Bone and Mineral
Prevalence of osteoporosis:

- **Over 10 million** US adults have osteoporosis.
- **Over 34 million** US adults have low bone density.

Vitamin D deficiency affects:

- **8% of US adults (age 20+ years)**
- **24% of US youth (age 11-18 years)**

Sex differences:

- **3x** higher in females than males
- **2x** more common in females than males

Lifetime risk of osteoporosis-related fractures:

- Approximately the same for adult males and females.

Cost burden:

- **$17 billion** direct costs associated with osteoporosis-related fractures in 2005.

Source:

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Mission Statement of the Endocrine Society
The mission of the Endocrine Society is to advance excellence in endocrinology and promote its essential and integrative role in scientific discovery, medical practice, and human health.

About Endocrine Facts and Figures
Endocrine Facts and Figures is a compendium of epidemiological data and trends related to a spectrum of endocrine diseases. The data is organized into nine chapters covering the breadth of endocrinology: Adrenal, Bone and Mineral, Cancers and Neoplasias, Cardiovascular and Lipids, Diabetes, Hypothalamic-Pituitary, Obesity, Thyroid, and Reproduction and Development.

All data is sourced from peer-reviewed publications, with an additional round of review by a group of world-renowned experts in the field. Additional oversight from the Endocrine Facts and Figures Advisory Panel ensured fair and balanced coverage of data across the therapeutic areas.

The first edition of Endocrine Facts and Figures emphasizes data on the United States. Future updates to the report will include additional data for other countries.

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For More Information
For more information, updates, and the online version of this report, visit: endocrinefacts.org

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Disclaimer
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I Overview

This chapter presents current available data on the epidemiology of bone and mineral diseases including osteoporosis, low bone mass (osteopenia), vitamin D deficiency, primary hyperparathyroidism, primary hypoparathyroidism, hypercalcemia, hypocalcemia, Paget’s disease of the bone, and phosphate disorders.

1.1 Epidemiology

According to the World Health Organization (WHO), in 1994 osteoporosis affected more than 75 million people in the United States (US), Europe, and Japan.\textsuperscript{1}

In 2010, Watts et al. reported that of Americans with osteoporosis and low bone mass, 80\% were women (mostly postmenopausal), and that at age 50, the projected lifetime risk of fractures was 39\% in Caucasian women and 13\% in Caucasian men.\textsuperscript{2} The National Health and Nutrition Examination Survey (NHANES) III (1988-94) estimated that by age 60 years, half of Caucasian US women have osteopenia or osteoporosis. Based on male bone density comparison values, 1-2 million men were estimated to have osteoporosis, and 8-13 million were estimated to have osteopenia.\textsuperscript{3} Table 1 shows data on the incidence of osteoporotic fractures as compared to other disorders in women.\textsuperscript{4-6}

1.2 Cost Burden

In 2005, there were over 2 million fractures associated with osteoporosis in the US. This number translated to a cost of approximately $17 billion, with men accounting for 29\% of the fractures and 25\% of the costs.\textsuperscript{4} In addition, in Europe and the Americas osteoporotic fractures accounted for 2.8 million disability-adjusted life years (more than those caused by hypertension and rheumatoid arthritis but less than those caused by diabetes mellitus or chronic obstructive pulmonary diseases).\textsuperscript{7} Table 2 presents data on the cost breakdown of osteoporotic fractures in the US.

By 2025, it is estimated that both the incidence and costs associated with osteoporosis will rise by 50\%, with over

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Table 1

<table>
<thead>
<tr>
<th>DATA SOURCE</th>
<th>POPULATION</th>
<th>DISORDER</th>
<th>INCIDENCE</th>
<th>REFERENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>US Census Bureau; US Nationwide Inpatient Sample Database</td>
<td>US Population</td>
<td>Fractures</td>
<td>1.4 million</td>
<td>Burge et al. 2007\textsuperscript{4}</td>
</tr>
<tr>
<td>American Heart Association</td>
<td>Total new and recurrent strokes among all US women</td>
<td>New strokes</td>
<td>373,000</td>
<td>Rosamond et al. 2007\textsuperscript{2}</td>
</tr>
<tr>
<td>American Heart Association</td>
<td>Total new and recurrent myocardial infarction among all US women</td>
<td>Heart attacks</td>
<td>345,000</td>
<td>Rosamond et al. 2007\textsuperscript{2}</td>
</tr>
<tr>
<td>National Cancer Institute</td>
<td>New cases in the US</td>
<td>Invasive breast cancer</td>
<td>213,000</td>
<td>American Cancer Society. 2006\textsuperscript{6}</td>
</tr>
</tbody>
</table>

Abbreviations: US, United States

Table 2

<table>
<thead>
<tr>
<th>TOTAL NUMBER OF FRACTURES</th>
<th>DIRECT COSTS*</th>
<th>COST BREAKDOWN</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 million (71% in women)</td>
<td>$17 billion</td>
<td>Inpatient care: 57%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Long-term care: 30%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Outpatient care: 13%</td>
</tr>
</tbody>
</table>

Source: Burge et al. 2007\textsuperscript{4}

Note: *Number does not reflect lost productivity, unpaid caretaker time, transportation costs, and social services.
87% of the increase expected among those age 65-74 years. Table 3 summarizes the cost of osteoporotic fractures in the US, by sex, age, and race/ethnicity.

### Table 3
Cost of osteoporotic fractures among United States adults age 50 years and older, by sex, age group, and race/ethnicity, 2005.

<table>
<thead>
<tr>
<th>Race/Ethnicity</th>
<th>Age 50-64 years</th>
<th>Age 65-74 years</th>
<th>Age 75-84 years</th>
<th>Age ≥85 years</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>WOMEN</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>$1.4</td>
<td>$1.6</td>
<td>$4.6</td>
<td>$5.1</td>
</tr>
<tr>
<td>African American</td>
<td>$0.5</td>
<td>$0.5</td>
<td>$0.5</td>
<td>$0.3</td>
</tr>
<tr>
<td>Hispanic</td>
<td>$0.5</td>
<td>$0.5</td>
<td>$0.3</td>
<td>$0.2</td>
</tr>
<tr>
<td>Other</td>
<td>$0.3</td>
<td>$0.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>MEN</strong></td>
<td>$0.8</td>
<td>$0.7</td>
<td>$1.3</td>
<td>$1.4</td>
</tr>
</tbody>
</table>

Source: Burge et al. 2007

### 1.3
**SCIENTIFIC BREAKTHROUGHS**

#### 1.3.1
From Mechanisms of Bone Metabolism to Therapeutic Applications

Table 4 summarizes the many recent and emerging therapies targeting bone metabolism.

#### 1.3.2
The Hormonal Interface Between Bone and Other Organ Systems

Besides its mechanical function, bone is itself an endocrine organ. For example, undercarboxylated osteocalcin is secreted by osteoblasts and has been implicated in the regulation of insulin secretion, insulin intolerance, and glucose homeostasis in patients with type 2 diabetes mellitus or on a high-fat diet. Bone has also been associated with a lipotoxicity-associated loss of insulin receptors, resulting in insulin resistance. Similarly, others have shown that osteocalcin enhances the synthesis of adiponectin, which is involved in glucose regulation and the breakdown of fatty acids in animals fed a normal diet.

### Table 4
Summary of scientific breakthroughs in bone metabolism and potential therapeutic applications.

<table>
<thead>
<tr>
<th>THERAPEUTIC TARGET</th>
<th>DESCRIPTION</th>
<th>STATUS</th>
<th>REFERENCE</th>
</tr>
</thead>
</table>
| RANKL              | RANKL is a cytokine that regulates skeletal metabolism. | Denosumab, a RANKL inhibitor, was first approved by the US FDA in 2010 for postmenopausal osteoporosis; now it has additional approved indications. | Takayanagi. 2009
| Sclerostin         | Sclerostin is a negative regulator of bone mass; inhibiting sclerostin increases bone formation. | An antibody that targets sclerostin (decreasing endogenous levels of sclerostin while increasing BMD) is currently in phase-III clinical trials. | Compton and Lee. 2014
| Cathepsin K        | Cathepsin K is produced by activated osteoclasts; it degrades type 1 collagen and, thus, helps to initiate the bone resorption process. | Cathepsin K inhibitor phase 3 clinical trials have been completed. | Costa et al. 2011
| PTHrp              | PTHrp regulates endochondral bone development and can simulate some of the actions of parathyroid hormone. | Abaloparatide, a synthetic PTHrp analog, phase 3 clinical trial has been completed. | Leder et al. 2014

Abbreviations: RANKL, receptor activator of nuclear factor κB ligand; US, United States; FDA, Food and Drug Administration; PTHrp, parathyroid hormone-related protein; BMD, bone mineral density
In addition to its effects on metabolism, osteocalcin appears to act also via the testis to regulate reproductive functions in male mice through its effects on testosterone production.17

1.3.3

**Intercellular Communication Systems Among Bone Cells (Osteoblasts, Osteoclasts, and Osteocytes)**

Research has indicated that the continuous modeling and remodeling of bone is controlled by signals exchanged between effector cells. Specifically, osteoblast-lineage cells—including osteoblast progenitors, matrix-producing osteoblasts, bone-lining cells, and matrix-embedded osteocytes—stimulate osteoclast differentiation by producing inhibitory and stimulatory factors.18

Until recently, osteocytes have been considered passive and metabolically inactive cells. However, current evidence indicates that osteocytes are multifunctional cells that play important roles in the homeostasis and/or regulation of bone mineral, phosphate, and calcium metabolism. Osteocytes also coordinate the skeleton’s response to mechanical loading. They survive for decades within the bone matrix, which makes them among the body’s longest-living cells.19 These processes require tight control of the bone remodeling process, which involves ensuring the availability of mesenchymal precursors and local signaling molecules that promote differentiation in the osteoblast lineage.20 Furthermore, during their development from pluripotent precursors to matrix-embedded osteocytes, osteoblast-lineage cells produce regulatory signals that control the differentiation and activity of bone-forming osteoblasts and bone-resorbing osteoclasts.21

1.3.4

**New Skeletal Imaging Modalities and their Clinical Applicability**

In addition to probing the signaling pathways by which bone is modeled or remodeled, advancements in skeletal imaging are also noteworthy. These are summarized in Table 5.

## II OSTeOPOrOSIS

Osteoporosis is a progressive disorder of bone, defined as a condition resulting in an increased risk of skeletal fractures due to a reduction in bone mass and deterioration of skeletal microstructure.27 It is characterized by low bone mass, microstructural deterioration, and porous bone, which collectively are associated with higher fracture risk.2 Although osteoporosis has a higher overall prevalence in women, it is also a concern in men. Beyond aging and the menopause, there are other well-defined conditions that lead to bone loss (see discussions in section 3).28

<table>
<thead>
<tr>
<th>Skeletal Imaging Modality</th>
<th>Potential Therapeutic Application</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR-pQct</td>
<td>HR-pQct helps to identify microstructural deterioration and reduced bone strength.</td>
<td>Nishiyama and Shane, 201322</td>
</tr>
<tr>
<td>TBS</td>
<td>TBS is a texture analysis of lumbar spine DXA images. It infers bone microarchitecture not shown by DXA; TBS has been used in cross-sectional and longitudinal studies to predict fractures in combination with DXA.</td>
<td>Silva et al., 201423</td>
</tr>
<tr>
<td>μCT</td>
<td>Total area ratios derived from μCT 2-dimensional measurements of bone area may predict bone porosity. In humans, μCT can only be used on ex vivo specimens due to the radiation exposure.</td>
<td>Sandino et al., 201424</td>
</tr>
<tr>
<td>Hand-held reference point indentation instrument</td>
<td>Results are reported as an index of bone material strength and have been helpful in assessing this element of bone quality in diseases such as diabetes mellitus.</td>
<td>Farr et al., 201425 and Randall et al., 201326</td>
</tr>
</tbody>
</table>

Abbreviations: μCT, micro-computed tomography; HR-pQCT, high-resolution peripheral quantitative computed tomography; DXA, dual-energy x-ray absorptiometry; TBS, trabecular bone score
2.1 PREVALENCE AND INCIDENCE
The National Osteoporosis Foundation reported an overall 10.3% prevalence of osteoporosis in American adults aged 50 years or older, based on bone mineral density (BMD) at the femoral neck and lumbar spine. In 2010, this translated to 10.2 million individuals. An additional 43.4 million Americans (prevalence 43.9%) in the same age group were estimated to have low bone mass (osteopenia). Altogether, osteoporosis is thought to cause an estimated 2 million fractures each year in the US.

In 2013, it was reported that osteoporosis affects 8 million US women. As osteoporosis can manifest as fractures occurring at multiple skeletal sites, the incidence of fractures is a barometer of overall prevalence. Table 6 shows the rate of incident fractures among US men and women. Overall, the lifetime risk of wrist, hip, or vertebral fracture was estimated to be 30-40% in developed countries, nearly the same risk as that for coronary heart disease.

Data from NHANES III suggest that more than half of Americans age ≥ 50 years have osteoporosis or low bone mass at the femur neck or lumbar spine (Table 7).

As mentioned above, about 75-80% of Americans with osteoporosis are women, and most are postmenopausal. At age 50 years, the lifetime risk of developing osteoporosis-related fractures is about 40% for Caucasian women and 13% for Caucasian men. By age 60 years, approximately 50% of US women have osteopenia (low bone mass) or osteoporosis. In addition, it is estimated that more than 20% of postmenopausal women exhibit prevalent vertebral fractures. Table 8 summarizes the prevalence of low BMD at the femoral neck in postmenopausal US women by race/ethnicity.

Estimates suggest that by 2025 the incidence of osteoporosis will rise by 50%, and over 87% of this increase will occur among those age 65-74 years. Other researchers have highlighted the negative outcomes associated with recurrent fractures and observed that first and repeat fractures increased by 60-70% per decade of age in a study population age 50-90 years; in this group, repeat fractures were more common among patients with low BMD.

2.2 DEMOGRAPHIC DIFFERENCES
Data presented in Table 2 suggest that increasing age is a risk factor for the increased cost of osteoporosis. In addition, Table 7, which includes data about age, race, and incidences of osteoporosis, suggests that the total number of fractures alone is not directly correlated with costs.

| Table 6 | Incidence of fractures among men and women in the United States, 2005. |
|---------|-------------------|-------------------|-------------------|
|         | WOMEN             | MEN               |                  |
| Age     |                   |                   |                  |
| 50-64 years | 372,180          | 234,499           |                  |
| 65-74 years | 298,938          | 130,250           |                  |
| 75-84 years | 445,937          | 129,882           |                  |
| ≥ 85 years     | 338,788          | 100,222           |                  |
| Race/Ethnicity |               |                   |                  |
| Caucasian    | 1,290,168        | 477,852           |                  |
| African American | 58,923          | 48,525            |                  |
| Hispanic     | 61,668           | 41,134            |                  |
| Other        | 45,085           | 27,341            |                  |
| Total        | 1,455,843        | 594,852           |                  |
| Source: Burge et al. 2007^4 |

| Table 7 | Skeletal status (femur neck or lumbar spine) of United States adults age ≥ 50 years. |
|---------|-------------------------------------|-------------------------------------|
| STATUS  | PERCENTAGE                          |
| Normal  | 48%                                 |
| Low bone mass (osteopenia) | 49%                               |
| Osteoporosis | 9%                                 |
| Source: Looker et al. 1997^3 |

Note: Percentages do not sum to 100% due to double counting of osteoporosis patients with disease at other sites.

| Table 8 | Low bone mineral density at the femoral neck in postmenopausal United States women. |
|---------|-----------------------------------------------|-----------------------------------------------|
| RACE/ETHNICITY | PREVALENCE  | RACE/ETHNICITY | PREVALENCE  |
| Caucasian     | 21%                 | African American | 10%                 |
| Mexican American | 16%              | Source: Looker et al. 1997^3 |
Table 9 shows the cost burden of osteoporosis by race/ethnicity in 5-year increments from 2005-2025. In this time period, costs are expected to rise 175% among Hispanic and other race/ethnic groups, 79% among African-Americans, and 37% among Caucasians.4

2.3 LIFE EXPECTANCY AND MORTALITY

Fracture is the most significant clinical manifestation of osteoporosis. While fractures may occur in any bone, they tend to occur at sites of low BMD.2 Hip fractures are the most serious complication of osteoporosis, with almost 50% of patients requiring assistance with activities of daily living such as walking 1 year after occurrence.35 Table 10 summarizes data on 1-year mortality rates associated with osteoporotic hip and vertebral fractures.

Among Thai men age ≥ 50 years who sustained a hip fracture following a simple fall, 1-year mortality was 21.1%, approximately 9.3 times the expected mortality rate for this age group. Delayed treatment or the absence of treatment for osteoporosis correlated with higher mortality.38 A similar study of Thai adults age ≥ 50 years, who sustained a hip fracture following a simple fall, reported a 1-year mortality rate of 31% in men, and 16% among women. This study reported that greater mortality was associated with men, age ≥ 70 years, and non-operative treatment.39

Due in part to their greater BMD as compared to Caucasian American women, African American women have about half the rate of hip and vertebral fractures. Even so, mortality following hip fracture is greater among African American women than their Caucasian counterparts, possibly because the former tend to be older at the time of fracture, to have more comorbidities, or to face greater disparities in care. While Caucasian women are about twice as likely to experience hip fractures compared to Caucasian men.40

While osteoporotic fractures are usually precipitated by a fall, they may also occur during routine daily activities.

Table 9

<table>
<thead>
<tr>
<th>RACE/ETHNICITY</th>
<th>2005</th>
<th>2010</th>
<th>2015</th>
<th>2020</th>
<th>2025</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caucasian</td>
<td>14,951</td>
<td>16,188</td>
<td>17,254</td>
<td>18,543</td>
<td>20,548</td>
</tr>
<tr>
<td>African American</td>
<td>709</td>
<td>830</td>
<td>959</td>
<td>1,102</td>
<td>1,268</td>
</tr>
<tr>
<td>Hispanic</td>
<td>754</td>
<td>1,007</td>
<td>1,305</td>
<td>1,647</td>
<td>2,071</td>
</tr>
<tr>
<td>Other</td>
<td>502</td>
<td>655</td>
<td>844</td>
<td>1,077</td>
<td>1,381</td>
</tr>
<tr>
<td>Total</td>
<td>16,916</td>
<td>18,680</td>
<td>20,362</td>
<td>22,369</td>
<td>25,268</td>
</tr>
</tbody>
</table>

Note: Costs in $US millions, unadjusted for inflation

Table 10

<table>
<thead>
<tr>
<th>FRACTURE</th>
<th>DATA SOURCE</th>
<th>POPULATION</th>
<th>1-YEAR MORTALITY</th>
<th>REFERENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hip fracture</td>
<td>Population-based, prospective, matched-pair cohort study (1986-1995), US</td>
<td>Adults age ≥ 50 years</td>
<td>&gt; 31% 17%</td>
<td>Forsen et al. 1999³⁶</td>
</tr>
<tr>
<td>Vertebral fracture</td>
<td>Health Insurance Review Assessment Service (2005-2009), Korea</td>
<td>Adults age ≥ 50 years</td>
<td>14.6% 7.16%</td>
<td>Lee et al. 2012³⁷</td>
</tr>
</tbody>
</table>

Abbreviations: US, United States
In addition, incident non-traumatic fractures at typical osteoporotic sites (i.e., hip, vertebral, and upper arm fractures) are associated with increased mortality.\textsuperscript{41} Table 11 presents data on mortality rates in men and women who experienced incident fractures in osteoporotic sites including hip, vertebrae, wrist, and humerus.

A 34-year prospective observational study assessing the correlation of early menopause and risk of osteoporosis reported that women who underwent menopause before age 47 years had a greater risk of osteoporosis (RR 1.83, 95% CI 1.22-2.74), fragility fracture (RR 1.68, 95% CI 1.05-2.57), and mortality (RR 1.59, 95% CI 1.04-2.36), by age 77 years.\textsuperscript{43}

2.4 KEY TRENDS AND HEALTH OUTCOMES

Measuring BMD is the primary technique for diagnosing and monitoring osteoporosis for postmenopausal women and men age $\geq 50$ years.\textsuperscript{7} Table 12 shows the WHO operational criteria for classifying osteoporosis based on BMD, expressed as a T-score. In brief, the T-score compares a subject’s BMD with the mean value for young normal adult subjects and expresses the difference as a standard deviation.

Some authors have objected to overreliance on T-scores and have pointed out that factors such as family history, laboratory results, genetic influences, or the presence of fragility fractures should be considered along with T-scores.\textsuperscript{44,45} It has been suggested that additional data be considered when physicians evaluate T-scores.\textsuperscript{46} For example, the WHO fracture risk assessment tool (FRAX) incorporates dual-energy x-ray absorptiometry (DXA) as well as seven independent risk factors for the assessment of fracture risk in subjects with osteopenia.\textsuperscript{7,47}

As per the Bone Mass Measurement Act of 1998, all US women age >65 years, and men age >70 years are expected to undergo BMD testing. In addition, the 2013 Position Development Conference of the International Society for Clinical Densitometry recommended bone density tests in the presence of risk factors for low bone mass, such as low body weight, prior fracture, high-risk medication use, or diseases or conditions associated with bone loss for both postmenopausal women age < 65 years and men age < 70 years.\textsuperscript{48}

Systematic reviews published in 2012 and 2014 addressed the effects of long-term hormone therapy for perimenopausal and postmenopausal women and the effects of steroidal contraceptives on bone fractures in women.\textsuperscript{49,50} The first review acknowledged that hormone therapy can be effective in preventing postmenopausal osteoporosis, but also noted that the treatment is recommended only for women who are at elevated risk for osteoporosis and have no contraindications, and when non-estrogen therapies are not suitable. The second review examined 19 randomized controlled trials that evaluated the effectiveness of various steroidal contraceptives and noted that none had fracture as an outcome. Reviewers concluded that, based on existing information in 2014, they could not determine if steroidal contraceptives influence fracture risk.

### Table 11

<table>
<thead>
<tr>
<th>DATA SOURCE</th>
<th>POPULATION</th>
<th>TYPE OF FRACTURE</th>
<th>POST-FRACTURE MORTALITY RATE</th>
<th>REFERENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthcare databases for the Province of Manitoba (1986 -2007; 15-year follow-up), Canada</td>
<td>Adults age $\geq$ 50 years</td>
<td>Hip, vertebral, humerus, wrist, among others*</td>
<td>50.1% 44.8%</td>
<td>Morin et al. 2010\textsuperscript{41}</td>
</tr>
<tr>
<td>Multicenter osteoporosis study (1995-1997; 5-year follow-up), Canada</td>
<td>Adults age $\geq$ 50 years</td>
<td>Hip</td>
<td>23.5% 23.5%</td>
<td>Loannidis et al. 2009\textsuperscript{42}</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vertebral</td>
<td>18.2% 15.7%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Forearm or wrist</td>
<td>11.5% 8.1%</td>
<td></td>
</tr>
</tbody>
</table>

Note: *, 66% of fractures were located at sites other than hip and vertebrae
The US Food and Drug Administration (FDA) drugs approved for the treatment of osteoporosis include: calcitonin; bisphosphonates (alendronate, alendronate with cholecalciferol [vitamin D3], ibandronate, risedronate, and zoledronic acid); raloxifene, an estrogen agonist/antagonist; conjugated estrogens/bazedoxifene, a tissue-selective estrogen complex; teriparatide, the 1-34 fragment of parathyroid hormone; and denosumab, an antibody directed against receptor activator of nuclear factor κB ligand (RANKL).51

A review published in 2009 discussed emerging treatments, including agents that show antiresorptive effects and anabolic effects and an agent that may combine both mechanisms of action.52 Other authors have reviewed emerging biologic agents that may help stimulate new bone formation.53

Table 13 summarizes the main currently available pharmacotherapies for treating osteoporosis in the US, along with their benefits and some potential associated adverse effects.54

Even though older men are twice as likely as women to die after hip fracture,55 osteoporosis is usually considered a “woman's disease” due to higher overall prevalence in women.56 Due to its higher prevalence, pharmaceutical companies target new drug candidates for the primary prevention of fractures almost exclusively for registration purposes in postmenopausal women.56 Accordingly, there is more evidence on the effects of osteoporosis medications in women than in men.

An Australian study of 1,223 women and 819 men aged ≥ 60 years who were treated with bisphosphonates, hormone therapy (women only), and calcium with or without vitamin D found reduced mortality among women and men who received bisphosphonates.57 A systematic review on the use of bisphosphonates beyond 3 years showed an association with reduced fractures and increased BMD, and recommended assessing patients with T-scores > -2.5 at the end of treatment for possible drug discontinuation with continued monitoring.58 A retrospective analysis of a US claims database that included 57,913 postmenopausal women age ≥ 55 years who filled one or more pharmacy claims for a bisphosphonate or non-bisphosphonate (e.g., raloxifene, calcitonin, or teriparatide) found that only 23,430 (40.5%) subjects were compliant. Noncompliant participants had a 20% greater risk of fracture and 13% higher medical costs.59 These results confirm and expand findings from an earlier and similar study in Canada that reported a

### Table 12

<table>
<thead>
<tr>
<th>Classification of osteoporosis</th>
<th>T-Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>0 to -0.99</td>
</tr>
<tr>
<td>Osteopenia (low bone density)</td>
<td>-1.0 to -2.49</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>≤ -2.5</td>
</tr>
<tr>
<td>Severe or established osteoporosis</td>
<td>&lt; -2.5 with fracture</td>
</tr>
</tbody>
</table>


### Table 13

<table>
<thead>
<tr>
<th>Pharmacotherapy</th>
<th>Efficacy</th>
<th>Adverse Effects/Reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bisphosphonates</td>
<td>Decreased vertebral, non-vertebral, and hip fractures</td>
<td>GI symptoms with oral bisphosphonates; acute-phase reactions with IV bisphosphonates</td>
</tr>
<tr>
<td>Raloxifene</td>
<td>Decreased vertebral fractures</td>
<td>Increased risk of VTE and mortality</td>
</tr>
<tr>
<td>Teriparatide</td>
<td>Decreased vertebral and non-vertebral fractures</td>
<td>Injection site reactions, nausea, dizziness</td>
</tr>
<tr>
<td>Denosumab</td>
<td>Decreased vertebral, non-vertebral, and hip fractures</td>
<td>Eczema, increased risk of cellulitis (in phase 3 clinical trial)</td>
</tr>
<tr>
<td>Hormone therapy</td>
<td>Decreased vertebral, non-vertebral, and hip fractures</td>
<td>Increased risk of VTE, breast cancer, and CV disease in women &gt; 10 years after menopause</td>
</tr>
</tbody>
</table>

Source: Kling et al. 2014

Abbreviations: GI, gastrointestinal tract; VTE, venous thromboembolism; CV, cardiovascular; IV, intravenous

Note: *GI symptoms include nausea, vomiting, abdominal pain, dyspepsia, esophagitis, or reflux.
16% lower osteoporosis-related fracture rate among medication-compliant women age >50 years.60

III OSTEOGENA
(LOW BONE MASS)

Low bone mass, also termed, osteopenia, is defined as bone density in which the T-score is between 1.0 and 2.49 (standard deviations below average (-1.0 to -2.49)) in postmenopausal women and men age >50 years.61

3.1 PREVALENCE AND INCIDENCE

The prevalence of osteopenia is higher in women than men (Table 14).3 Several conditions have been associated with the greater likelihood of reduced bone mass. A European study has linked metabolic syndrome with a higher prevalence of low bone mass in middle-aged men.62 Long-term antiepileptic drug use has also been associated with both osteopenia and osteoporosis.63

3.2 DEMOGRAPHIC DIFFERENCES

In 2010, researchers compared the prevalence of osteopenia in the femur neck and total hip in US men and women 50 years of age or older in terms of sex and race; in addition, they compared data from NHANES III and NHANES 2005–2006 (Table 15).64 With the exception of osteopenia in the total hip among Mexican American women, the prevalence between the two datasets did not differ significantly.

Table 14

<table>
<thead>
<tr>
<th>DATA SOURCE</th>
<th>POPULATION</th>
<th>PREVALENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>NHANES, Centers for Disease Control and Prevention 2005-2006</td>
<td>Nationally representative sample of US population age ≥ 50 years</td>
<td>MEN: 28-47%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>WOMEN: 30-50%</td>
</tr>
</tbody>
</table>

Source: Looker et al. 19973

Abbreviations: NAHES, National Health and Nutrition Examination Survey

Note: NHANES III aimed to provide reliable estimates for three racial/ethnic groups: non-Hispanic Caucasians, non-Hispanic African Americans, and Mexican Americans. Number eligible to participate = 10,995; number interviewed = 8,654 (74%); number examined = 7,155 (65%).

Table 15
Osteopenia in the femur neck and total hip in United States men and women age 50 years and older of different races: comparison of data from NHANES III (n = 6,401) and NHANES 2005–2006 (n = 1,601).

<table>
<thead>
<tr>
<th></th>
<th>FEMUR NECK</th>
<th>TOTAL HIP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic Caucasian</td>
<td>51%</td>
<td>52%</td>
</tr>
<tr>
<td>Non-Hispanic African American</td>
<td>36%</td>
<td>36%</td>
</tr>
<tr>
<td>Mexican American</td>
<td>47%</td>
<td>38%</td>
</tr>
<tr>
<td>Total</td>
<td>49%</td>
<td>50%</td>
</tr>
<tr>
<td>Men</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic Caucasian</td>
<td>25%</td>
<td>33%</td>
</tr>
<tr>
<td>Non-Hispanic African American</td>
<td>20%</td>
<td>22%</td>
</tr>
<tr>
<td>Mexican American</td>
<td>27%</td>
<td>34%</td>
</tr>
<tr>
<td>Total</td>
<td>34%</td>
<td>32%</td>
</tr>
</tbody>
</table>

Source: Looker et al. 201064

Note: *, p < 0.05 between NHANES III and NHANES 2005-2006 within sex and race with Bonferroni adjustment.
3.3 LIFE EXPECTANCY AND MORTALITY
An Australian study reported that among patients aged 60 years or older, those with osteopenia (with or without osteoporosis) experienced a greater burden of fractures and associated mortality.65

3.4 KEY TRENDS AND HEALTH OUTCOMES
It is important to distinguish between patients with osteopenia who require treatment and those who do not, since osteopenia is not a disease but a condition that may or may not be associated with increased fracture risk. To this end, it is recommended that clinicians assess risk in patients with DXA-defined osteopenia using a risk calculator such as the FraX, developed by the WHO’s Collaborating Centre for Metabolic Bone Diseases at Sheffield University, rather than by exclusively using T-scores.66,67 Many individuals who should be treated are not being treated, despite the availability of a number of effective pharmacologic agents.68 Data from FRAX and DXA analyses may be effective in suggesting appropriate therapies for those who meet guidelines.66

IV VITAMIN D DEFICIENCY
In 2011, the Endocrine Society reported that between 20-100% of US, Canadian, and European elderly men and women suffered from vitamin D (25-hydroxyvitamin D, or 25(OH)D) deficiency. It also reported that children and young- and middle-aged adults worldwide were equally at risk of vitamin D deficiency.69 In addition, national surveillance data has shown an increase in vitamin D insufficiency and deficiency within the US population.70 However, the US Preventive Services Task Force recently concluded that the current evidence remains insufficient to recommend universal vitamin D screening.71 There is an additional evidence gap in understanding the effects of and needs for vitamin D supplementation, particularly in establishing risk-benefit ratios for various populations.72 Researchers seem to agree, in principle, that the adequate intake of vitamin D and calcium along with moderate weight-bearing exercise is helpful in preventing and treating osteoporosis,2,27,54,73 but opinions differ with respect to the target level for Vitamin D adequacy.

4.1 PREVALENCE AND INCIDENCE
Estimates of prevalence and incidence are impacted by the cutoffs used to define vitamin D deficiency and insufficiency. There are some areas of disagreement, most notably between the 2011 clinical practice guideline from the Endocrine Society69 and the 2011 dietary reference intake guideline from the Institute of Medicine (IOM).74 Table 16 summarizes these discrepancies.

Applying the IOM cutoffs to the NHANES dataset (2001-2006), researchers estimate that two-thirds of the US population had sufficient levels of serum 25-hydroxyvitamin D [25(OH)D] (Table 17).75 Table 18 lists the most recent epidemiological data for children and adolescents (published prior to the most recent guidelines).76

4.2 DEMOGRAPHIC DIFFERENCES
The prevalence of vitamin D deficiency increases significantly with age until age 30 in men and age 18 in women. After adjusting for age and season, women are at higher risk for vitamin D deficiency than men. However, there were no notable sex differences in risk for vitamin D insufficiency (Table 19).

The Centers for Disease Control has reported, based on IOM cutoffs, that non-Hispanic African Americans and Mexican Americans are at higher risk of vitamin D deficiency and insufficiency than non-Hispanic Caucasians (Table 20). However, the IOM has noted that caution should be used when interpreting serum 25(OH)D

<table>
<thead>
<tr>
<th>Table 16</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Comparison of Endocrine Society and Institute of Medicine cutoffs for serum 25-hydroxyvitamin D levels used to define deficiency, insufficiency, and sufficiency.</strong></td>
</tr>
<tr>
<td><strong>GUIDELINE</strong></td>
</tr>
<tr>
<td><strong>GUIDELINE</strong></td>
</tr>
<tr>
<td>Endocrine Society</td>
</tr>
<tr>
<td>Institute of Medicine</td>
</tr>
</tbody>
</table>
Table 17
Comparison of Endocrine Society and Institute of Medicine cutoffs for serum 25-hydroxyvitamin D levels used to define deficiency, insufficiency, and sufficiency.

<table>
<thead>
<tr>
<th>DATA SOURCE</th>
<th>POPULATION</th>
<th>SERUM 25-HYDROXYVITAMIN D CONCENTRATION</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>DEFICIENT (&lt;12 NG/ML)</td>
<td>INSUFFICIENT (12-20NG/ML)</td>
<td>SUFFICIENT (20-50 NG/ML)</td>
<td>EXCESSIVE, POTENTIALLY HARMFUL (&gt; 50 NG/ML)</td>
</tr>
<tr>
<td>NHANES 2001-2006</td>
<td>US population, ages 1 year and older</td>
<td>8%</td>
<td>24%</td>
<td>67%</td>
<td>1%</td>
</tr>
</tbody>
</table>

Source: Looker et al. 201175

Abbreviations: US, United States; NHANES, National Health and Nutrition Examination Survey

Table 18
Prevalence of vitamin D deficiency in United States adolescents.

<table>
<thead>
<tr>
<th>DATA SOURCE</th>
<th>POPULATION</th>
<th>SERUM 25-HYDROXYVITAMIN D CONCENTRATION</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Youth and Adolescent Questionnaire, 2001-2003</td>
<td>Boston Children’s Hospital patients, age 11-18 years</td>
<td>24.1%</td>
<td>42.0%</td>
<td></td>
</tr>
</tbody>
</table>

Source: Gordon et al. 200476

Table 19
Prevalence of vitamin D deficiency and insufficiency in the United States population age 1 year and older by sex based on Institute of Medicine criteria.

<table>
<thead>
<tr>
<th>DATA SOURCE</th>
<th>POPULATION</th>
<th>SERUM 25-HYDROXYVITAMIN D CONCENTRATION</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>DEFICIENT (&lt;12 NG/ML)</td>
<td>INSUFFICIENT (12-20 MG/ML)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MEN</td>
<td>WOMEN</td>
</tr>
<tr>
<td>NHANES 2001-2006</td>
<td>US, age ≥ 1 year</td>
<td>6%</td>
<td>23%</td>
</tr>
<tr>
<td></td>
<td>MEN</td>
<td>10%</td>
<td>24%</td>
</tr>
</tbody>
</table>

Source: Looker et al. 201175

Abbreviations: US, United States; NHANES, National Health and Nutrition Examination Survey

Table 20
Prevalence of vitamin D deficiency and insufficiency in the US population by race and ethnicity based on Institute of Medicine criteria.

<table>
<thead>
<tr>
<th>DATA SOURCE</th>
<th>POPULATION</th>
<th>SERUM 25-HYDROXYVITAMIN D CONCENTRATION</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>DEFICIENT (&lt;12 NG/ML)</td>
<td>INSUFFICIENT (12-20 MG/ML)</td>
</tr>
<tr>
<td></td>
<td>NON-HISPANIC CAUCASIAN</td>
<td>MEXICAN AMERICAN</td>
<td>NON-HISPANIC CAUCASIAN</td>
</tr>
<tr>
<td>NHANES 2001-2006</td>
<td>US, age ≥ 1 year</td>
<td>3%</td>
<td>18%</td>
</tr>
<tr>
<td></td>
<td>NON-HISPANIC AFRICAN AMERICAN</td>
<td>MEXICAN AMERICAN</td>
<td>NON-HISPANIC AFRICAN AMERICAN</td>
</tr>
<tr>
<td></td>
<td>MEXICAN AMERICAN</td>
<td>32%</td>
<td>41%</td>
</tr>
</tbody>
</table>

Source: Looker et al. 201175

Abbreviations: US, United States; NHANES, National Health and Nutrition Examination Survey
levels in non-Caucasian populations, as they may have better skeletal status despite lower serum 25(OH)D values.74

A study of adolescents at Boston Children’s Hospital revealed a higher prevalence of vitamin D deficiency in African American adolescents compared to their Hispanic, Asian, and non-Hispanic Caucasian counterparts (Table 21).76 No statistically significant differences in the prevalence of vitamin D deficiency between female (26.0%) and male (20.6%) adolescents were noted in this study.

4.3

**LIFE EXPECTANCY AND MORTALITY**

A Cochrane Review examined the use of vitamin D and its analogues for preventing fractures in older men and postmenopausal women and included 53 trials that enrolled 91,791 patients.28 The primary outcome was hip fracture. The authors found high-quality evidence that vitamin D plus calcium supplementation was associated with a small reduction in hip fracture (9 trials, 49,853 patients, RR 0.84, 95% CI 0.74–0.96, P = .01). Still, the authors concluded that supplementation with vitamin D alone is not likely to prevent fractures (at least in the doses and formulations currently used), but supplementation with vitamin D and calcium may help to prevent them.

The IOM and Endocrine Society guidelines agree that vitamin D does not seem to be associated with non-skeletal outcomes such as death, cardiovascular disease, or quality of life, and that routine screening of the general population is unnecessary.77

4.4

**KEY TRENDS AND HEALTH OUTCOMES**

Vitamin D can be obtained through sun exposure, but throughout the world, the sun, for a variety of reasons, is no longer a primary source of vitamin D. Dietary sources of vitamin D are also potentially available but they are generally limited. The Centers for Disease Control reports that the use of vitamin D supplements increased from 1988 to 2006, regardless of age or sex (Table 22).

However, it is likely that there are many patients with vitamin D deficiency who are not receiving vitamin D supplements. An analysis of the Research Patient Data Registry at the Partners HealthCare System (Boston, MA) showed that two-thirds of primary care patients with vitamin D deficiency (defined using the IOM cutoff of 25(OH)D < 20 ng/ml) did not receive a prescription for vitamin D supplements.78 Some sex and racial/ethnic differences in prescription rates were also noted in the study, as summarized in Table 23. However, since doses of vitamin D are generally available without a prescription, these findings do not mean that subjects with vitamin D deficiency did not take supplements.

### Table 21

<table>
<thead>
<tr>
<th>DATA SOURCE</th>
<th>POPULATION</th>
<th>VITAMIN D DEFICIENT (SERUM 25-OH VITD ≤ 15 NG/ML)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>NON-HISPANIC CAUCASIAN</td>
</tr>
<tr>
<td>Youth and Adolescent Questionnaire, 2001-2003</td>
<td>Boston Children's Hospital patients, age 11-18 years</td>
<td>6.1%</td>
</tr>
</tbody>
</table>

Source: Gordon et al. 200476

### Table 22

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>20-39 years</td>
<td>22.2%</td>
<td>26.5%</td>
<td>30.3%</td>
<td>33.8%</td>
</tr>
<tr>
<td>40-59 years</td>
<td>26.0%</td>
<td>38.0%</td>
<td>31.1%</td>
<td>45.0%</td>
</tr>
<tr>
<td>60+ years</td>
<td>23.7%</td>
<td>44.0%</td>
<td>29.7%</td>
<td>56.3%</td>
</tr>
</tbody>
</table>

Source: Gahche et al. 201178
Even though universal screening for vitamin D deficiency is not currently recommended, the frequency of vitamin D testing has increased markedly in recent years. An analysis of Medicare Part B reimbursements for laboratory tests showed an 83-fold increase in vitamin D test reimbursements from 2000 to 2010.80

To determine the effectiveness of vitamin D supplementation for improving BMD in children, researchers examined six randomized, placebo-controlled clinical trials that lasted at least 3 months and involved healthy children and adolescents (ages 1 month to < 20 years) with bone density outcomes. Subgroup analyses were based on sex, stage of puberty, dose of vitamin D, and baseline serum vitamin D levels among 343 patients who received placebo and 541 who received vitamin D with or without calcium. The authors reported non-significant trends toward increased lumbar spine BMD in patients who received supplemental vitamin D, and similarly small effects on total bone mineral content. In patients with low serum vitamin D levels, supplementation was associated with statistically significant effects on bone mineral content and lumbar spine BMD (approximately equivalent to increases of 2.6% and 1.7%, respectively). Based on these findings the authors suggested vitamin D supplementation may be beneficial in children with low serum vitamin D levels.81

Table 24 summarizes findings following vitamin D supplementation in selected groups.

Evidence gaps and data inconsistencies have led to differing opinions regarding the outcomes resulting from vitamin D deficiency and supplementation. As noted in Table 16 above, the IOM and the Endocrine Society provide different cutoffs for the diagnosis of vitamin D insufficiency and deficiency. Reactions to these guidelines and areas of disagreement are summarized in Table 25.

When discussing breakthroughs in the field of vitamin D deficiency, meta-analyses, treatment guidelines, and other research reports often identify the lack of high-quality, long-term, placebo-controlled studies as obstacles that prevent firm conclusions about treatment outcomes.28,69,77,81,82,86 Indeed, some researchers have cautioned against the use of a single cutoff value to determine vitamin D deficiency because of the wide individual variability in response to vitamin D and interactions with calcium.89 Furthermore, these researchers noted that most of the evidence that supported the beneficial effects of vitamin D supplementation was based on observational studies, whereas controlled clinical trials are required for the conclusive demonstration of such benefits. Similarly, the US Preventive Services Task Force recommendations for vitamin D and calcium to prevent fractures (2013) found most of the evidence in favor of supplementation insufficient, except for data regarding community-dwelling adults age ≥65 years who are at increased risk of falls.90,91

V PRIMARY HYPERPARATHYROIDISM

Primary hyperparathyroidism (PHPT) results from an excess of parathyroid hormone (PTH) secreted by one or more of the four parathyroid glands due to parathyroid adenoma, parathyroid hyperplasia, or (very rarely) parathyroid carcinoma.

5.1 PREVALENCE AND INCIDENCE

The most recent prevalence estimates of PHPT are 1-4 per 1,000, with a 3-fold higher prevalence in women than men.82 The Rochester-Olmsted County Epidemiology Project observed a rise and fall in the annual incidence of PHPT from 1965 to 2010.93 A significant increase was noted in 1974, following the implementation of routine testing of serum calcium. Interestingly, a second peak started in 1998 in conjunction with the introduction of national osteoporosis screening guidelines. During the most recent period examined (1998-2010), the overall age- and sex-adjusted incidence rate has been reported to be 50.4 per 100,000.93 Trends in PHPT incidence in this cohort are summarized in Table 26.

5.2 DEMOGRAPHIC DIFFERENCES

Overall, PHPT is more prevalent in women than men, with the highest incidence in postmenopausal women.84

The introduction of the multichannel screening test into clinical medicine is primarily responsible for the change in recognition of PHPT in the 1970s. As countries implemented biochemical screening, which routinely measured serum calcium, PHPT became commonly recognized as noted above. Most of these “newly discovered” individuals were asymptomatic women in
# Table 23

<table>
<thead>
<tr>
<th>PATIENTS WITH VITAMIN D DEFICIENCY WHO WERE PRESCRIBED SUPPLEMENTS</th>
<th>OVERALL</th>
<th>NON-HISPANIC CAUCASIAN</th>
<th>NON-HISPANIC AFRICAN AMERICAN</th>
<th>HISPANIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>33.8%</td>
<td>30.9%</td>
<td>37.8%</td>
<td>38.4%</td>
</tr>
<tr>
<td>Male</td>
<td>7.5%</td>
<td>28.0%</td>
<td>37.9%</td>
<td>31.8%</td>
</tr>
<tr>
<td>Female</td>
<td>26.3%</td>
<td>32.1%</td>
<td>37.8%</td>
<td>40%</td>
</tr>
</tbody>
</table>

Source: Chandler et al. 2014

# Table 24

<table>
<thead>
<tr>
<th>GROUP</th>
<th>OBSERVATION/INTERVENTION</th>
<th>OUTCOMES</th>
<th>REFERENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postmenopausal women (Women’s Health Initiative)</td>
<td>Identified 11 clinically relevant risk factors: age, race (ethnicity), self-reported health, weight, height, physical activity, parental hip fracture, fracture history after age 54, current smoking, corticosteroid use, and treatment for diabetes</td>
<td>Small but significant positive effect on hip bone density after supplementation with vitamin D and calcium; an intention-to-treat analysis found no significant reduction in fractures</td>
<td>Jackson et al. 2014, Clarke et al. 2012</td>
</tr>
<tr>
<td>Men ≥ 70 years and men 50-69 years (Endocrine Society)</td>
<td>Risk factors for men in the younger cohort included low body weight, fracture during adulthood, smoking, alcohol abuse</td>
<td>Recommended pharmacologic treatments, lifestyle modifications, follow-up with DXA</td>
<td>Watts et al. 2012</td>
</tr>
<tr>
<td>3-year RCT in 208 healthy postmenopausal African American women (50-75 years)</td>
<td>Placebo, 20 μg/day (800 IU) vitamin D3 with calcium supplementation (intake of 1200-1500 mg/day); after 2 years, the supplemented group’s vitamin D3 dose was increased to 50 μg/day</td>
<td>BMD measured at 6-month intervals; no observed effect of vitamin D supplementation on bone loss or turnover</td>
<td>Aloia et al. 2005</td>
</tr>
<tr>
<td>2-year double-blind RCT in 103 postmenopausal African American women</td>
<td>Vitamin D supplementation (1000 IU/day); monitored parathyroid hormone levels and determined vitamin D receptor polymorphisms</td>
<td>No difference in BMD between placebo and supplemented groups; femoral neck BMD increased in those with the FF polymorphism</td>
<td>Nieves et al. 2012</td>
</tr>
<tr>
<td>International meta-analysis</td>
<td>4,082 patients in 23 studies</td>
<td>No effect of ethnic differences in response to vitamin D supplementation</td>
<td>Reid et al. 2014</td>
</tr>
</tbody>
</table>

Abbreviations: DXA, dual-energy x-ray absorptiometry; RCT, randomized controlled clinical trial; BMD, bone mineral density

# Table 25

<table>
<thead>
<tr>
<th>DATA SOURCE</th>
<th>RECOMMENDATION</th>
<th>COMMENTS</th>
<th>REFERENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heaney and Holick (2011)</td>
<td>Agree with Endocrine Society that serum levels of vitamin D should be 30 ng/mL</td>
<td>Note that supplementation with 600 IU/day, if the body’s only source, would not produce serum 25-hydroxyvitamin D level of 10 ng/mL</td>
<td>Heaney et al. 2011</td>
</tr>
<tr>
<td>IOM response to Endocrine Society (2012)</td>
<td>Three main areas of disagreement</td>
<td>Dispute benefits of serum 25-hydroxyvitamin D levels of 30 vs. 20 ng/mL for general and at-risk populations; disagree with definition of vitamin D deficiency as &lt; 20 ng/mL; disagree about definitions and characteristics of at-risk subgroups</td>
<td>Rosen et al. 2012</td>
</tr>
</tbody>
</table>

Abbreviations: IOM, Institute of Medicine
Researchers at a large tertiary referral center examined electronic medical records of 2.7 million patients over a 2-year period and identified 95 with a recorded diagnosis of PHPT, of whom 16 underwent parathyroidectomy. Among hypercalcemic patients identified in the electronic medical records, PTH values were not obtained from 67%, which (the authors conclude) led to underdiagnosis and undertreatment of PHPT.

Analysis of active enrollees in Kaiser Permanente Southern California showed some racial and ethnic differences in the epidemiology of PHPT (Table 27). Incidence was highest among African American patients, and racial/ethnic differences were more pronounced among older patients.

5.3
LIFE EXPECTANCY AND MORTALITY
The ability to recognize asymptomatic hyperparathyroidism has led to discussions about how to manage this disease. A 1998 population-based study by researchers at the Mayo Clinic that examined data between 1965 and 1992, identified 435 cases of PHPT; of those, 126 patients underwent parathyroid surgery. Patients who underwent surgery had higher serum calcium levels than those who were observed without surgery (mean ± SD 11.3 ± 0.7 vs. 10.7 ± 0.4 mg/dL, respectively, \( P < .001 \)), and age-adjusted multivariate analysis showed that the highest quartile of serum calcium levels was an independent predictor of mortality (RR = 1.3 per mg/dL, 95% CI 1.1-1.6, \( P < .02 \)). An Australian study found significantly greater mortality (\( P < .001 \)) among a group of 561 patients with PHPT than in the general population. Mortality rates were similar regardless of whether the patients’ serum calcium levels were above or below 12 mg/dL.

Among 1,049 patients with overt PHPT and 388 matched patients with mild PHPT, 62.2% and 53.3% were cured at 5 months following surgery (\( P \leq .01 \)) and had equivalent Kaplan-Meier disease-free survival following surgery.

| Table 26 | Age- and sex-adjusted annual incidence of primary hyperparathyroidism. |
| --- | --- | --- | --- |
| DATA SOURCE | POPULATION | YEARS | INCIDENCE PER 100,00 PERSON-YEARS |
| Rochester-Olmsted County Epidemiology Project medical records | Residents of Olmsted County, Minnesota | 1965-1974 | 15 |
| | | 1974-1984 | 121.7 |
| | | 1984 | 37.3 |
| | | 1998-2007 | 86.2 |
| | | 2007 | 31.3 |
| Source: Griebeler et al. 2015

| Table 27 | Age-adjusted incidence and prevalence of primary hyperparathyroidism by sex and race/ethnicity. |
| --- | --- | --- | --- |
| RACE/ETHNICITY | INCIDENCE (PER 100,000) | PREVALENCE (PER 100,000) |
| | WOMEN | MEN | WOMEN | MEN |
| Caucasian | 81.0 | 29.4 | 201.0 | 69.1 |
| African American | 92.0 | 46.0 | 321.7 | 138.4 |
| Asian | 51.8 | 27.9 | 103.1 | 63.1 |
| Hispanic | 48.6 | 17.1 | 118.3 | 39.9 |
| Other | 25.4 | 5.9 | 50.1 | 10.3 |
| Source: Yeh et al. 2013

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5.4 KEY TRENDS AND HEALTH OUTCOMES
Revised guidelines for the management of asymptomatic PHPT were published in 2014 and included recommendations for the extensive evaluation of patients’ skeletal and renal systems, inclusion of these results in surgery guidelines, and the development of specific guidelines regarding parathyroid surgery. More data are now becoming available about the clinical presentation of a new variant of hyperparathyroidism, normocalcemic PHPT, in which PTH levels are elevated, while serum calcium levels are consistently normal. This occurs in the absence of secondary causes of hyperparathyroidism, such as renal disease or vitamin D deficiency. We are also seeing improvements in imaging and analytical techniques for detecting skeletal and renal involvement in asymptomatic hyperparathyroidism. In patients who do not meet guidelines for parathyroidectomy, a conservative, non-interventional follow-up regimen is recommended as a reasonable option. However, the recent workshop on the management of asymptomatic PHPT noted that parathyroid surgery can be performed in patients who don’t meet guidelines for surgery if they and/or their physician make that decision, as long as there are no medical contraindications. While it has been suggested that cardiovascular morbidity and mortality may be related to PHPT, most of these observations come from a time when PHPT was a symptomatic disease. The extent to which the cardiovascular system is involved and associated with increased morbidity and mortality in PHPT is not known. The consequences of successful parathyroidectomy on this and other “off target” manifestations of PHPT remain uncertain.

Current guidelines recommend parathyroid surgery for patients with symptomatic PHPT or with asymptomatic PHPT who meet one of the following guidelines: serum calcium > 1mg/dL above the upper limit of normal, calculated creatinine clearance < 60mL/min, evidence for kidney stones or nephrocalcinosis by history or by imaging studies, osteoporosis by T-score, previous fragility fracture, and age < 50 years.

Patients with asymptomatic PHPT who do not meet the guidelines for surgery or with contraindications for surgery should be followed. In those who meet densitometric surgical guidelines but who are not going to have parathyroid surgery, antiresorptive therapy and the monitoring of biochemical data and bone densitometry is appropriate. For individuals who meet surgical guidelines by virtue of the serum calcium level but who do not undergo parathyroid surgery, calcimimetic therapy has been proven to be helpful.

In an Australian multicenter retrospective cohort study, 4,569 patients (3,585 women) underwent either focused parathyroidectomy or open four-gland parathyroid exploration. The former was associated with fewer operative complications but higher persistence rates that nonetheless were resolved by early reoperation, and both procedures had similarly low long-term recurrence rates (5-year recurrence rates of 0.6% vs. 0.4%, respectively, P = 0.08). Other researchers compared minimally invasive parathyroidectomy with open four-gland parathyroid exploration in a cohort of 1,083 patients and reported that patients undergoing open four-gland parathyroid exploration experienced more post-operative transient hypocalcemia. In comparison, patients undergoing minimally invasive parathyroidectomy appeared to have a greater long-term recurrence rate. Therefore, proper patient selection and counseling of these risks is necessary for either approach.

VI HYPOPARATHYROIDISM
Hypoparathyroidism is a rare disease characterized by low serum calcium levels, elevated serum phosphorous levels, and inappropriately low levels of PTH. In treating the disorder, physicians are challenged to manage hypocalcemia and concurrently to avoid hypercalciuria, which can lead to nephrocalcinosis, kidney stones, and even chronic kidney disease.

6.1 PREVALENCE AND INCIDENCE
It has been estimated that 60-80,000 patients in the US have hypoparathyroidism. This projection was largely based on the analysis of a large proprietary health plan claims database, which identified 8,901 cases (7.6% prevalence) of hypoparathyroidism among 117,342 procedures that may impact the parathyroid glands (e.g., thyroidectomy, neck dissection, radiation).

Most reports indicate that thyroid or neck surgery is infrequently associated to chronic hypoparathyroidism. For example, analysis of the aforementioned database from 2007 to 2008 found that of the 8,901 cases of hypoparathyroidism, 75% were transient and 25% were chronic. Similarly, surgeons at the Mayo Clinic reported that among 241 pediatric thyroid surgeries performed
between 1993 and 2012, only four led to permanent hypoparathyroidism.113 Among patients who have had thyroid surgery, a study in Poland found that permanent hypoparathyroidism occurred in 8.5% of patients, especially following total thyroidectomy (20.2%), near-total thyroidectomy (6.7%), or subtotal thyroidectomy (4.2%). With respect to complications related to postsurgical hypoparathyroidism, Danish researchers reported such patients did not have increased risks of cataracts, spinal stenosis, fracture, or gastrointestinal cancers, and their risk of upper-extremity fracture was significantly decreased (HR 0.69, 95% CI 0.49–0.97) compared to age- and sex-matched population controls.114 However, they did find that postsurgical hypoparathyroidism was associated with an increased risk of depression, other neuropsychiatric diseases, and infections.

A study in Denmark identified the prevalence of nonsurgical hypoparathyroidism as 2.3 per 100,000.115 Compared to age- and sex-matched population-based controls, patients did not have increased mortality but did have a reduced risk of malignant diseases (HR 0.44). In comparison, however, they had an increased risk of renal insufficiency (HR 6.01), cardiovascular disease (HR 1.91), neuropsychiatric complications (HR 2.45), infections (HR 1.94), seizures (HR 10.05), cataracts (HR 4.21), and upper-extremity fractures (HR 1.93).

6.2 LIFE EXPECTANCY AND MORTALITY

A study of the Danish National Patient Registry found no differences in mortality between patients with postsurgical hypoparathyroidism versus age- and gender-matched controls.116

6.3 KEY TRENDS AND HEALTH OUTCOMES

A 1-year cohort study of 120 patients with confirmed hypoparathyroidism reported that rates of stage 3 or higher chronic kidney disease were 17-20 fold higher than those of age-matched norms.117 Because of the frequent presence of hyperphosphatemia, hypoparathyroidism can be associated with deposits of calcium–phosphate complexes in soft tissues.110 Hypoparathyroidism can occur in isolation (e.g., following surgery), as an autoimmune presentation, or in association with hereditary defects that include abnormalities of PTH biosynthesis, PTH secretion, or parathyroid gland development.110

Administering the synthetic or recombinant fragment of human parathyroid hormone 1-34 [PTH (1–34)] has been shown to benefit patients with hypoparathyroidism. This truncated form of PTH which has been approved for the treatment of osteoporosis is not approved for the treatment of hypoparathyroidism in the US. The full-length molecule [PTH (1–84)] is approved for the treatment of hypoparathyroidism in the United States.110,111,118 One review expressed optimism that these treatments may lower or eliminate the need for supplemental calcium and vitamin D; the review called for long-term studies of safety and efficacy.118 In 2010, a 24-month open-label study of PTH (1–84) in 30 patients with hypoparathyroidism reported significantly reduced requirements for supplemental calcium and vitamin D (P < .05 for both comparisons).119 A later group of researchers reported that hypoparathyroidism compromised patients’ quality of life; the researchers updated a 1-year study of recombinant human PTH (1–84)120 by conducting a 5-year open-label study of the product.118 In their intention-to-treat analysis, they found that quality of life measures began to improve after 2 months and persisted through 5 years (P = .001), as did biochemical and skeletal indexes (P < .0001). Other researchers conducted a 6-month, double-blind, placebo-controlled study of PTH (1–84) in 62 patients and did not find an improvement in patients’ quality of life, although they noted that the high level of hypercalcemia among their patients may have been a potentially confounding factor.121

VII PAGET’S DISEASE OF BONE (OSTEITIS DEFORMANS)

A 2014 clinical practice guideline from the Endocrine Society defined Paget’s disease of bone (osteitis deformans) as a chronic, benign disorder that affects one or more bones. It begins with bone resorption by large osteoclasts followed by a high rate of formation of poorly organized bone, resulting in both a marked increase of bone cell activity and abnormal bone structure.122

7.1 PREVALENCE AND INCIDENCE

The authors of the 2014 Paget’s Disease of Bone Endocrine Society Clinical Practice Guideline estimated that rates of Paget’s disease in the US are approximately 2-3% among patients ≥ 55 years and suggested a 10-
20% incidence of autosomal dominant transmission within families affected by the disease.\textsuperscript{122}

7.2 DEMOGRAPHIC DIFFERENCES
The sequestosome 1 gene, which affects osteoclast biology, has been implicated in familial Paget’s disease,\textsuperscript{123,124} and various studies have reported that mutations in this gene occur in 25-50% of patients with familial Paget’s disease.\textsuperscript{125} Other studies have concluded that genetic mutations alone are insufficient to cause the disease, and that exposure to environmental factors (e.g., measles virus nucleocapsids or other factors) are likely involved.\textsuperscript{126} Still other researchers have highlighted an increased prevalence of vitamin D deficiency in Paget’s disease patients.\textsuperscript{127} Because most patients are asymptomatic, disease discovery typically is empirical and results from either elevated serum alkaline phosphatase levels or a radiograph or bone scan ordered for another disorder. The most frequently affected bones are the pelvis, vertebrae, skull, femur, and tibia.\textsuperscript{122}

7.3 LIFE EXPECTANCY AND MORTALITY
A retrospective case review in Hong Kong from 2000 to 2010 identified seven patients (5 men, 2 women, mean age 66) with x-ray or CT findings of Paget’s disease.\textsuperscript{128} Most patients had polyostotic disease, and during follow-up did not present any Paget’s disease-related complications or malignant transformations. Investigators studying pharmacologic treatments reported similar results (see next section).

7.4 KEY TRENDS AND HEALTH OUTCOMES
According to the Endocrine Society guideline, pharmacological treatment of both asymptomatic and symptomatic patients involves bisphosphonates.\textsuperscript{122} A recent review generally concurred with these findings, but noted that treatment benefits in asymptomatic patients are controversial and are not evidence-based and thus should be individualized with careful monitoring.\textsuperscript{129} This author summarized studies that compared the efficacy of different bisphosphonates in the treatment of Paget’s disease and concluded that zoledronic acid is an attractive option, in part because it does not have the negative gastrointestinal effects associated with oral bisphosphonates that often lead to noncompliance. Others have reported similarly favorable outcomes following treatment with zoledronic acid.\textsuperscript{130-132} Denosumab, a monoclonal antibody that binds to RANKL and inhibits osteoclastic bone resorption, has been used in some patients who do not respond well to bisphosphonates. Calcitonin, which was used before bisphosphonates became widely available, shows untoward side effects and generally should be used only in patients who cannot tolerate bisphosphonates.\textsuperscript{129}

Several studies have suggested that the occurrence and severity of Paget’s disease is declining worldwide. Other studies have reported the effectiveness of pharmaceutical agents in reducing pain, improving patients’ quality of life, normalizing bone turnover, and healing lytic lesions.\textsuperscript{125} Conditions associated with Paget’s disease are generally of greater clinical concern than the disease itself. For example, Pagetic osteosarcoma is a rare complication of Paget’s disease. A group of Italian researchers found that between 1961 and 2006, patients treated at their hospital for Pagetic osteosarcoma had poor outcomes following surgery either with or without subsequent chemotherapy or radiotherapy.\textsuperscript{133}

8 PHOSPHATE DISORDERS

Adults consume approximately 1.5 g of phosphorous per day, and ingestion and excretion of phosphate is tightly regulated because of its structural role in bone and its central role in functions such as the formation of phospholipids and the generation of adenosine triphosphate.\textsuperscript{134}

Hypophosphatasia is a rare inherited disorder that disrupts the development of bones and teeth due to mutations in the tissue non-specific \textit{ALPL} gene, which is responsible for the production of alkaline phosphatase.\textsuperscript{135} The disease can affect babies in utero as well as infants, children, and adults.\textsuperscript{136} Hypophosphatasia has been reported to be especially prevalent in inbred Mennonite families from Manitoba, Canada. About four in 100 individuals are carriers, and one in 2,500 newborn children manifests a severe case of the disease. In addition, the incidence of the severe forms in Toronto, Canada was estimated to be 1 in 100,000 live births.\textsuperscript{137,138} The first enzyme-replacement therapy\textsuperscript{139} for patients with hypophosphatasia, Strensiq (asfotase alfa), is currently pending approval consideration by the FDA.

Hypophosphatemia is an uncommon disorder that can result from changes in renal phosphate handling,
often as a result of excess fibroblast growth factor 23 (FGF23).\textsuperscript{140} Osteocytes in bone produce FGF23; in addition to lowering serum 1,25-dihydroxyvitamin D levels, excess FGF23 causes hypophosphatemic osteomalacia. Secondary hyperparathyroidism may result from chronic phosphate supplementation over many years. In contrast, FGF23 deficiency leads to elevated serum 1,25-dihydroxyvitamin D levels and familial hyperphosphatemic tumoral calcinosis.\textsuperscript{140-142}

Researchers have associated excess phosphorus intake with the disruptions of mineral metabolism, vascular calcification, impaired kidney function, and bone loss.\textsuperscript{143} In addition, it has been suggested that excess extracellular phosphate may be involved in the secretion and actions of FGF23 and PTH. As a result, elevated dietary phosphorus may contribute to renal failure, cardiovascular disease, osteoporosis, and hypocalcaemia.\textsuperscript{144,145}

Little to no information is available regarding the epidemiology of phosphate disorders in the US.
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