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Publication Date

2005-04-01

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Osteoporosis: diagnosis, treatment and its association with lung disease

by

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B.S. (University of Wisconsin) 2002

A thesis submitted in partial satisfaction of the

requirements for the degree of

Masters of Science
in

Health and Medical Sciences

in the

GRADUATE DIVISION

of the

UNIVERSITY OF CALIFORNIA, BERKELEY

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Professor William Satariano, Chair

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Spring 2005

BACKGROUND AND SIGNIFICANCE OF OSTEOPOROSIS

Osteoporosis is a disease characterized by low bone mass, abnormal skeletal microarchitecture and increased fragility[1]. Although there is a normal decline in bone mass that is expected with aging, particularly in women after menopause, some people experience loss of bone mass to a greater extent, putting them at risk for such sequelae as vertebral compression fractures, Colles' wrist fractures and atraumatic hip fractures. The terms 'atraumatic', 'low-energy' and 'fragility' fractures will be used in this paper to refer to those fractures that occur as a result of falling from a standing height or less, a standard clinical criteria to define osteoporotic fractures. Although other factors including skeletal geometry and genetics play an important role in the risk of fracture, low bone mass is one of the strongest predictors of fragility fracture. Fragility fractures of the hip and spine are associated with considerable morbidity and mortality rates that are preventable by diagnosing and treating osteoporosis early on.

It is estimated that 39.6% of women over 50 years of age have osteopenia, a low bone mass state that is intermediate between normal and osteoporotic bone mass [2], and 7.2% have osteoporosis. Women with osteoporosis have a fracture rate four times that of women with normal bone mineral density [3]. In the US, approximately 44 million people [4] suffer from osteoporosis and the estimates of their medical care costs range from \$1 billion each year [5] to \$8.7 billion [6]. When hip fractures result, they lead to a one year mortality rate up to 20-25% and a 2-3 fold increase risk in subsequent fracture [7].

Many risk factors for the development of osteoporosis have already been identified. Women, especially those who have already gone through menopause and

experienced a decline in estrogen levels are at a greatly increased risk [1, 8]. Increasing age in both sexes increases the likelihood of osteoporosis and it has been found that whites are more affected than blacks, Hispanics or Asians [2, 3, 9-11]; however, minority groups have been understudied relative to whites. There are also many drugs that lead to bone loss, some of which include corticosteroids, anticonvulsants, heparin, thyroid hormone and alcohol [1, 8, 9]. Other factors include immobilization, loss of height, low body weight, a family history of osteoporosis, and vitamin D and calcium insufficiency and deficiency [8, 10, 12-14].

When a patient manifests several of these risk factors, the provider needs to be aware and carry a high degree of suspicion of osteoporosis, especially given that osteoporosis is asymptomatic until a fracture occurs. The next step, after identifying an at-risk patient is to order a DXA scan, a bone mineral density test which is a procedure normally covered by most insurance plans and considered to be the gold standard in osteoporosis diagnosis [15-17]. It is a relatively inexpensive test and is now covered under most insurance plans, including Medicare. Unfortunately, many individuals who are at high risk for osteoporosis are never referred for bone mass measurements.

Once a diagnosis of osteoporosis is made, several pharmacologic interventions are available that have been shown to slow the decline in bone mineral density, result in increases in bone mass and fracture reduce fracture risk. Calcium and Vitamin D are basic measures that should be provided to all individuals at risk for osteoporosis. Calcitonin, bisphosphonates, hormone replacement therapy, and selective estrogen receptor modulators are all viable pharmacological options for the treatment and prevention of osteoporosis [9, 10, 15, 18-20]. These agents do not build new bone but

work by inhibiting the resorption of bone, which is the primary disturbance in most cases of postmenopausal osteoporosis. Recently, recombinant human parathyroid hormone (PTH) has been approved for use in osteoporosis. hPTH is the only anabolic agent available and results in dramatically increased bone mass, improved skeletal architecture and reductions in vertebral and non-vertebral fractures [21, 22]. In addition to slowing or reversing the loss of bone, it has also been shown that patients receiving any type of osteoporosis treatment have decreased mortality [23].

Despite the existence of known risk factors, efficient diagnostic procedures and appropriate medications, osteoporosis continues to be frequently under-diagnosed. The occurrence of a fragility fracture is a strong sign that an elderly person has osteoporosis and should be evaluated and treated [17, 24, 25]. In post-menopausal women, it is estimated that at least 80-90% of wrist, hip and vertebral fractures arise from underlying osteoporosis [26]. And having a fracture at any of these sites is associated with a two-fold increase in risk for a subsequent fracture[7]. However, studies have indicated that the majority of patients who are seen for a non-traumatic fracture are not diagnosed or treated for the underlying disease. A study of 311 hip fracture patients in Canada revealed that only about 20% were diagnosed or treated for osteoporosis [27]. One study from Massachusetts indicated that 46% of women with vertebral compression fractures were diagnosed [28] and another similarly indicated this rate to be 44% [26]. However, other studies have shown that only 29% [29], 18.5% [30] and as few as 3% of patients with fragility fracture are evaluated or treated for low bone density [31]. Additionally, some studies have indicated that there may be differences in evaluation rates depending on the age [26, 32] and the gender [28] of the patient and the type of clinic in which they

are seen [29]. Generally, there are biases among physicians that osteoporosis is a disease of postmenopausal Caucasian women, leading to higher treatment rates in that population. The results of these studies vary widely depending on the sample size, the study location, the type of hospital and the type of fracture.

The current body of literature regarding the health care of hip fracture patients deals mainly with secondary or tertiary medical centers serving mostly white populations. The Highland Hospital campus in Oakland, CA, part of the Alameda County Medical Center, represents an urban, primary care facility that treats mainly underserved patients of ethnic minorities. Patient characteristics, such as age, gender, ethnicity, comorbidities and type of fracture, and the trends in the health care of hip fracture patients at the APMC have not been previously studied. With the high proportion of ethnic minorities and people with potentially more serious or numerous health concerns, some of the characteristics such as age and gender ratios at Highland Hospital may differ from the types of hospitals or communities typically studied in the osteoporosis literature. Additionally, local studies can help to promote the implementation of protocols and public health screening programs. Understanding the demographics and medical conditions of fragility hip fracture patients at Highland may help guide public health intervention efforts and heighten the physicians' awareness of the existence of osteoporosis in other groups. With the steadily increasing elderly population in the US, hip fracture rates are expected to rise dramatically. Osteoporosis is a considerable public health issue that merits a thorough evaluation and discussion in the medical literature.

The purpose of this study was to generate data that would describe the characteristics of hip fracture patients at the APMC, to generate information that will be

useful in planning future studies and in designing programs for fracture prevention and osteoporosis treatment at APMC. We hypothesize that the rate of treatment of osteoporosis prior to or after hip fracture in patients presenting to APMC is less than 20% and that the patient characteristics may differ from those at tertiary care facilities serving primarily insured white populations.

RESEARCH DESIGN AND METHODS

A list of hip fracture patients admitted to the Alameda County Medical Center between January 1, 1999 and August 31, 2003 was generated by searching for ICD-9 codes that indicate a discharge diagnosis of hip fracture (ICD 820.0, 820.1, 820.2, 820.3, 820.8, 820.9). The list consisted of 132 patients. 21 of these charts could not be located at Highland Hospital and of the 111 charts reviewed, only 74 actually contained informative data for hip fracture. To de-identify the data for patient confidentiality, each case was assigned a random alphanumeric code that had no reference to the patient's name or medical record number. A list of medical record numbers of the charts reviewed was kept in a separate, locked file, to avoid a duplicate review of the same chart. HIPAA specified identifiers such as name, birth date, and social security number were not recorded.

Charts were reviewed for the following information: Age at hip fracture, gender, weight, ethnicity, type of fracture, circumstances of fracture (trauma, atraumatic, fall), family history, pre-existing medical conditions, history of previous fracture, medications and supplements (including calcium), smoking, alcohol use, clinical consideration of the diagnosis of osteoporosis documented in the medical record, measures of bone mass,

treatment for osteoporosis, length of hospital stay and whether the patient was discharged to their home or to a skilled nursing facility, or died while in the hospital. We recorded how many patients, according to the information in the chart, were diagnosed with osteoporosis prior to their fracture and how many were diagnosed and treated for osteoporosis after their hip fracture. All hospital notes, outpatient notes and diagnostic data in the ACMC chart were reviewed. When information was not available, this was noted. All statistical analysis was done using STATA 7 Software.

The protocol for this research project was declared exempt from full Committee review by the UC Berkeley Committee for the Protection of Human Subjects, as project number 2004-1-69. The protocol was also reviewed by the ACMC IRB and declared exempt. Consent of individuals was not required because only existing documents were used and all data was de-identified.

RESULTS

Data describing the baseline characteristics and fracture types of the hip fracture patients is listed in Table 1.

Table 1: Characteristics of hip fracture patients.*

	Traumatic Fractures (n=30)	Low-energy Fractures** (osteoporotic) (n=43)	All Hip fractures (n=73)
Males	27	15	42
Age (mean)	44.04	63.4	50.95
Weight (mean)	180.46	171.7	
Women	3	28	31
Age (mean)	28.33	76.11	71.48
Weight (mean)	137.87	129.8	
Race/Ethnicity			
White	11	17	28
Black	11	8	19
Asian	0	10	10

Hispanic	5	6	11
Other	0	1	1
Unknown	3	1	4
Fracture Type (# of patients)			
Intertrochanteric or trochanteric	13	25	38
Femoral neck, transcervical or subcapital	11	16	27
Subtrochanteric	3	1	4
Other	3	1	4

* This data does not include 4 fractures that were diagnosed as pathological/malignant processes.

**Low energy fractures are those that resulted from a fall from standing height or less and indicate a high probability of osteoporosis.

Males are more likely to have had traumatic fractures than are women ($p < 0.001$) and patients with traumatic fractures are significantly younger than low-energy fracture patients ($p < 0.001$). The difference in the average age between the men and the women low-energy hip fracture patients is significant at $p = 0.009$. There were 6 men under the age of 60 who suffered a low-energy fracture; five of them had comorbidities that increased the risk of osteoporosis. A 40-year-old and a 47-year-old suffered from alcoholism, a 46-year-old had multiple sclerosis, a 49-year-old had schizophrenia and dementia, and a 59-year-old had hemiparesis secondary to a stroke. One 59-year-old had no identified comorbidities.

Table 2: Causes of traumatic hip fractures.

Causes of Traumatic Hip Fractures	Number of Patients
motor vehicle accident	14
fall from ladder, fence, roof or stool	5
auto vs cyclist, pedestrian or wheelchair	4
gunshot	4
bike crash	2
suicide attempt	1

Data describing the health of the hip fracture patients is presented in Table 3.

Table3: Patient health characteristics

	Traumatic fractures (n=30)	Low-energy fractures (n=43)	All Hip Fractures† (n=73)
Average # of medications	1.13	3.59	2.52
Average length of hospital stay	10.79	7.44	8.68
# with 1 or more comorbidities	17	37	54
average # of comorbidities	1.03	3.14	2.27
# with previous fractures recorded in chart	3	9	12
# of patients on illicit drugs	8	3	11
# of patients discharged to home†	16	9	25
# of patients transferred to SNF or other hosp†	11	31	42
# of patients who died while in the hospital	0	2‡	2
# with one or more osteoporosis or fall risk factors	5	23	27

† Due to missing data, these numbers do not add up to the total number of hip fractures analyzed.

‡ The 2 patients who died while in the hospital were both males, ages 59 and 62. The 59-year-old had pneumonia, CVA hemiparesis, HTN, respiratory failure, DM, and renal failure and the 62-year-old died of liver failure secondary to cirrhosis, and also had hepatitis C, opioid dependence, an abscess, malnutrition, and renal failure.

Comorbidities

When the number of comorbidities was divided into 3 categories (0-1, 2-4 and 5 or more) there was no difference in the number of comorbidities between men and women ($p=.519$). There was no difference in the number of patients with osteoporosis or fall risk factors between men and women ($p=.988$).

Figure 1: Frequency of the number of comorbidities among traumatic and fragility fracture patients.

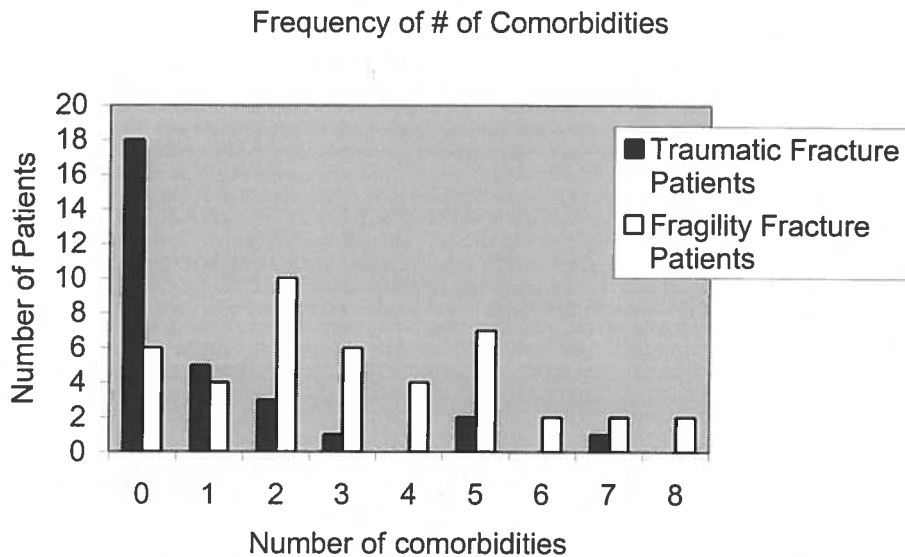


Table 4: Comorbidities among hip fracture patients, number of patients.

Health disorders	Men		Women	
	Low-energy Fractures (n=15)	Traumatic (n=27)	Low-energy fractures (n=28)	Traumatic (n=3)
Hypertension	6	6	15	0
Cardiovascular Disease	4	0	11	0
Pulmonary Disease	1	0	5	0
Endocrinological	2	4	11	0
Psychiatric illness	4	1	10	1
Neurological	5	3	7	0
Alcohol abuse	2	4	1	0
Other drug abuse	2	4	1	0
Renal failure	2	1	1	0
Liver failure	1	0	0	0
Malignancy (or history of)	2	0	6	0
Musculoskeletal	1	1	1	0
Rheumatic	0	0	1	0
Gastrointestinal	1	0	4	0

Pre-fracture Health

Among the 43 fragility fracture patients, 8 patients (5 women and 3 men) had a

prior diagnosis of osteoporosis indicated in the chart, 5 were taking either calcium supplements, vitamin D or an anti-resorptive prior to fracture. Four low-energy fracture patients were taking either steroids or anti-convulsants prior to their fracture and four of the women had had hysterectomies.

Post-fracture Care

Among the 43 fragility fracture patients, 0 charts recorded whether there was a family history for osteoporosis or hip fracture and 0 new DXA/bone density scans were ordered. There were no new mentions of osteoporosis in the charts. Three patients received pathology reports that indicated “bone loss” but the results of these reports were not mentioned elsewhere in the charts. Four patients not previously taking calcium or vitamin D were given calcium and/or vitamin D, but only 3 of these orders showed up on the final discharge medication list. One patient was given a recommendation in a medicine consult note to start alendronate, but this was not followed up on elsewhere in the chart.

DISCUSSION

Nature of the Hip Fracture

We found that 59% of hip fracture patients admitted to Highland Hospital were fragility fractures while 41% were due to traumatic incidents (19.2% to motor vehicle accidents, 6.8% due to significant falls, 5.5% to other traffic accidents and 5.5% to gunshot wounds). Similar percentages for MVA's and fragility fractures have been reported elsewhere[33]. However, only 35.7% of male patients had fragility fractures, far fewer than the 84% in the North-Savo province of Finland reported by Huuskonen et

al[34]. Oakland probably has higher incidences of motor vehicle accidents and gunshot injuries than Finland does, which could account for the higher percentage of traumatic fractures. Many studies have shown a higher incidence of hip fractures in urban populations than in rural areas [11] and it is hypothesized that this is partly due to decreased physical activity, poorer nutrition, higher rates of comorbidities and greater use of drugs and alcohol, but it could also be due to more MVA's and other traumatic injuries.

Age and Gender

Younger ages at the APMC

The average age of the women with fragility hip fractures in this study was 76.1 years and the men averaged 63.4 years. These ages are younger than those other studies have reported. The average age of men and women with all types of hip fractures combined in another US study by Bahl et al [33] was 76 years, however this includes a younger group of traumatic hip fracture patients. Wehren et al [35] found the average age at fragility hip fracture for white women to be 81 years; Kannus reported 78.9 years for the women and 69.0 years for the men in Finland[11] while Heikkinen and Huuskonen reported similar ages for Finland and the UK [34, 36]; the men in a Norwegian study averaged 76.6 years and the women 82.1 years [37]; in Australia, Port revealed that 60% of the fragility hip fracture patients were over 80 years of age [38]; in Canada the average age of men and women combined was 85.7 years [27].

These other populations studied may be living in areas better served than the APMC population studied here, and may generally be in better health. In contrast to our

study, most of the other studies were done with predominantly Caucasian populations. It is disconcerting that average ages of both men and women in the ACMC population were considerably younger than those in the other studies.

However, it is somewhat problematic to compare this hospital-based study with other community-based studies. It is possible that the older hip fracture patients are more likely to have Medicare and are thus able to utilize facilities other than the ACMC, resulting in the appearance that fragility hip fracture patients in the Highland area are younger than in other studies. In the future, it would be illustrative to compare this hospital-based study with another primary care facility in an equally underserved urban area.

Differences in age between men and women

There was a significant difference in the age at fracture between men and women in this study, with the men fracturing at younger ages, even among the fragility fracture groups. While Huuskonen and Kannus both reported younger ages among the male hip fracture patients in Finland, this finding is in contrast to some studies that report lower bone mineral density in women for any given age and fractures typically occurring 10-15 years later in men than in women[35].

Huuskonen et al [34] also found that among hip fracture patients, the men were significantly younger than the women (average age 74 years versus 79 years, $p < 0.001$). Kudlacek et al [39] also found that men experience vertebral fractures at a higher QCT level (a measure of BMD) than do women. It is possible, that despite womens' propensity to lose bone density faster and at younger ages than men, fractures don't occur until a lower BMD is reached, thus women's fractures occur later in life. To truly

examine fracture risk, it would be necessary to also record the number of falls that both men and women experience in order to gain a better idea of their true exposure to fracture risk. It is also possible that men are more susceptible to the negative effects of other chronic diseases on bone density. This could be a particularly significant factor in the APMC population where many patients suffer from comorbidities.

Ratio of men to women

The ratio of female to male fragility hip fracture patients observed in this study (1.87) is lower than the global European ratio observed in 2000 (3.7) [40] and than the worldwide ratio of 2.57 [11]. Our study found that 65% of the fragility hip fracture patients were women, while other comparable studies have found 68-75% of the fractures to be among women [11, 27, 33, 34, 37, 38]. Clearly, there are many genetic and environmental factors that affect males and females differently with regards to their risk of hip fracture. This study shows that in the Oakland area, male fragility hip fractures may occur more commonly than would be predicted. Perhaps bone mineral density in men is more readily affected by comorbidities than women's BMD.

Comorbidities and Mortality

Wehren et al [35] reported a similar proportion of women hip fracture patients with hypertension (54.6%) as we found in our study (53.6%), as well as cancer (18.0% vs our 21.4%) and a similar proportion of patients with a previous diagnosis of osteoporosis (16.8%) compared to our 17.9%. Our study found a higher proportion with cardiovascular disease (42.9%) than did Wehren (27.3%); but among men, we had lower rates of cardiovascular disease than Huuskonen et al found in Finland (60.2%)[34]. It is

likely that either the population that Highland Hospital serves has an overall higher rate of cardiovascular disease than other areas that have been studied, or that the difference in ages of the two fracture populations accounts for the differences in CV disease rates. However, it has been proposed that there are similar underlying pathological mechanisms between cardiovascular disease and osteoporosis. This is based on evidence that dyslipidemia, inflammation, and high levels of homocysteine and nitric oxide are associated with both diseases. Moreover, it has been shown that statins, used to inhibit atherogenesis may also stimulate bone formation while bisphosphonates, used in the treatment of osteoporosis, have been shown to inhibit atherogenesis. [41, 42]

Although the rate of entry into a skilled nursing facility was found to be quite high (31/43), this number also includes the patients who were only temporarily placed in a facility for rehabilitation after their hip fracture. We have no way of knowing how many of these patients resided permanently in a SNF after their hip fracture, but it may be considerably fewer. Two of the 43 fragility patients in this study died and both were male. Cree et al [43] reported a 3-month mortality rate of 8% and a 3-month institutionalization rate of 17% among the patients who were “of adequate cognitive status to be interviewed.” The study also found increasing age, and low mental status to be risk factors for both mortality and institutionalization and that males were at higher risk of mortality than females, even after controlling for age and mental status. Fransen et al. found a similar male gender bias in mortality and institutionalization [44]. It may be that when males suffer a hip fracture, they are already sicker with other comorbidities than women. Alternatively, males may suffer higher complication rates from surgery or during recovery from the hip fracture itself or, may suffer longer delays in being

diagnosed with osteoporosis because they are not considered to be “at risk.”

Lack of diagnosis and treatment

One 3 of the 43 fragility hip fracture patients had documentation in their charts indicating that they were given an anti-osteoporosis medication after their hip fracture. This rate is even lower than the rates of diagnosis and treatment found in many other studies, as summarized in the introduction. The lower rates of diagnosis and treatment at Highland may reflect differences in the quality of the documentation of patient care at Highland or a true difference in patient care due to the lack of an osteoporosis management program, less awareness regarding osteoporosis among practicing physicians, poorer outpatient follow-up in specialty clinics, or availability of DXA, among many other reasons. It is clear that the low rates of diagnosis and treatment of osteoporosis are not confined to underserved primary care centers such as Highland Hospital. Why is this such a widespread phenomenon?

Access to care

Some studies have demonstrated a lack of knowledge and/or education regarding osteoporosis. In the UK, a survey of 1153 general practitioners revealed that 88% of respondents rated their exposure to teaching about osteoporosis in medical school as “minimal/none” while 54.5% rated postgraduate exposure as “minimal/none.” Most alarming was that 2/3 of the respondents were unconvinced of the effectiveness of pharmacological interventions [45] despite the fact that this has been very well documented in the literature. Perhaps there are also misunderstandings about insurance coverage for BMD testing. Although it hadn’t been covered in the past, in 1998

Medicare began covering BMD tests for anyone with one of five diagnoses including postmenopausal women at risk for osteoporosis, patients with vertebral abnormalities, those on glucocorticoids, those with primary hyperparathyroidism and those with established osteoporosis for the purpose of monitoring efficacy of treatment[46]. Despite this seemingly adequate coverage, it may in reality be more difficult to get patients approved than it appears. There is currently a bill pending in California that would require that insurance companies doing business in CA to cover the cost of DXA[24]. Even if coverage is made available, the availability of DXA equipment is limited in many areas.

Physician responsibility

There also seems to be a question of whose responsibility it is to treat osteoporosis. It has been shown that primary care physicians are less likely to diagnose and treat osteoporosis than endocrinologists or rheumatologists [47, 48]. Yet Simonelli found that orthopedic surgeons, those who consistently interact with fragility hip fracture patients, place osteoporosis management in the responsibilities of the primary care physician[49].

It doesn't appear that receiving a hospitalist consultation improves osteoporosis treatment [29] or that referral to a primary care physician necessarily does either. Skedros et. al [50] implemented a referral program for fragility fracture patients to PCPs. The 14 orthopedic surgeons treating these patients sent letters to PCP's telling them of the patients' fractures and their concern about osteoporosis while the patients were also told to call the PCPs to make appointments. Only 30 of 69 patients ended up seeing a PCP within 6 months and of those, only 23.3% received a DXA scan and only 13.3%

were prescribed anti-resorptive therapy. 5 of the 14 orthopedic surgeons did not comply with the study and 7 did not consistently send out the referral letters to the PCPs or remind patients to make a PCP appointment. The authors hypothesized that osteoporosis is not considered to be in the realm of diseases that orthopedic surgeons handle and that there is a hesitancy to prescribe pharmacologic treatment due to adverse effects. They claim that there is “no mandate that orthopedic surgeons have training for the medical treatment of patients with senescent or metabolic bone diseases such as osteoporosis.”

In Australia, recommendations have been published to place more responsibility among orthopedic surgeons for the prevention of further fractures secondary to osteoporosis. Similarly, Great Britain has issued guidelines for the prevention and treatment of osteoporosis to be shared among several medical specialties, including orthopedic surgeons. Perhaps the US could benefit from similar guidelines, not just with regard to who ought to receive treatment, but also which physicians should be taking responsibility for managing such patients. In the US, several educational and interventional programs have been implemented to address the lack of management of fragility fracture patients including one at the Mayo Clinic in Rochester and one at Northwestern Memorial Hospital [47], but we have yet to see if these will prove effective.

Clinical Inertia

The failure within the health care system to diagnose and treat osteoporotic patients could be considered an example of “clinical inertia.” Clinical inertia is a phenomenon that has been described with respect to hyperglycemia, hypertension and lipid abnormalities, as “recognition of the problem, but failure to act” [51]. Recent

advances in research and technology now allow us to detect these “abnormalities” in patients that may not yet show any physical signs or symptoms of the existing problems. However, we know that the long-term sequelae of such diseases as hypertension and hypercholesteremia can be life-threatening and decent pharmacological interventions exist. Yet, many physicians fail to treat asymptomatic patients for these disorders, at a stage when the treatment may be most appropriate and effective. For example, only 53% of hypertensive patients are treated and only 17-23% of those with hypercholesterolemia are treated. While 73% of diabetic patients receive some form of treatment, a mere 33% reach acceptable levels according to the published guidelines[51]. Osteoporosis is one more disease on the list of disorders that are silent, yet treatable, until a critical stage is reached. Like hypertension and lipid abnormalities, the prevalence and consequences of low bone mineral density have been a relatively recent discoveries. Thus, it may partially be a matter of time before physicians become adequately educated on the diagnostic procedures and available treatments and we see an improvement in the quality of care.

Similar to blood cholesterol values, the BMD values are not something that is seen during a physical exam with a patient. The fact that they may be filed in a different section of the medical chart from the history and physical could prevent physicians from being adequately aware of those values and less likely to treat osteoporosis. The advent of portable, easy to use bone densitometry devices may improve this situation and make bone mineral density a value as easy to access as blood pressure. Until then, however, it will be important to alert physicians to the fact that BMD is another lab value crucial to a patient’s health.

Ageism

Another reason for the low treatment rates could be due to the age of fragility fracture populations in general. Terrie Wetle [52] suggests that physicians often make the mistake of assuming that because, in general, elderly populations have poorer prognoses, cognitive impairment and decreased quality of life, that all elderly individuals manifest these characteristics. Wetle cites evidence that we see a higher incidence of “inadequate treatment” of breast cancer among more elderly populations compared to younger populations and proposes that it is due to the attitude that the elderly have poorer prognoses anyway, so why bother to treat them? Another explanation is based on the belief that older patients do not tolerate aggressive treatments as well as younger patients. As a result, physicians are less likely to prescribe a medication or are more prone to prescribe a lower dose. This leads to a poorer outcome and only enhances the belief that the elderly don’t have as strong of an ability to overcome their illnesses. A similar phenomenon could be present among the predominantly elderly ACMC patient population in this study.

Other priorities

The ACMC fragility fracture patients are a group with a high number of comorbidities. Physicians may not recognize a high degree of need to treat osteoporosis when any given patient is also experiencing renal failure and heart disease and COPD. The perceived urgency of osteoporosis treatment may simply be quite low given the range of other diseases each patient is experiencing. An important question to answer is, does a focus on the treatment of other diseases necessarily preclude adequate diagnosis and treatment of osteoporosis? Given that other “silent” diseases have seen improvements in frequency and quality of care over time and given that osteoporosis

medications are typically not contraindicated for patients with a high number of comorbidities or those on many medications, I don't believe it should.

How to Improve Care

There are examples of changes in health care systems that have resulted in better post-fracture care. McLellan et al [53] designed a study that is an excellent example of what can be done to help improve the diagnosis and treatment of osteoporosis. A Fracture Liaison Service was created in Glasgow, UK in order to assure that more low-trauma fracture patients were evaluated and treated for osteoporosis. Once it was determined that orthopedists thought family practice physicians were responsible for evaluating bone mineral density and that family practice physicians were not actually equipped to run DXA tests or informed enough to choose a pharmacological treatment, Osteoporosis Specialist Nurses (OSNs) were designated to identify all patients with new low-trauma fractures. They did so by visiting hospital wards, fracture clinics and emergency departments. The OSNs determined who needed bone mineral density testing, who could be put on anti-osteoporosis medications immediately and who needed further blood testing to rule out secondary osteoporosis, all according to a flow chart, specifying protocols depending on fracture types, T-score guidelines and patient characteristics. They then compiled recommendations that were sent to the general practitioners. In 18 months, a total of 4,671 low-trauma fracture patients were seen and participated in the Fracture Liaison Service evaluation. 73.5% were assessed and or treated for osteoporosis. 14.9% declined assessment and/or treatment and 4.7% were still awaiting DXA. A total of 35.9% of the patients were given treatment: bisphosphonates

(26.1%), raloxifene (0.4%), HRT (2.5%) or Ca and vitamin D (6.9%). It was determined that 20.5% did not need treatment. These diagnosis and treatment rates are the highest of any published rates and should encourage the implementation of similar liaison services wherever possible.

Perhaps all the research that has provided evidence that osteoporosis is under-diagnosed and under-treated has already had some effect. Bahl et al showed that hip fracture patients at the University of Pittsburgh Medical Center were 2.25 times as likely to be diagnosed with osteoporosis in 2000 as they were in 1995 (18% vs. 4%) [33]. In 1995, only 2% were discharged with an antiresorptive agent while in 2000, 15% were given an antiresorptive. A study done at two university medical centers and one university-affiliated community hospital in New York and Philadelphia found that treatment rates improved steadily each year from 11% in 1997 to 29% in 2000 ($p < 0.001$) [54]. In all likelihood, these changes are related to the approval of alendronate that occurred in 1996.

Limitations of this study

This study was considerably limited by the number of hip fracture charts I was able to review and by the missing data in those charts. Due to the low number of complete charts and the rarity of documentation of osteoporosis management, we were unable to analyze the characteristics of the patients who did receive some type of care. The general characteristics of the hip fracture patients may only be applicable to the population that the ACMC serves; however, it is likely that other urban medical centers could have similar findings.

Since all of the data in the study was obtained solely from information in the charts, it is likely to be incomplete with regard to comorbidities, diagnostic evaluations, family history information, etc. Only the current medications were recorded and any supplements or medications that the patient failed to report were not included. Any patients who were diagnosed and/or treated for osteoporosis after their discharge from the hospital were not recognized in this study. Thus, both the mortality rate and the diagnosis and treatment rates were probably underestimated.

In this study, we used fragility fractures as a marker for osteoporosis, however this has limitations. Some of the traumatic fractures in this study may actually have occurred in the presence of or due to underlying osteoporosis. Likewise, some “fragility fractures” may have occurred in people with normal BMD. By categorizing patients into fragility and traumatic fractures, we have a less accurate identification of the truly osteoporotic patients than we would if bone mineral density scans were done.

Implications of this Study

This study has indicated that at Highland Hospital, the great majority of fragility hip fracture patients are not diagnosed with or treated for osteoporosis. There may be a need to appropriate the responsibility of the management of osteoporosis to a specific specialty of physicians, so that patients do not “fall through the cracks” of a disorganized medical system. Perhaps more important that assigning responsibility is simply a need to increase awareness among all physicians who may encounter fragility fracture patients. It is imperative that physicians be educated on the risk factors of osteoporosis, the consequences of untreated disease and the high risk of mortality and morbidity that

fractures carry. This study found a wide range of ethnicities and ages in the hip fracture patients and a considerable proportion of them were men. Osteoporosis is often thought of as the elderly white woman's disease, when in actuality, the Highland hip fracture population spans a much wider range of patients, in terms of gender, age and ethnicity. Educational programs ought to emphasize this diversity of fragility fracture patients.

A high number of comorbidities was also found among the fragility hip fracture patients. Regardless of whether these comorbidities are a causal factor in the development of osteoporosis, this finding suggests that perhaps it might be reasonable to consider screening all patients who are hospitalized with a high number of comorbidities for low bone mineral density, or at least those with cardiopulmonary disease and osteoporosis risk factors. Further studies would want to investigate the cost-effectiveness of such a screening, to determine which comorbidities are most closely associated with the increased risk of fracture and if any of those conditions are causally related to osteoporosis.

Educational programs also need to stress that despite the existence of several important comorbidities that require intensive management, this does not override the necessity to treat osteoporosis nor does it preclude the use of anti-resorptive medications. Osteoporosis may initially be an 'invisible' disease process to the patient, but with the availability of bone densitometry, it should no longer be so invisible to physicians. Because of the potential severity of resultant fractures, osteoporosis should certainly not be so disregarded by the physicians involved in fracture care.

In this study, we found a high number of comorbidities among fragility hip fracture patients presenting to Highland Hospital. Although this study was not designed

to determine whether there was any causal effect of these comorbidities on decreased bone mineral density or fracture risk, it is known that other systemic diseases affect BMD. This is referred to as “secondary osteoporosis” in the literature. Most of the diseases that can cause secondary osteoporosis deserve more attention to elucidate the pathophysiology involved and effective preventive measures.

Pulmonary disease is one of the comorbidities observed in this study whose association with osteoporosis has been considered in the literature, but analyzed quantitatively in few large studies. The following study is meant to address the association between pulmonary disease and BMD and fracture incidence.

THE ASSOCIATION BETWEEN PEAK EXPIRATORY FLOW, SELF-REPORTED COPD AND THE RATE OF BONE LOSS IN OLDER WOMEN

BACKGROUND

Chronic obstructive pulmonary disease (COPD) has been shown to be associated with decreased bone mineral density (BMD) and also with increased incidence of vertebral fractures in both human and animal models [55-57]. Up to 60% of patients admitted to the hospital with COPD exacerbations have been shown to have osteoporosis [58] and COPD patients have shown a fourfold increase in severe vertebral fractures [59]. COPD could cause decreased BMD in several ways, including weight loss, reduction in physical activity, nutritional depletion, decreased sunlight exposure, hypogonadism, hypercapnia, increased corticosteroid use and the hypercatabolic effects of the inflammatory process [55-60]. It has also been suggested that changes in balance and

coordination are associated with COPD, which could lead to an increase in fracture incidence regardless of the effect on BMD [61].

The evidence that COPD is associated with BMD is not conclusive, however, as other studies have failed to find an association between COPD and BMD [62].

Furthermore, many of the previously published studies had fewer than 200 subjects, few objectively quantified the degree of pulmonary obstruction and there have been no published prospective studies that have examined the rate of BMD loss as an outcome. This study will quantify lung function using percent predicted peak expiratory flow and will examine BMD loss in a large sample of older women with and without lung disease.

Peak expiratory flow (PEF) is the “largest expiratory flow achieved with a maximally forced effort from a position of maximum inspiration[63]” and is a measure of the degree of pulmonary obstruction and lung function. The British Thoracic Society guidelines do not recommend the use of PEF for the diagnosis of COPD because it is more variable and not as sensitive to mild airflow limitation as forced expiratory volume (FEV_1), which is the gold standard in pulmonary function testing [64]. However, PEF is a simple measure to take, has a strong correlation with FEV_1 [65] and is commonly used in the monitoring of asthma, another common obstructive lung disease. Llewellyn *et al* found that the average difference between FEV_1 and PEF in COPD patients was only about 7% [66], less than the difference seen between FEV_1 and PEF in asthmatic patients. For clinical evaluation, rather than use the absolute value of PEF, which is dependent on age and body size, a person’s predicted PEF is usually calculated, and their lung function is determined by the percent predicted PEF that they can achieve.

This study examines the rates of BMD loss at the femoral neck, trochanter and

total hip in women with and without a self-reported pre-existing diagnosis of COPD and longitudinally examines the effect of percent predicted PEF on bone loss at these three hip sites. This may help identify people at greater risk for osteoporosis, help us understand more about risk factors for bone loss and the data may eventually help us explore common therapeutic options.

METHODS

Subjects

The Study of Osteoporotic Fractures (SOF) is an observational study that included 9,704 participants recruited at four clinical centers in 1986, to examine risk factors for osteoporotic fractures in elderly women. Participants were recruited from mailings to women over age 65 identified from community-based listings, such as memberships of large health maintenance organizations, and clinic visits have occurred approximately every two years since the baseline exam. Clinical centers for the study are located in Baltimore, Maryland (University of Maryland); Portland, Oregon (Kaiser Center for Health Research); Minneapolis, Minnesota (University of Minnesota); and the Monongahela Valley near Pittsburgh, Pennsylvania (University of Pittsburgh). The San Francisco Coordinating Center (University of California, San Francisco and California Pacific Medical Center Research Institute) coordinates the study. Appropriate institutional review boards approved the SOF study and study participants provided written informed consent.

The Study of Osteoporotic Fractures (SOF) has been approved by the University of California, San Francisco CHR, current approval number # H378-00742-19. The

study has also been approved by IRBs at each institution where subjects were recruited and examined as well as by the University of California, Berkeley, project # 2004-6-197.

No new measurements on the SOF participants were completed for this protocol. None of the 18 HIPPA identifiers listed on the Committee for Protection of Human Subjects, UC Berkeley website will be given with the data set. All variables will remain unidentified.

PEF and COPD definitions

Participants included in this analysis are the 4088 women who completed PEF and BMD testing at Visit 4 (1992-1994) and had follow-up BMD testing at Visit 6 (1997-1998).

Peak Expiratory Flow Measurement

PEF was measured at Visit 4 with a Mini-Wright peak flow meter (L/min). Each woman had three trials and the maximum reading was used in the analysis. Predicted Peak Flow (PEFR) was calculated with the following formula:

$$\log_e(\text{PEF predicted}) = 0.376 \log_e(\text{age}) - 0.0120(\text{age}) - 58.8/\text{height} + 5.63$$

where age is in years and height is in cm [67].

Participants were categorized into four groups based on their percent predicted PEF. These categories are based on the International Consensus Report on the Diagnosis and Management of Asthma and the Global Strategy for Asthma Management and Prevention which defines <30%, 30-60%, 60-80% and >80% predicted PEF as life-

threatening, severe, moderate and mild asthma[68]. PEF guidelines for COPD have not yet been established.

Also at Visit 4, participants reported “Has a doctor ever told you that you had chronic obstructive lung disease (COPD), chronic bronchitis, asthma or emphysema?”

Bone Mineral Density Measurement

BMD was measured at the femoral neck, trochanter and total hip by dual-energy x-ray absorptiometry with Hologic QDR-1000 scanners (Hologic, Inc. Bedford, MA) at Visit 4 and Visit 6. Change in BMD is expressed as percent change in BMD. The mean coefficient of variation is 1.2% for the femoral neck [69]. Measurement method details, densitometry quality control procedures and the precision of the measurements have been published elsewhere [69-71].

Other Covariates

Other variables considered in this analysis were taken from various visits and include the following:

From Visit 1: age at menopause and pack-years of smoking history (packs/year x number of years of smoking)

From Visit 2: age at menarche

From Visit 3: estrogen use in the past 30 days and use of “prednisone pills, cortisone pills and other steroid pills” in the past 12 months

From Visit 4: age, weight (kg), height (cm), exercise (women were asked, “do you walk for exercise?”), current/past/never smoking habits, drinks/week in past 30 days, self-reported COPD, baseline BMD, grip strength (kg), current beta-blocker use, current use of inhaled corticosteroids and self-rated health status (participants were asked, compared

to other people your age, how would you rate your overall health? 1=excellent, 2=good, 3=fair, 4=poor, 5=very poor). More details on these measurements are described elsewhere [8, 70].

Statistical Analysis

Baseline characteristics were compared between women with and without a self-reported diagnosis of COPD at visit 4, and also across women in 4 different categories of percent of predicted peak expiratory flow (>80%, 60-80%, 30-60% and <30%). Two-sided t-tests allowing for unequal variances between variables were used for continuous variables in the COPD comparisons, and the ANOVA test was used for the PEF category comparisons. Chi-square tests were used for all categorical variable comparisons.

Linear regression analysis included a self-reported diagnosis of COPD at Visit 4 as the independent variable and the percent change in BMD between visit 4 and 6 as the dependent variable. We also examined the association between percent predicted PEF at visit 4 and the percent change in BMD in separate models. For each analysis, three groups of women were separately analyzed: all women, women who have never smoked (labeled “non-smokers”) and women who have some smoking history (labeled “smokers”). Within each group, several models were constructed: age adjusted; age, weight and weight loss adjusted, and a multivariate model. The multivariate model was created using forward stepwise selection and the following variables were considered for inclusion: age, weight at V4, weight loss/gain from V4 to V6, height, years since menopause, age at menopause, age at menarche, current smoking (yes/no), pack-years of smoking history, alcohol use, grip strength, walks for exercise, self-rated health status,

oral and inhaled corticosteroid use in the past 12 months, current beta-blocker and estrogen use, baseline femoral neck, total hip and greater trochanter BMD. Variables that were not significant in the model and did not increase the R-squared value were not included. When two models seemed equally plausible, the R-squared value was used to determine which model was a better fit for the data. Additional analyses were run excluding estrogen users at Visit 4.

A p-value of 0.05 was considered significant. Analyses were conducted using STATA 7.0 and SAS version 9.1.

RESULTS

Descriptive Data

A total of 6688 women were queried regarding medical conditions and had measurement of PEF and hip BMD at the 4th exam; of these, 4088 had repeat measurement of hip BMD at a 6th exam, an average of 4.45 ± 0.55 years later. At Visit 4, the mean age was 76.7 ± 4.8 years. A total of 869 (13%) reported previously ever having received a diagnosis of COPD, and the mean percent predicted PEF was $84.4 \pm 20.5\%$. The mean total hip BMD at visit 4 was $0.749 \text{ g/cm}^2 \pm 0.129$, and mean change in total hip BMD between visit 4 and visit 6 was $-3.10\% \pm 5.88$. A comparison of baseline characteristics between the 4 pulmonary function groups is given in table 1.

Table 1. Baseline characteristics of women in 4 pulmonary function categories.

	Normal PEF>80% (n=2805)	Moderate PEF 60-80% (n=909)	Severe PEF 30-60% (n=341)	Life- threatening PEF<30% (n=33)	p-value ⁱ
Body Characteristics					
Age at baseline (yr)	76.2	77.0	77.8	78.1	<0.001
Current weight (kg)	67.4	65.1	63.3	59.6	<0.001
Weight change, V4 to V6 (%)	-1.6	-2.1	-2.4	-3.2	0.040
Height (cm)	158.9	157.5	156.8	156.8	<0.001
Age at last period	48.4	47.8	47.5	47.0	0.001
Years since menopause	27.9	29.3	30.4	31.3	<0.001
Age at Menarche	13.0	13.0	13.1	13.0	0.877
Grip Strength (kg)	18.8	17.3	16.4	14.8	<0.001
Self-rated good health status (% reporting excellent or good)	84.90	76.72	72.22	58.70	<0.001
Follow up time, V4 to V6 (years)	4.45	4.45	4.46	4.56	0.638
Lifestyle					
Any past smoking history (%)	34.66	38.98	51.57	68.48	<0.001
Pack-years (packs/day*yrs smoked)	7.56	10.89	17.27	28.85	<0.001
Drinks/week in past 30 days	1.2	1.5	1.7	1.1	<0.001
Takes walks for exercise (%)	54.2	45.8	38.3	25.0	<0.001
Medications					
Corticosteroids	3.2	4.8	8.4	10.9	<0.001
Inhaled corticosteroids	0.7	2.4	6.7	10.9	<0.001
Beta-blockers	13.2	14.7	14.5	8.7	0.225
Estrogen use	16.9	13.0	14.4	9.8	0.001
Severity of COPD					
Predicted peak flow (L/min)	393.2	389.6	386.8	386.1	<0.001
Self-reported COPD, prior to V4 (%)	5.5	12.6	26.6	45.6	<0.001
BMD at Visit 4					
Baseline Femoral neck BMD (g/cm ³)	.648	.624	.622	.607	<0.001
Baseline Trochanteric BMD (g/cm ²)	.575	.546	.533	.515	<0.001
Baseline Total hip BMD (g/cm ³)	.760	.729	.716	.697	<0.001
% Change in BMD Visit 4 to Visit 6					
Femoral neck BMD change (%)	-2.0	-2.6	-3.4	-5.6	<0.001
Trochanteric BMD change (%)	-2.5	-3.6	-3.7	-6.7	<0.001
Total hip BMD change (%)	-2.7	-3.8	-4.0	-6.7	<0.001

i. P-values from unadjusted F-tests for the ANOVA for continuous variables; chi² test for categorical variables.

Association between COPD and BMD

There were no significant associations ($p<0.05$) between self-reported COPD and percent change in BMD at any of the hip BMD sites.

Association between PEF and BMD

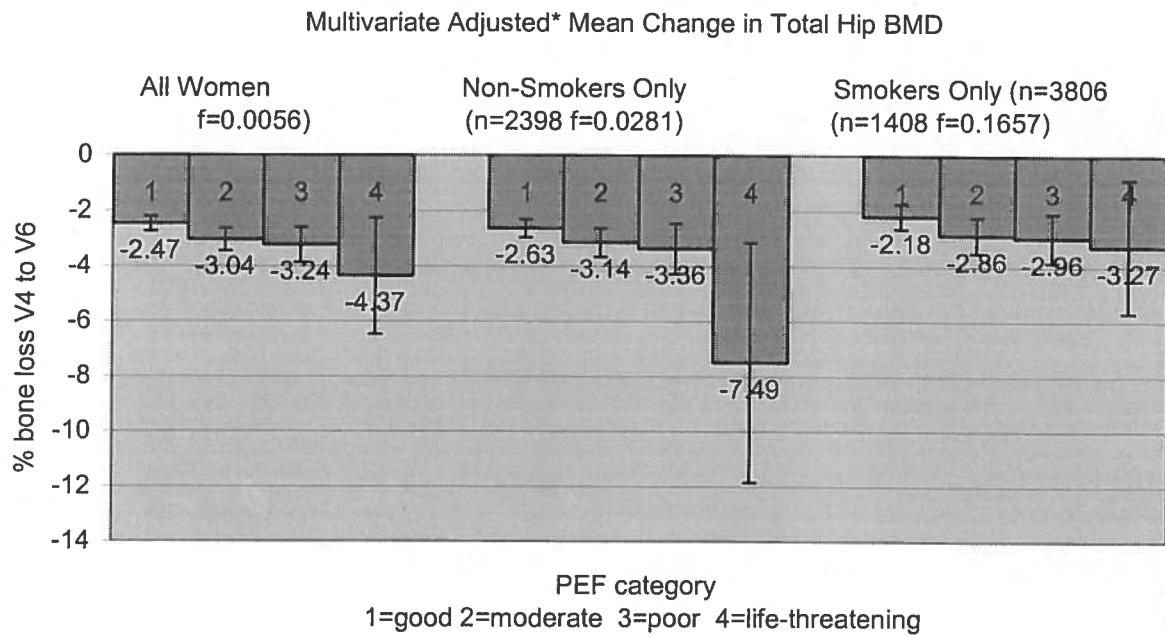
There is a significant difference in bone loss across the four pulmonary function categories in all of the models for the total hip, with the exception of the multivariate adjusted model for smokers only (Table 2). This difference across groups was slightly attenuated in the fully adjusted model and in the group of women who have a history of smoking. Analysis of the femoral neck and trochanter sites yielded similar results (not shown).

Table 2: Adjusted Mean Change in Total Hip BMD/Year by Lung Function Category

Adjusted Mean Change in Total Hip BMD/Year by Lung Function Category						
		Normal PEF >80%	Moderate PEF 60-80%	Poor PEF 30-60%	Life- threatening PEF <30%	F value
All women	unadjusted (n=4088, $r^2=0.01$)	-0.61	-0.85	-0.89	-1.50	<0.001
	age, weight, weight loss adjusted (n=4015, $r^2=0.12$)	-0.50	-0.65	-0.68	-1.16	<0.001
	multivariate adjusted* (n=3806, $r^2=0.12$)	-0.56	-0.68	-0.73	-0.98	0.0056
Non-smokers Only	unadjusted (n=2535, $r^2=0.01$)	-0.64	-0.88	-0.91	-2.60	<0.001
	age, weight, weight loss adjusted (n=2495, $r^2=0.11$)	-0.55	-0.68	-0.72	-2.42	0.0229
	multivariate adjusted* (n=2398, $r^2=0.11$)	-0.59	-0.70	-0.76	-1.68	0.0281
Smokers Only	unadjusted (n=1533, $r^2=0.01$)	-0.56	-0.80	-0.89	-1.15	<0.001
	age, weight, weight loss adjusted (n=1520, $r^2=0.14$)	-0.41	-0.61	-0.62	-0.68	<0.001
	multivariate adjusted* (n=1408, $r^2=0.16$)	-0.49	-0.64	-0.66	-0.73	0.1657

*adjusted for age, weight, weight loss/gain V4 to V6, age at menarche, baseline BMD at V4, pack-years smoking history, use of estrogen and beta-blockers at V4, and use of steroids, prednisone or cortisone pills in the past 12 months.

Figure 1: Multivariate adjusted mean change in total hip BMD over the study period (4.45 years).



In multivariate models using percent predicted peak flow as continuous variable, each standard deviation decrease in percent predicted peak flow was associated with a .081% further decrease in BMD/year ($p < 0.001$). This association was also significant for non-smokers (0.09% $p = 0.002$) and for smokers only (0.07% $p = 0.037$). Analysis of the femoral neck and trochanter yielded similar results, except that the association was not significant in the smokers group. Multivariate models included age, weight, weight gain/loss, beta blocker, pack years, estrogen, steroid use, and baseline BMD. All other baseline variables listed in Table 1 were insignificant in the models.

DISCUSSION

Decreasing lung function across four categories was shown to be significantly associated with greater bone loss in three different hip BMD sites in this study. This

association was still significant after controlling for exercise, corticosteroid use, and weight loss, three commonly hypothesized links between bone loss and lung disease. However, because exercise was found not to be significant in the final model, it was excluded. After controlling for weight, weight loss/gain, age at menarche, pack-years of smoking history, baseline BMD and use of estrogen, steroids and beta-blockers, women with good pulmonary function (percent predicted PEF >80%) lost an average of 0.56% BMD at the total hip per year while women with moderate lung function (percent predicted PEF 60-80%) lost 0.68%/year, women with poor lung function lost 0.73%/year and women with life-threatening lung function (PEF<30%) lost an average of 0.98%/year.

Although the increased bone loss across lung function categories was statistically significant, it remains to be determined if the association is clinically significant. Bone loss of 5% or greater per year mandates treatment [72], but the average rates of bone loss observed in even the poor lung function groups in this study did not reach such severity. In any given individual, a 2% difference in two different BMD readings can be considered within the accuracy of the dual x-ray absorptiometry machines [24], and does not necessarily raise concern. However, if the increased bone loss seen in women with poor lung function increases their fracture incidence, then this association should be considered clinically significant. Additionally, it has already been shown that women with lung disease have lower baseline BMD [73], so an accelerated loss in women with lung disease is more critical than in healthy women.

Systemic inflammation may be partly accountable for the link between COPD and bone loss. A meta-analysis by Gan *et al* [74] showed that people with COPD have higher

serum levels of several inflammatory markers, including C reactive protein, fibrinogen, leukocytes, and TNF- α . TNF- α is known to be associated with increased protein breakdown and to stimulate bone resorption [75, 76] while IL-6 stimulates formation of osteoclasts, the cells responsible for bone resorption [77]. It is hypothesized that either the inflammatory response seen in the lungs overflows into the systemic circulation or that an underlying constitution puts some people at risk for both pulmonary and systemic inflammation.

At all three hip BMD sites, in all models, the relationship between lung function and BMD was stronger among non-smokers than among women who have some smoking history. Women with no history of smoking and life-threatening pulmonary function had the greatest bone loss of any group. It appears that lung disease in the absence of smoking may indicate severe systemic illness or inflammatory processes that may lead to both obstructive lung disease and considerable bone loss. In contrast, increasing severity of lung disease in smokers does not appear to lead to increased bone loss. Perhaps smokers, regardless of measured lung function, will have a certain level bone loss. Additionally, those who report a smoking history are more likely to have poorer lung function; perhaps the gradient of lung function amongst smokers is less, and we are therefore limited in our ability to detect an effect.

In this study, COPD was not found to have an association with rate of bone loss. A self-reported diagnosis of COPD may not be as sensitive a measure of lung function as PEF. Some women who received a diagnosis of asthma as children, but are currently healthy, may have reported COPD; additionally, women who currently have COPD may not yet have been diagnosed by a physician.

Another variable commonly associated with both lung disease and BMD loss is decreased exercise [8]. In this study, our adjustment for exercise was crude: women were asked at visit 4 “do you walk for exercise?” The variable was not significant in any of the models. Better ascertainment of exercise level and intensity exercise may allow for description of the effects of exercise on the lung function/bone loss relationship.

There are a few other important limitations in our study. First, regarding the PEF measures: the fact that height differs between those with high and low percent predicted PEF values raises two concerns. One, perhaps the formula for generating the predicted peak flow over predicts PEF for shorter people. Two, shorter women may be more prone to pulmonary obstruction. It is known that vertebral fractures caused by low BMD lead to decreased height and also restrict lung function. Thus, if women with pre-existing vertebral fractures were included in the analysis, it could lead to an overestimation of the association between BMD loss and lung function.

PEF may not be the ideal marker to use for pulmonary disease, as it tends to be less sensitive than FEV_1 . It is known to be highly dependent on the effort expended by the patient [63]. Thus, both motivation and respiratory muscle strength will affect the reading and, unlike for FEV_1 , there is no way to ascertain if the patient has “performed the maneuver correctly [78].” PEF tends to correlate with changes in the size of only the large airways while FEV_1 is more associated with changes in both large and medium airways [63] and can differentiate between restrictive and obstructive pulmonary disease patterns. There is also a diurnal variation in PEF that reaches up to 50% in asthmatic patients [63]. If the time of the PEF test was not held constant across the subjects in SOF, this could easily confound the results. Furthermore, PEF tends to indicate disease

when FEV₁ would fall in a normal range [66] so some patients may have been categorized as having more severe pulmonary disease than they have in actuality. Since there are no published guidelines to determine COPD severity based on PEF, we used the guidelines for asthmatic patients. Using different parameters may have led to different results. Ideally, a similar study could be carried out with FEV₁ measurements for comparison. However, PEF is an easy test to administer and Butcher et al [61] found that there was a stronger association between PEF and functional balance measures than for FEV₁. So even though FEV₁ may be a more accurate measure for pulmonary disease severity, PEF might be more appropriate measure of overall functional performance, especially in the elderly.

Additionally, the R-squared values for the multivariate models presented here range between 0.11 and 0.16, indicating that the variables included predict only 11–16% of the rate of bone loss observed. This is consistent with other research; specifically, a cross-sectional study with men designed to identify the key variables associated with BMD found that despite including dozens of variables, only 19% of BMD at the femoral neck was explained by the resulting regression model and 13% of bone loss at the spine(unpublished) [72]. These percentages indicate that there are still many unidentified factors affecting BMD and the rate of bone loss. Another similar study in white women reported r-squared values of 0.39-0.40 for multivariate regressions predicting femoral neck BMD [79].

Another limitation is that some of the variables used in the multivariate regressions were taken from data obtained at earlier visits, a fact that could introduce bias into the data if women had since changed their habits. Estrogen and steroid use

information were ascertained at visit 3 and the number of pack-years a woman had smoked was obtained at visit 1, approximately 1-2 years and 4-6 years prior to Visit 4, respectively.

To our knowledge, this is the first report of an association between accelerated bone loss at the hip and compromised respiratory function, as measured by PEF, in elderly women. When the women were divided into those who have ever smoked and those who have never smoked, the association held only in the group of non-smokers, and was independent of corticosteroid use, weight, weight loss, age, baseline BMD, and estrogen or beta-blocker use. Pack-years of smoking history appears to explain much of the differences in rate of bone loss seen in smokers across lung function categories, since controlling for pack-years rendered the lung-function category predictor insignificant. Lung disease in the smoking group may have a separate etiology which is not as closely associated with bone loss, while lung disease among the non-smokers may have an etiology which is common to both lung function and bone loss. Regardless of the mechanism of association between PEF and bone loss, respiratory disease may indicate an increased risk of bone loss and fracture. Women with severe respiratory disease may be considered for regular measurement of BMD, as they are not only are they at risk for low baseline BMD, but also for accelerated bone loss.

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