zohar
Ben-Gurion: A Biography
 New York: Lambda Publishers; 1986

Submitted by:
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 Mexico City, Mexico

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Clinical efficacy of salmon calcitonin in Paget's disease of bone.

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Clinical interest in salmon calcitonin began in 1972 when this peptide was shown to be effective in the treatment of Paget's disease. Salmon calcitonin is more potent than porcine calcitonin, with human calcitonin intermediate in potency. Salmon calcitonin is a highly effective therapeutic agent in the treatment of Paget's disease. During chronic treatment with salmon calcitonin, alkaline phosphatase activity and urinary hydroxyproline excretion decrease on an average of 50% in patients with Paget's disease. Patients may experience a variety of clinical benefits during chronic treatment, including relief of bone pain, a reversal of neurological deficits, stabilization or improvement of hearing loss, and improvement of vascularity of bone. Radiologic healing of osteolytic lesions in particularly striking with calcitonin treatment. Paget's disease patients prefer treatment with salmon calcitonin administered by means of a nasal spray. Salmon calcitonin has an excellent safety profile and produces mild side effects in a small percentage of patients. The most common side effects associated with salmon calcitonin administration are nausea and facial flushing. It is unusual to observe severe side effects. In about 20% of patients, production of antibodies may neutralize the effects of the exogenously administered calcitonin; these patients respond to human calcitonin. At this time salmon calcitonin should still be considered a valuable therapeutic agent in the treatment of Paget's disease, particularly in patients with osteolytic lesions.

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Clinical significance of antibodies against calcitonin

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Key words: Calcitonin, neutralizing antibodies, secondary resistance, Paget's disease of bone, osteoporosis

Summary: Calcitonin (CT) inhibits osteoclast-mediated bone resorption and is being used to treat Paget's disease of bone, hypercalcemia of malignancy and postmenopausal osteoporosis. The formation of antibodies against heterologous calcitonins like salmon calcitonin (sCT) is common and occurs in 40–70% of the patients treated for more than 4 months. Not all of these patients, however, develop a secondary resistance to sCT, therefore the clinical significance of sCT antibodies is discussed controversially. In vivo and in vitro approaches demonstrate a neutralizing effect in 35 to 60% of the patient sera with antibodies against sCT. These neutralizing

antibodies appear to explain most cases of clinically relevant secondary resistance to sCT treatment, which occurs in 25–45% of the patients after treatment periods of 6 months and longer. A positive treatment response to human CT after development of secondary resistance to sCT proves the diagnosis of antibody related resistance. Few cases develop secondary resistance in the absence of sCT binding antibodies, the mechanism of this phenomenon is unclear. Antibody related resistance is a significant problem in long term treatment with sCT. Especially in conditions like postmenopausal osteoporosis, where no readily accessible marker of treatment response is available, the development of sCT antibodies and their possible neutralizing effect has to be considered.

Introduction

Calcitonin (CT) inhibits osteoclast-mediated bone resorption and is therefore used in the treatment of Paget's disease of bone, hypercalcemia of malignancy, and postmenopausal osteoporosis (Ziegler, 1978). Calcitonins used therapeutically include human CT, but also salmon, eel and porcine CT. Regarding the primary structure of the various CTs, a considerable interspecies variability exists. Porcine CT (pCT) shares only 14 amino acids, salmon CT (sCT), which has achieved the widest distribution among the calcitonins in therapeutic use, shares 16 of 32 amino acids with human CT (hCT). Therefore, it is not surprising that after parenteral use in humans the development of antibodies against sCT is reported in 40–70% of the

patients (De Rose et al., 1974; Haddad et al., 1972; Rojanasathit et al., 1974; Singer et al., 1972; Singer et al., 1980; Woodhouse et al., 1977). Whether this phenomenon is of any clinical significance, however, is controversial.

In Paget's disease patients usually respond to CT therapy with an initial reduction of alkaline phosphatase (AP) levels after the first months of treatment with a subsequent plateau at approximately 50% of initial AP values (Ziegler, 1978). Different from this "plateau phenomenon" is the development of secondary resistance to sCT treatment, defined as a deterioration of activity markers of a particular disease after an initial responsive phase. In Paget's disease of bone, where the AP levels

serve as an accurate marker of disease activity, secondary resistance has been reported in 5 to 40% of the patients (Rojanasathit et al., 1974; Woodhouse et al., 1977). Some studies report no evidence for a relation between antibodies and resistance (De Rose et al., 1974; Reginster et al., 1989; Woodhouse et al., 1977), whereas others have described an association (Grauer et al., 1990; Haddad et al., 1972; Levy et al., 1988; Rojanasathit et al., 1974; Singer et al., 1972). We review here the data supporting the controversial standpoints to discuss the clinical significance of sCT antibodies.

Methodological Considerations

Antibodies binding calcitonin

The serum of patients can be investigated for the presence of antibodies which bind to CT by immunoprecipitation (Haddad et al., 1972). Patient serum is incubated with iodinated sCT at multiple dilutions, then precipitated to separate bound and free hormone (Grauer et al., 1990; Haddad et al., 1972). The highest serum dilution associated with a bound/free ratio greater than 0.1 is considered a relevant antibody titer (Woodhouse et al., 1977). Pretreatment sera of the individual patients and sera of healthy volunteers can be used as negative controls, serial dilutions of antiserum raised against sCT in rabbits, goats or other suitable models serve as a positive control. This method will detect a variety of antibody clones formed in the patient during exposure to a heterologous calcitonin. The binding has shown to be specific, as competitive displacement could be achieved after addition of excess amounts of unlabelled sCT, but not hCT or pCT (Haddad et al., 1972). The presence of CT binding antibodies, however, does not necessarily indicate resistance to the hormone, unless their affinity, capacity, and nature of binding prevents the expected biological response (Hosking et al., 1979). The higher the antibody titer of CT binding antibodies, the more likely is the presence of biologically relevant neutralizing antibodies (Singer et al., 1980). In cases, however, where low to moderate titres of CT binding antibodies are present, further investigations are necessary to assess their functional significance (Grauer et al., 1993).

Antibodies which neutralize calcitonin bioactivity

Various methodological approaches have been applied to evaluate the neutralizing activity of the patient sera after CT treatment. The underlying principle always to be investigated, is whether patient serum can impair the biological action of a

given amount of exogenous CT in a defined biological system.

In vivo approaches

Patient testing

The application of a given amount of sCT to a patient should lead to a reduction of serum calcium levels in the next 4–12 hours after the injection. One possibility to assess acquired resistance to the treatment is to compare the hypocalcemic response in an individual patient before and after a given time of treatment. The hypocalcemic responses, however, display a considerable interindividual variability. The detection of mild to moderate acquired resistance will therefore be difficult if the hypocalcemic response of an individual patient prior to treatment is not known. Other systems which allow a statistical evaluation have therefore been applied.

Rat hypocalcemia bioassay

The first investigators in this field have used the classical bioassay system for CT, the rat hypocalcemia bioassay. This assay relies on the hypocalcemic effect produced by injection of calcitonin into young rats (Hirsch et al., 1964). This *in vivo* bioassay is an indirect quantitative determination of CT. It is designed to assess the relative biological potency of a CT test preparation in comparison to a defined standard preparation by comparing their biological effects on rats. The fall in serum calcium is in linear relation to the logarithm of the dose of calcitonin (Cooper et al., 1967; Kumar et al., 1965). Patient sera are serially diluted, mixed with a defined CT concentration and injected into fasted rats. 30–50 min after the injection, blood samples of the rats are obtained, serum calcium levels are determined and the hypocalcemic effect is compared to that achieved after addition of control serum to the CT samples (Haddad et al., 1972).

Other *in vivo* bioassays

Reginster et al. have published a modification of this well standardized approach. Here sCT is injected into rabbits in the presence or absence of IgG previously extracted from sCT binding antibody-containing patient sera, and the hypocalcemic effect is recorded (Reginster et al., 1990). Using this assay they find no evidence for a neutralizing activity in sera of 4 patients containing sCT binding antibodies. They conclude from these data

that sCT antibodies are of no functional significance. Although this rabbit hypocalcemia bioassay relies on the same principle as the rat hypocalcemia assay, the conclusions of the authors can be challenged from methodological and clinical grounds. For one, the authors do not report the use of a positive control, e.g. high-titer goat-anti sCT antibody, which raises doubts whether this system is as sensitive as the other established tests to detect a neutralizing activity of sCT antibodies. As no clinical resistance is reported in these four patients, another possible explanation for the discrepancy may be the absence of a neutralizing effect in the sera of these 4 particular patients investigated in their study (Reginster et al., 1990).

In vitro approaches

Several in vitro model systems have been established which allow comparison of the bioactivity of a given CT preparation with a standard preparation. Among the three established bioassay systems, the fetal long bone assay (Au et al., 1970), the isolated-osteoclast-assay (Chambers et al., 1986), and the T 47 D cell in vitro bioassay (Grauer et al., 1992), the latter has been used by several groups to investigate the presence of neutralizing antibodies (Grauer et al., 1990; Levy et al., 1988; Muff et al., 1991). A neutralizing effect is present if addition of patient serum impairs the expected biological response to CT in this system.

T 47D cell in vitro bioassay

The human breast cancer cell line T 47 D cells expresses specific high affinity calcitonin receptors linked to adenylate cyclase (Lamp et al., 1981). This biosystem has been successfully established and validated as an in vitro bioassay for calcitonins of several species (Grauer et al., 1992; Zanelli et al., 1990). A suspension of these cells is incubated with an individual patient's serum in the presence of various doses of salmon calcitonin. After 15 min cells are disrupted and intracellular cyclic AMP is determined. Each assay should include standard curves performed with the individual patient's serum, a pretreatment sample from the same patient and pooled sera from healthy volunteers as a negative control as well as goat-anti sCT serum as a positive control. Pre- and posttreatment samples that are considered to be negative for neutralizing antibodies vary within 10 percent of control values (Grauer et al., 1990).

Clinical Studies

There are numerous publications reporting the occurrence of calcitonin antibodies in patients

treated with salmon, porcine, and rare human calcitonin. They often represent consecutive updates with growing numbers of patients, therefore, wherever possible, the largest available series treated by a certain group has been considered. To investigate not only the occurrence of CT antibodies, but to clarify the problem of secondary resistance and the role of neutralizing antibodies the following questions need to be addressed:

(1) How frequently do antibodies against calcitonin occur and how long was the treatment period before they were first detected?

The largest series published to date includes 85 patients with Paget's disease of bone treated with sCT. Fifty-six of these patients (66%) developed sCT-binding antibodies (Singer et al., 1980). An overview of the relevant studies in the literature is given in Table 1. In the first three months of treatment, antibody formation is very uncommon, only one case with detectable antibodies after 6 weeks of treatment has been reported (Singer et al., 1972). In most patients antibodies occur after 4 to 12 months (Grauer et al., 1990; Singer et al., 1980), although studies with long term sCT treatment suggest that there is a further increase in the patients affected, even after one year of therapy (Reginster et al., 1993). An influence of the calcitonin dosage on the frequency of CT antibody formation could not be established.

(2) Is there evidence for secondary resistance in an individual patient and is it antibody related?

Only few studies imply that although formation of binding antibodies against sCT is frequent, they only rarely have clinical significance. After two 3-month courses of sCT Reginster et al. finds binding antibodies in 10 of 16 patients (62.5%), but does not detect a difference in the mean reduction of AP between the patients who form antibodies and those who do not. The follow-up period in this study is very short (maximum 6 months of treatment) and the antibody forming group is assessed without differentiating between patients developing secondary resistance and those who do not. These differences in study design may explain the contrast between these results and most others in the literature (Reginster et al., 1990). The answer to the question, whether sCT antibodies are of clinical importance, requires the monitoring of treatment efficacy in the individual patient. In Paget's disease determination of serum AP levels represents a simple, accurate and cheap way to assess disease activity. It is possible to quantitate a primary response to treatment after a period of 1

Table 1 Development of calcitonin binding antibodies

CT	patients	binding AB	duration of treatment	disease	reference
salmon	85	56 (66%)	1.5–84 months	Paget's	(Singer et al., 1980)
	45	22 (49%)	4–34 months	Paget's	(Haddad et al., 1976)
	44	15 (39%) 23 (52%) 27 (61%) 27 (61%)	6 months 12 months 18 months 24 months	PMO	(Reginster et al., 1993)
	30	15 (50%)	12 months	PMO	(Tagliaro et al., 1995)
	24	17 (71%)	24 months	PMO	(Gruber et al., 1984)
	20	8 (40%)	6 months	Paget's	(Hosking et al., 1979)
	19	7 (37%) 10 (53%)	6 months 10 months	PMO	(Muff et al., 1991)
	16	10 (62.5)	6 months	Paget's	(Reginster et al., 1990)
	16	11 (69%)	18–36 months	Paget's	(Woodhouse et al., 1977)
	9	7 (77%)	3–6 months	Paget's	(Grauer et al., 1990)
human	36	1 (3%)	4–15 months	Paget's	(Dietrich et al., 1979)
	33	1 (3%)	12–18 months	PMO	(Grauer et al., 1993)
	17	0	8–23 months	Paget's	(Ziegler et al., 1976)

AB: CT binding antibodies; Paget's: Paget's disease of bone; PMO: postmenopausal osteoporosis

to 6 months and a subsequent secondary increase. We found evidence for clinical resistance in 4 of 9 patients (44%) after intranasal sCT treatment for 7–12 months. In this preliminary study 7 of 9 patients, (77%) showed evidence for binding antibodies, but only the 4 patients with secondary resistance showed evidence for neutralizing antibodies in the T 47 D in vitro bioassay (Grauer et al., 1990). Others treated patients with Paget's disease, part of whom had received prior s.c. sCT treatment for 1 to 4 years, with intranasal sCT for 12 months. They found binding antibodies in 8 of 9 patients and a neutralizing activity in the T 47 D in vitro bioassay in 7 of 9 patients (Levy et al., 1988). A setback in these studies is the small number of cases available for investigation which might lead to an overestimation of the phenomenon. In Singer's series of 85 patients with Paget's disease, 22 patients (26%) returned to pretreatment levels despite continued sCT treatment. Nineteen of these 22 patients were among the 56 subjects who had developed binding antibodies against sCT. The antibody titers in these 19 individuals with secondary resistance were higher than in those without

a clinically detectable effect. This provided strong evidence for antibody related resistance in 19 of 85 patients (22%) which could be supported by a neutralizing activity in the rat in vivo bioassay. More puzzling was the behaviour of 3 of the 85 patients in this study with true secondary resistance but without the presence of sCT antibodies (Singer et al., 1980). Similar cases have been reported by others (Woodhouse et al., 1977), a conclusive explanation for this phenomenon remains to be established.

A major question concerning the significance of these antibodies for an individual patient is whether secondary resistance to a heterologous CT, allegedly due to neutralizing antibodies, can be overcome by treatment with human CT. Out of 27 patients in another study, 10 (37%) showed evidence for neutralizing antibody related secondary resistance to sCT, a subset of 5 of these patients was tested for their responsiveness to hCT-therapy which led to a biochemical improvement in each case (Haddad et al., 1983). A responsiveness to hCT after diagnosing antibody mediated secondary resistance to sCT was also found in other stud-

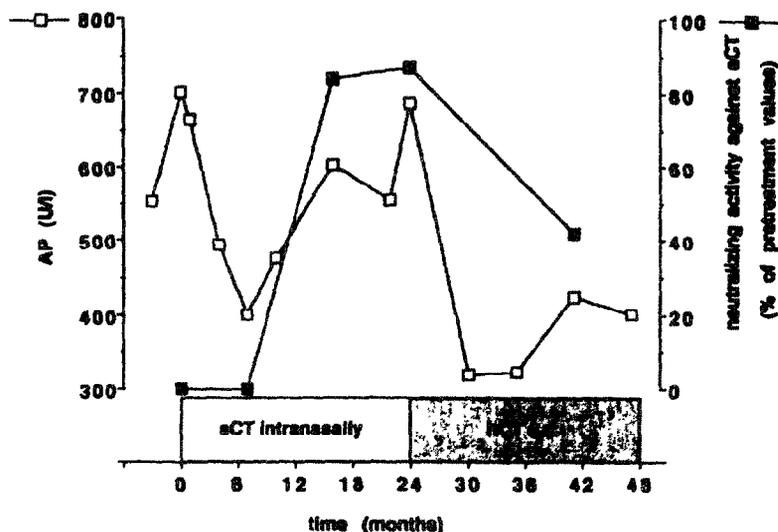


Fig. 1 Antibody mediated secondary resistance to sCT in a patient with Paget's disease of bone. A 72-year old female with monostotic Paget's disease of the femur was treated with 400 IU sCT intranasally/day for 24 months. Due to the development of secondary resistance, treatment was changed to hCT, (100 IU/day for the first six months and 3x100 IU/week for the following 18 months), which led to a sustained reduction of AP levels. The figure depicts the course of alkaline phosphatase levels (AP) (open squares) and of the sCT neutralizing activity of the patient's serum (closed squares), determined by T 47 D cell in vitro bioassay as previously described (Grauer et al. 1994). The inhibition of sCT mediated cAMP formation of T 47 D cells after addition of patient sera is considered as neutralizing activity and is expressed in % relative to the pretreatment control value of this patient (0%). The parallel occurrence of secondary resistance against sCT and of sCT antibodies with neutralizing activity in the serum of the patients combined with the responsiveness of the patient to subsequent hCT treatment supports the diagnosis of antibody mediated secondary resistance against sCT.

ies (Grauer et al., 1994; Muff et al., 1990; Singer, 1977), supporting the clinical relevance of antibody mediated resistance against sCT (Fig. 1).

Neutralizing antibodies against human CT have so far only been reported in one single case in the world literature (Grauer et al., 1993). The neutralizing activity of this patient's serum was very low compared to those known to induce secondary resistance against sCT. Therefore, there is no evidence so far that hCT treatment induces clinically relevant neutralizing antibodies.

Conclusion

The formation of antibodies against heterologous calcitonins is a common phenomenon, occurring in 50–70% of the patients, treated with sCT for at least 4–12 months. Longer periods of treatment seem to further enhance antibody formation. Most authors agree that there is a phenomenon like antibody related secondary resistance in sCT-treated patients. In nearly all clinical studies presenting data on measures of clinical efficacy in individual patients, patients with sCT binding antibodies show evidence of clinical resistance and/or neutralizing antibodies in 16% (Woodhouse et al., 1977) to 77% (Levy et al., 1988) of the patients treated and in 20 to 88% of the patients with binding antibodies. The high variation between these

two figures might be explained by the small sample size associated with a risk of under- or overestimation. Therefore, the largest series published so far including 85 patients may give the best estimate. Here sCT binding antibodies have been found in 66% of the patients, antibody mediated secondary resistance in 22%. The strongest argument for the presence of clinically significant antibody related CT resistance, however, is the positive response to hCT treatment in patients with secondary resistance to sCT, reported in several clinical studies (Grauer et al., 1994; Muff et al., 1990; Singer, 1977).

Other issues, however, are still controversial or unexplained. Some authors find a clear relation between the titer of neutralizing antibodies and their neutralizing potential (Singer et al., 1980), others find a neutralizing effect of patient serum and secondary resistance occasionally in the presence of low antibodies titres (Grauer et al., 1990; Woodhouse et al., 1977). The sCT-antibodies in these patients are polyclonal, therefore a high antibody titer may simply be associated with a higher probability that neutralizing antibody clones are present, without excluding their occurrence in patients with low antibody titres. This supports the recommendation to determine not only binding, but also neutralizing antibodies in patients where clinical resistance to sCT treatment is suspected but

hard to prove, i.e. in the absence of readily available markers of treatment efficacy, as in osteoporosis.

Neutralizing antibodies are found to be responsible for most cases of secondary resistance against sCT. Several patients, however, present with secondary resistance against sCT without detectable sCT antibodies (Hosking et al., 1979; Singer et al., 1980; Woodhouse et al., 1977). In some of these cases, an acute sCT administration may still lead to a hypocalcemic effect, the chronic administration, however, has lost the ability to control the disease activity. A conclusive explanation for this phenomenon is so far not possible, the mechanism may, however, be similar to the unexplained cases of resistance against human calcitonin and needs yet to be determined.

We conclude that antibody-mediated resistance is a relevant problem for patients under long term-treatment with heterologous calcitonins. In Paget's disease appropriate monitoring of disease activity will allow to identify clinical resistance, which is to be expected in 20 to 40% of the patients, and which will be due to neutralizing antibodies in most of these cases. Changing the treatment to human CT and a subsequent fall in AP levels will prove the diagnosis of antibody mediated secondary resistance. In osteoporosis, where the number of patients under long term treatment with sCT is much higher, the situation is more difficult. In long term sCT treatment for osteoporosis, the formation of sCT-binding and biochemically neutralizing antibodies against sCT appears to be similar to that in long-term treatment of Paget's disease (Muff et al., 1991). Here, however, no reliable biochemical marker will allow us to establish the diagnosis of secondary resistance in an individual patient. Serial bone mineral density measurements (BMD) might serve as a surrogate. The ability of BMD to detect secondary resistance in an individual patient, however, is hampered by the small increases in bone mineral density to be expected. Even if treatment with sCT is considered successful, the average increase in density values does not exceed 1–2%/year (Overgaard et al., 1990; Reginster, 1993; Reginster et al., 1994). A clinical study closely monitoring the efficacy of sCT treatment and the formation and significance of binding and neutralizing antibodies against sCT in the individual patients would be necessary. Until then caution is needed and the development of sCT antibodies should be monitored in patients under treatment with heterologous CT. If there is evidence for neutralizing antibodies, treatment should be changed to human CT or another suitable drug.

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