ORIGINAL ARTICLE

Osteoporosis in Multiple Endocrine Neoplasia Type 1

Severity, Clinical Significance, Relationship to Primary Hyperparathyroidism, and Response to Parathyroidectomy

John R. Burgess, MD, FRACP; Ruben David, BSc; Timothy M. Greenaway, PhD, FRACP; V. Parameswaran, PhD; Joseph J. Shepherd, MD, FRACS

Background: Sporadic primary hyperparathyroidism (PHPT) occurs most frequently in postmenopausal women. Multiple endocrine neoplasia type 1 (MEN 1) is an autosomal-dominant disease in which mild to moderate PHPT develops in most gene carriers by 20 years of age. Primary hyperparathyroidism associated with MEN 1 is typically recurrent, despite initially successful subtotal parathyroidectomy. Osteoporosis is considered a complication of sporadic PHPT and an indication for parathyroidectomy. In the setting of MEN 1, however, the relationship of bone mass to PHPT, fracture risk, and parathyroidectomy is unknown.

Hypothesis: Parathyroidectomy improves bone mineral density for patients with primary hyperparathyroidism in the setting of MEN 1.

Design: Case series.

Setting: Tertiary referral center.

Patients: Twenty-nine women with MEN 1 belonging to a single family with a history of MEN 1.

Interventions: Parathyroidectomy.

Main Outcome Measures: Bone mineral density (BMD) and history of skeletal fracture.

Results: Osteopenia and osteoporosis were diagnosed in 41% and 45% of patients, respectively. Forty-four percent of patients with uncontrolled PHPT had severe osteopenia (T score, <−2.0) by 35 years of age. Reduction in BMD was greatest at the femoral neck. Reduced BMD was associated with an increased likelihood of skeletal fracture ($P = .05$). Patients with uncontrolled PHPT had lower femoral neck and lumbar spine BMDs than those in whom PHPT was controlled by parathyroidectomy ($P = .005$ and .02, respectively). Successful parathyroidectomy improved femoral neck and lumbar spine BMDs by a mean ± SEM of 5.2% ± 2.5% and 3.2% ± 2.9%, respectively.

Conclusions: Osteoporosis is a frequent and early complication of PHPT in MEN 1. Despite difficulty in achieving a cure of PHPT in MEN 1, parathyroidectomy has an important role in the optimization of BMD for patients with MEN 1.

Arch Surg. 1999;134:1119-1123

From the Departments of Diabetes and Endocrine Services (Drs Burgess, Greenaway, and Parameswaran) and Clinical Chemistry (Mr David), Royal Hobart Hospital, and the Department of Surgery, University of Tasmania (Dr Shepherd), Hobart, Australia.

SPORADIC PRIMARY hyperparathyroidism (PHPT) is a recognized cause of osteoporosis in the general population, and reduced bone mineral density (BMD) is an important risk factor for skeletal fracture.[1,2] Most articles[2,3] describing the relationship between sporadic PHPT and BMD have focused on PHPT occurring in postmenopausal women. In this setting, parathyroidectomy is almost always curative of PHPT, resulting in up to a 20% increase in BMD during the first year after surgery.[2]

Recent articles[4-7] draw attention to the high rate of recurrent PHPT in patients with multiple endocrine neoplasia type 1 (MEN 1), an autosomal-dominant disease characterized by PHPT, gastroenteropancreatic tumors, and pituitary neoplasia. The most frequent abnormality in MEN 1 is PHPT.[7] Although results of earlier studies suggested that PHPT usually developed after 20 years of age, it is now apparent that mild-to-moderate hypercalcemia typically begins during adolescence.[7-10] More than 90% of MEN 1 gene carriers manifest this abnormality by 30 years of age.[7] Despite "optimal" parathyroidectomy, PHPT recurs in more then 60% of patients with MEN 1 within a decade of surgery.[4] For this reason, the merit of undertaking parathyroid surgery in asymptomatic young patients with PHPT and mild hypercalcemia is debated. The impact of PHPT on bone mass and the risk of skeletal fracture in the context of MEN 1 have not been previously reported, to our knowledge.

©1999 American Medical Association. All rights reserved.
Downloaded From: http://archsurg.jamanetwork.com/ on 08/01/2015

PATIENTS AND METHODS

Previous research[10] has identified several families with MEN 1 in Tasmania, Australia. Consenting individuals participated in research into the pathogenesis, natural history, and clinical management of MEN 1.[7,10] This program was approved by the research and ethics committees of the Royal Hobart Hospital, Hobart, Australia. In this article, we review the results of BMD assessment for 29 MEN 1–affected women from a large kindred designated Tasman I. Evaluation of BMD using an x-ray densitometer (model QDR-2000; Hologic, Bedford, Mass) at the femoral neck (FN) and lumbar spine (LS) (frontal plane) was performed as part of a routine clinical protocol for evaluation of PHPT. The impact of parathyroidectomy was assessed using cross-sectional and longitudinal BMD data. To determine the clinical impact of reduced BMD, patients were prospectively surveyed regarding any history of axial and appendicular skeletal fracture.

DEFINITIONS

Hyperparathyroidism is characterized by (1) an albumin-corrected calcium level greater than 2.55 mmol/L (>10.2 mg/dL), (2) an ionized calcium level (corrected to pH 7.4) greater than 1.29 mmol/L (>5.16 mg/dL), or (3) a total calcium level greater than 2.75 mmol/L (>11.0 mg/dL). Elevation of serum calcium concentrations was confirmed on 2 or more separate occasions in the presence of a nonsuppressed PTH level (measured by several immunoassays during patient follow-up). Results are expressed as the ratio of the measured value to the upper limit of the reference range for the assay.

Controlled PHPT is defined as resolution of hyperparathyroidism for at least 4 years after parathyroidectomy, and uncontrolled PHPT is defined as no previous parathyroidectomy or recurrence of PHPT before postoperative year 4. These definitions are based on results of previous research[4] showing that recurrent PHPT occurs in less than 25% of patients with MEN 1 within 4 years of parathyroidectomy.

T score is the number of SDs from mean sex-appropriate peak bone mass; *Z* score is the number of SDs from mean sex- and age-appropriate bone mass. T scores for osteopenia, severe osteopenia, and osteoporosis are <–1.0, <–2.0, and <–2.5, respectively.

The extent of pituitary and pancreatic disease was assessed by computed axial tomography, magnetic resonance imaging, sonography, and biochemical assay.

Numerical data are presented as mean ± SEMs. χ^2 and unpaired *t* tests were used where appropriate for data comparison.

The relevance of existing studies of sporadic PHPT and bone mass to patients with MEN 1 is uncertain. In MEN 1, PHPT evolves during a period critical to the accretion of peak bone mass.[7] The impact of deranged parathyroid physiologic features during this phase of bone maturation is unclear. Moderate-to-severe parathyroid hormone (PTH) excess has been associated with osteoporosis, whereas mild excess (such as may occur early in the pathogenesis of PHPT) is potentially responsible for increased trabecular bone mass.[11,12] This article addresses the impact of PHPT on peak BMD and on fracture risk in MEN 1, which cannot be predicted from available data.

We review the clinical, biochemical, and BMD data for 29 women with MEN 1, examining the role and timing of parathyroidectomy in relation to the optimization and preservation of bone mass.

RESULTS

Femoral neck and LS BMDs were assessed in 29 women with MEN 1 (**Table 1**). Age at assessment was 43.6 ± 2.9 years (absolute range, 19.6-76.3 years). Twelve patients (41%) had osteopenia and 13 (45%) had osteoporosis. Overall, reduced bone mass was most evident at the FN (*Z* score, –1.31 ± 0.17 SD), although the LS BMD was also reduced (*Z* score, –0.86 ± 0.20 SD) ($P = .05$). A past history of skeletal fracture was reported by 5 patients (50%) in the lowest tertile for bone mass compared with 1 patient (10%) in the highest tertile ($P = .05$).

Reduced bone mass was associated with advancing age and uncontrolled PHPT (Table 1, **Table 2**, and **Figure 1**). After adjusting for age, BMD was significantly higher in patients with controlled vs uncontrolled PHPT (Tables 1 and 2 and Figure 1). By 35 years of age, 44% of patients with uncontrolled PHPT had severe osteopenia. The degree of PTH elevation, rather than hypercalcemia, correlated most closely with BMD (**Figure 2**). Hypogonadism, menopausal status, and nonparathyroid endocrine neoplasia were not significantly associated with reduced bone mass (Table 1).

Preoperative and postoperative assessments of BMD were available for 5 patients who underwent successful parathyroidectomy (ie, improvement in BMD of 5.2% ± 2.5% and 3.2% ± 2.9% at the FN and LS, respectively, at mean 18 months follow-up [range, 12-24 months]).

COMMENT

This study is retrospective and uses predominantly cross-sectional data. Moreover, the analysis is confined to women. Despite these limitations, it is the first study to document bone mass comprehensively in the setting of MEN 1. Reduced BMD occurred frequently and prematurely in most patients studied (Table 1). Loss of bone mass was progressive from early in the third decade of life, with severe osteopenia affecting 44% of patients by age 35 years (Table 2 and Figure 1). In accordance with results of other studies,[1,2] FN bone mass is more severely affected than that of the LS. Reduced BMD was of clinical significance, associated with an increased prevalence of skeletal fracture.

The cross-sectional data presented in Figure 1 show that osteopenia occurs early in the third decade of life. Primary hyperparathyroidism is the most common endocrine abnormality observed in MEN 1.[6,7,9] Considerable interpatient variability exists for the severity of hypercalcemia

©1999 American Medical Association. All rights reserved.
Downloaded From: http://archsurg.jamanetwork.com/ on 08/01/2015

Table 1. Characteristics of 29 Women With Multiple Endocrine Neoplasia Type 1 Assessed for Bone Mineral Density*

	Z Score					
	>–1.0		–1.0 to 2.0		<–2.0	
Patient Characteristics	**FN (n = 12)**	**LS (n = 14)**	**FN (n = 9)**	**LS (n = 9)**	**FN (n = 8)**	**LS (n = 6)**
Age, mean ± SEM, y	51.4 ± 5.5	53.8 ± 3.4	40.1 ± 3.8	51.4 ± 5.1	35.7 ± 2.8	35.2 ± 3.6
Controlled PHPT, %†	58	50	22	22	0	0
Uncontrolled PHPT, %‡	42	50	78	78	100	100
Gastrinoma, %	17	21	22	11	13	1
Prolactinoma, %	17	21	33	33	13	0
Postmenopausal, %	58	36	22	4	0	0

*FN indicates femoral neck; LS, lumbar spine (frontal plane); and PHPT, primary hyperparathyroidism.
†Controlled PHPT is parathyroidectomy achieving more than 4 years of normocalcemia.
‡Uncontrolled PHPT is recurrence of PHPT within 4 years of parathyroidectomy or no history of parathyroidectomy.

Table 2. Bone Mineral Density in Controlled and Uncontrolled PHPT*

Skeletal Site	Controlled PHTH *Z* score (T score)	Uncontrolled PHTH *Z* score (T score)	*P*
Age, y	49.8 ± 4.4	40.8 ± 3.7	.16
Femoral neck	–0.61 ± 0.25 (–1.66 ± 0.39)	–1.63 ± 0.19 (–2.33 ± 0.18)	.002
Lumbar spine	–0.15 ± 0.34 (–1.01 ± 0.43)	–1.18 ± 0.23 (–1.72 ± 0.28)	.009

*PHPT indicates primary hyperparathyroidism. Values are given as mean ± SEM.

and rate of disease progression. Aside from PHPT and advancing patient age, other osteoporosis risk factors were not increased in the patients studied (Table 1).

Severity of PHPT is often reported in relation to the degree of hypercalcemia.[3,4,13,14] Although some clinical manifestations of PHPT such as neuromuscular symptoms correlate well with hypercalcemia, our data indicate that hypercalcemia is a poor risk marker for osteoporosis in MEN 1. These data indicate that even mild and asymptomatic hypercalcemia can be associated with reduced BMD. Therefore, patients with mild hypercalcemia should be considered at risk for osteoporosis, particularly if serum PTH is elevated greater than twice the upper limit of normal. Regular evaluation of BMD should be undertaken in all patients with MEN 1 and PHPT.

In sporadic PHPT, parathyroid adenoma accounts for more than 90% of disease, and permanent restoration of normocalcemia is typically achieved after surgery in most patients.[4] In patients with MEN 1, however, PHPT frequently recurs, despite initially successful parathyroidectomy.[4] The National Institutes of Health Consensus Development Conference[15] statement on the management of PHPT proposed parathyroidectomy for sporadic PHPT that occurs in any individual younger than 50 years. In the context of MEN 1, however, asymptomatic patients with "mild" hypercalcemia are often managed more conservatively.[16] This approach perhaps derives from a perception of mild biochemical disease and the perceived difficulties of achieving and maintaining long-term normocalcemia in patients with MEN 1.

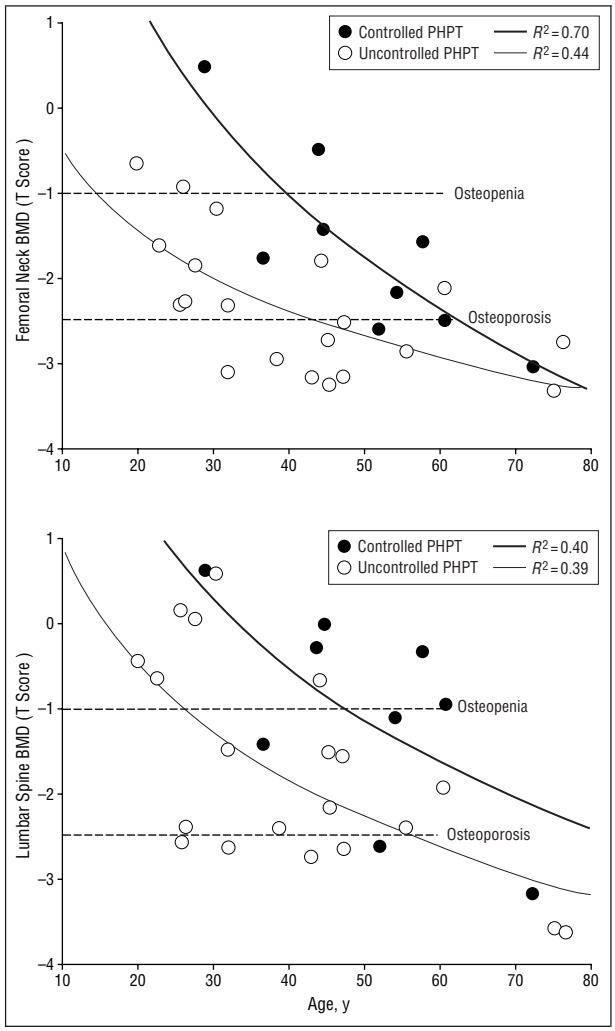

Figure 1. *Bone mineral density (BMD) in 20 patients with uncontrolled and 9 patients with controlled primary hyperparathyroidism (PHPT). Uncontrolled PHPT is defined as recurrence of PHPT within 4 years of parathyroidectomy or no history of parathyroidectomy; controlled PHPT, parathyroidectomy achieving greater than 4 years of normocalcemia.*

Bone mass reduction associated with PHPT is PTH dependent.[11] Previous studies[2,17,18] in the context of sporadic PHPT have shown improvement in cortical and trabecular BMD after successful parathyroidectomy. The

©1999 American Medical Association. All rights reserved.
Downloaded From: http://archsurg.jamanetwork.com/ on 08/01/2015

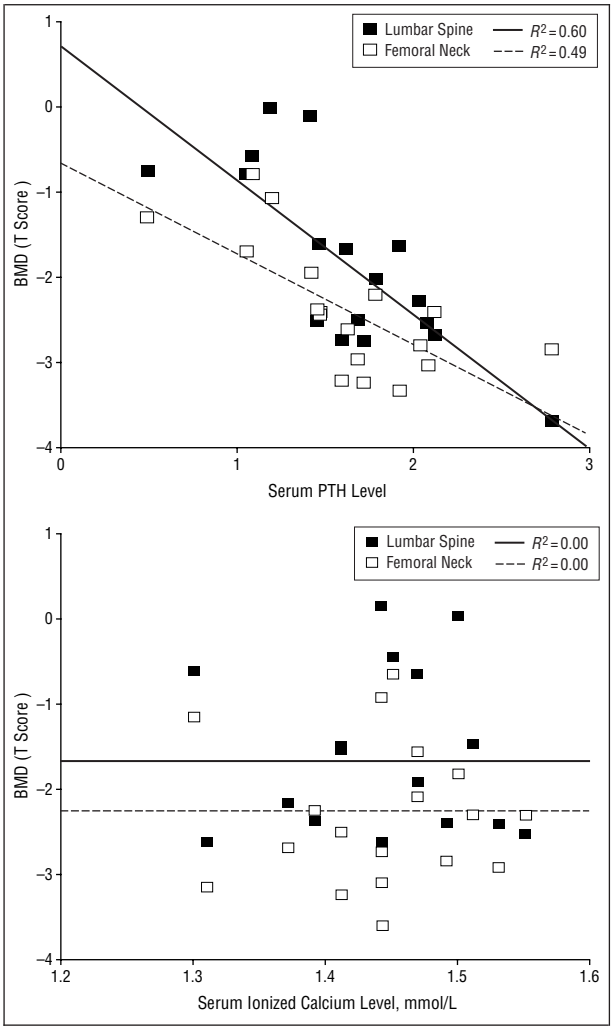

Figure 2. *Relationship of bone mineral density (BMD) T score to severity of primary hyperparathyroidism (PHPT) in patients with uncontrolled PHPT. Serum parathyroid hormone (PTH) level—highest PTH level recorded in the 12 months before BMD assessment—is expressed as a ratio to the upper limit of the assay reference range. Serum ionized calcium level is the highest ionized calcium level recorded in the 12 months before BMD assessment. To convert ionized calcium from millimoles per liter to milligrams per deciliter, divide millimoles per liter by 0.25.*

magnitude of improvement varies with skeletal site and preoperative bone mass.[19] On balance, patients with the lowest preoperative BMD achieve the greatest relative increases in bone mass after treatment of hyperparathyroidism. A significant improvement in BMD is achieved in the first 12 months after control of PHPT.[2,17,18] However, this response seems to have a limited capacity to restore bone mass. Thus, although successful surgery improves BMD, restoration of age-appropriate bone mass is not achievable if osteopenia is advanced. Therefore, prevention of osteopenia by prompt treatment of PHPT, even in young patients, seems to be the most effective strategy for ensuring the long-term adequacy of BMD in patients with MEN 1.

This study provides support for parathyroidectomy to be undertaken early in the evolution of PHPT. Prompt initial treatment of PHPT and long-term maintenance of normocalcemia are likely to be the most effective strategies for the optimization and preservation of bone mass in patients with MEN 1. Patients with any degree of sustained hyperparathyroidism in conjunction with osteopenia should be considered candidates for parathyroidectomy. In addition to a reduced risk of skeletal complications, long-term maintenance of normocalcemia in patients with MEN 1 may also reduce the likelihood of enteropancreatic neoplastic complications.[20]

Results of studies[21-23] in the general population also show that use of calcitriol, hormone replacement therapy, and bisphosphonate drugs improves BMD in patients with osteoporosis. The role of such adjuncts to parathyroidectomy—or as secondary therapies for patients with MEN 1 and PHPT uncontrolled by parathyroidectomy—is unknown. However, in the setting of osteoporosis, treatment in addition to parathyroidectomy seems appropriate. Long-term medical treatment of sporadic PHPT using agents such as calcimimetics has also been described.[24] However, although prolonged amelioration of hypercalcemia is possible, the effect on bone mass may be adverse.[24] Parathyroidectomy, therefore, remains the initial treatment-of-choice for the preservation of bone mass in the context of MEN 1–related PHPT.

CONCLUSIONS

Reduction in bone mass is evident in most women with MEN 1 by 35 years of age. Reduced BMD is associated with an increased likelihood of skeletal fracture. Successful parathyroidectomy and maintenance of normocalcemia is associated with improved LS and FN BMDs.

We advocate (1) screening of all patients with MEN 1 and PHPT for osteoporosis; (2) prompt treatment of emergent, asymptomatic PHPT in those with a BMD below age- and sex-matched means; (3) lifelong follow-up of parathyroid status and reoperation when PHPT recurs; and (4) use of adjunctive medical therapies (bisphosphonate drugs, hormone replacement therapy [if appropriate], or calcitriol) in addition to parathyroidectomy when osteoporosis is present.

Supported by a research grant from the Cancer Council of Tasmania, Tasmania, Australia.

Presented in abstract form at the 1998 Annual Scientific Meeting of the Endocrine Society of Australia, Perth, Australia, August 25, 1998.

Reprints: J. R. Burgess, MD, FRACP, Department of Diabetes and Endocrine Services, Royal Hobart Hospital, GPO Box 1061L, Hobart 7001, Australia (e-mail: jburges @postoffice.utas.edu.au).

REFERENCES

1. Ross PD. Risk factors for osteoporotic fracture. *Endocrinol Metab Clin North Am.* 1998;2:289-301.
2. Silverberg SJ, Locker FG, Bilezikian JP. Vertebral osteopaenia: a new indication for surgery in primary hyperparathyroidism. *J Clin Endocrinol Metab.* 1996;81:4007-4012.
3. Sorva A, Valvanne J, Tilvis RS. Serum ionised calcium and the prevalence of primary hyperparathyroidism in age cohorts of 75, 80 and 85 years. *J Intern Med.* 1992;231:309-312.
4. Burgess J, David R, Parameswaran V, et al. The outcome of subtotal parathyroidectomy for the treatment of hyperparathyroidism in multiple endocrine neoplasia type 1. *Arch Surg.* 1998;133:126-129.

©1999 American Medical Association. All rights reserved.
Downloaded From: http://archsurg.jamanetwork.com/ on 08/01/2015

5. Brandi ML, Marx SJ, Aurbach GD, et al. Familial multiple endocrine neoplasia type 1: a new look at pathophysiology. *Endocr Rev.* 1987;8:391-405.
6. Padberg B, Schroder S, Capella C, et al. Multiple endocrine neoplasia type 1 (MEN 1) revisited. *Virchows Arch.* 1995;426:541-548.
7. Burgess JR, Greenaway TM, Shepherd JJ. Expression of the MEN 1 gene in a large kindred with multiple endocrine neoplasia type 1. *J Int Med.* 1998;243:465-470.
8. Thompson NW. The surgical management of hyperparathyroidism and endocrine disease of the pancreas in the multiple endocrine neoplasia type 1 patient. *J Int Med.* 1995;238:269-280.
9. Skogseid B, Rastad J, Oberg K. Multiple endocrine neoplasia type 1: clinical features and screening. *Endocrinol Metab Clin North Am.* 1994;23:1-18.
10. Shepherd JJ. The natural history of multiple endocrine neoplasia type 1: highly uncommon or highly unrecognized? *Arch Surg.* 1991;126:935-952.
11. Silverberg SJ, Shane E, de la Cruz L, et al. Skeletal disease in primary hyperparathyroidism. *J Bone Miner Res.* 1989;4:283-291.
12. Slovik DM, Rosenthal DI, Doppelt SH, et al. Restoration of spinal bone in osteoporotic men by treatment with human parathyroid hormone (1-34) and 1,25-dihydroxy vitamin D. *J Bone Miner Res.* 1986;1:377-381.
13. Ljunghall S, Hellman P, Rastad J, et al. Primary hyperparathyroidism: epidemiology, diagnosis and clinical picture. *World J Surg.* 1991;15:681-687.
14. Lundgren E, Rastad J, Thrufjell E, et al. Population-based screening for primary hyperparathyroidism with serum calcium and parathyroid hormone values in menopausal women. *Surgery.* 1997;121:287-294.
15. National Institutes of Health Consensus Development Conference on Diagnosis and Management of Asymptomatic Primary Hyperparathyroidism. Diagnosis and management of asymptomatic primary hyperparathyroidism. *Consens Statement.* 1990;8:1-18.
16. Mallette L. Management of hyperparathyroidism in the multiple endocrine neoplasia syndromes and other familial endocrinopathies. *Endocrinol Metab Clin North Am.* 1994;1:19-36.
17. Silverberg SJ, Gartenberg F, McMahon DJ, et al. Increased bone mineral density following parathyroidectomy in primary hyperparathyroidism. *J Clin Endocrinol Metab.* 1995;80:729-734.
18. Abugassa S, Nordenstrom J, Eriksson S, et al. Skeletal remineralisation after surgery for primary and secondary hyperparathyroidism. *Surgery.* 1990;107:128-133.
19. Minisola S, Rosso R, Romagnoli E, et al. Trabecular bone mineral density in primary hyperparathyroidism: relationship to clinical presentation and biomarkers of skeletal turnover. *Bone Miner.* 1993;20:113-123.
20. Burgess JR, Greenaway TM, Parameswaran V, et al. Enteropancreatic malignancy in MEN 1: risk factors and pathogenesis. *Cancer.* 1998;83:428-434.
21. Reid IR. The roles of calcium and vitamin D in the prevention of osteoporosis. *Endocrinol Metab Clin North Am.* 1998;2:389-398.
22. Lindsay R. The role of oestrogen in the prevention of osteoporosis. *Endocrinol Metab Clin North Am.* 1998;2:399-409.
23. Watts NB. Treatment of osteoporosis with bisphosphonates. *Endocrinol Metab Clin North Am.* 1998;2:419-439.
24. Collins MT, Skarulis MC, Bilezikian JP, et al. Treatment of hypercalcaemia secondary to parathyroid carcinoma with a novel calcimimetic agent. *J Clin Endocrinol Metab.* 1998;83:1083-1088.

IN OTHER AMA JOURNALS

JAMA

Hospital Peer Review and the National Practitioner Data Bank: Clinical Privileges Action Reports

Laura-Mae Baldwin, MD, MPH; L. Gary Hart, PhD; Robert E. Oshel, PhD; Meredith A. Fordyce, PhC; Robin Cohen, MPH; Roger A. Rosenblatt, MD, MPH

Context: The National Practitioner Data Bank (NPDB) is believed to be an important source of information for peer review activities by the majority of those who use it. However, concern has been raised that hospitals may be underreporting physicians with performance problems to the NPDB.
Objective: To examine variation in clinical privileges action reporting by hospitals to the NPDB, changes in reporting over time, and the association of hospital characteristics with reporting.
Design: Retrospective cohort study of privileges action reports to the NPDB between 1991 and 1995, linked with the 1992 and 1995 databases from the Annual Survey of Hospitals conducted by the American Hospital Association.
Setting and Participants: A total of 4743 short-term, nonfederal, general medical/surgical hospitals throughout the United States that were continuously open between 1991-1995 and registered with the NPDB.
Main Outcome Measures: (1) Reporting of 1 or more privileges actions during the 5-year study period and (2) privileges action reporting rates (numbers of actions reported per 100 000 admissions).
Results: Study hospitals reported 3328 privileges actions between 1991 and 1995; 34.2% reported 1 or more actions during the period. The range of privileges action reporting rates for these hospitals was 0.40 to 52.27 per 100 000 admissions, with an overall rate of 2.36 per 100 000 admissions. The proportion of hospitals reporting an action decreased from 11.6% in 1991 to 10.0% in 1995 ($P = .008$). After adjustment for other factors, urban hospitals had significantly higher reporting than rural hospitals (adjusted odds ratio [OR], 1.21 [95% confidence interval {CI}, 1.02-1.43]), while members of the Council of Teaching Hospitals of the Association of American Medical Colleges had significantly lower reporting than nonmembers (adjusted OR, 0.54 [95% CI, 0.40-0.73]). There were notable regional differences in reporting, with the east south Central region having the lowest rate per 100 000 admissions (1.49 [95% CI, 1.33-1.65]).
Conclusions: The results of this study indicate a low and declining level of hospital privileges action reporting to the NPDB. Several potential explanations exist, 1 of which is that the information reported to the NPDB is incomplete. (*1999;282:349-355*) www.jama.com

Corresponding author and reprints: Laura-Mae Baldwin, MD, MPH, University of Washington, Department of Family Medicine, Box 354696, Seattle, WA 98195-4696 (e-mail: lmb@u.washington.edu).

©1999 American Medical Association. All rights reserved.
Downloaded From: http://archsurg.jamanetwork.com/ on 08/01/2015