Chapter 12
Bone Health in Midlife Women

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Introduction

Osteoporosis and low bone mass (formerly osteopenia) are common disorders characterized by a decrease in bone mass and a reduction in bone micro-architecture and strength (ISCD 2013). This decline in bone integrity can lead to a heightened risk of fractures, disability, and chronic pain. Because many people are not aware they have low bone density until they experience a fracture, osteoporosis is known as a "silent epidemic," and has been identified as a major public health problem that affects populations worldwide (Bartl and Frisch 2004; IOF 2010). While men and women are both at risk for low bone density and fractures, particularly with advancing age, women at midlife are arguably the most vulnerable demographic group.

How have researchers and clinicians made and continue to make visible this invisible or "silent" epidemic, in particular, for midlife women who represent the highest risk group? In this chapter, we present an overview of the available techniques that cast light on this condition so that global treatment and prevention efforts may be more effectively targeted. Furthermore, this chapter will highlight that even when these techniques are available, bone health status can continue to be obscured and remain invisible to those individuals seeking answers. There are many reasons for this: first, we establish that knowing one's bone density value alone may not provide a reliable predictor of fracture risk; second, as techniques improve, those measures that we traditionally associate with bone fragility, may not be as

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predictive as originally thought. Finally, because of the many potential influences on bone maintenance and loss during the female life span, particularly at midlife, what we expect to observe may not always be supported by population-level data.

Bone Health in Midlife Women

Although advancing age is a key contributor to bone loss in both sexes (Frost 2003), a number of factors have been implicated in the development of osteoporosis including genetics (Ferrari et al. 1998), physical activity (Dargeant-Molina et al. 1996; Kemper et al. 2000; Proctor et al. 2000), and diet and lifestyle (Anderson et al. 2004; Bunker 1994; Dawson-Hughes 2004). However, because of its multifactorial etiology, establishing a causal relationship with bone loss for any one of these factors has been challenging (e.g., Hernández-Avila et al. 1993; Lazenby 1997; Sampson 2002).

Females are especially susceptible to the development of low bone density, particularly as they enter perimenopausal and postmenopausal life. While one in five men will experience an osteoporotic-related fracture, one out of every two women over age 50 is at risk (NOF 2014). This vulnerability is due in major part to the obligatory cessation of ovarian function and subsequent reduction in production of critical bone-maintaining hormones including estrogens and progesterone (Galloway 1997). Estrogens, through a complex interaction with bone cells, cytokines, and calcium-regulating hormones, play a central role during the course of the female life span by influencing bone and collagen formation, and increasing intestinal absorption and retention of calcium. These hormones also inhibit bone remodeling by reducing the number of cells that are responsible for bone resorption and formation (Agarwal and Stuart-Macadam 2003; Galloway 1997; Guyton and Hall 2011). Similar benefits are afforded by progesterone, which may serve to promote bone accrual and turnover (Prior 1990). Consequently, menopause-related decline in ovarian function leads to an imbalance of hormones in favor of bone resorption.

The relationship between bone health and reproduction does not begin and end with menopause; rather, reproductive patterns influence bone density across the female life span. More specifically, because of the fluctuating nature of circulating hormones across female reproductive life, bone density levels undergo oscillations. While peak bone mass is achieved in early adulthood, bone density changes have been well documented across various reproductive states including pregnancy and lactation (e.g., Ensom et al. 2002; Sowers et al. 1993). During pregnancy, the maternal skeleton typically exhibits an increase in bone mass, which is most likely due to higher levels of estrogens that inhibit bone loss, and in some cases, promote bone accretion (e.g., Lees et al. 1998). Pregnancy-related weight gain (i.e., increased bone loading), as well as greater intestinal calcium absorption, also contribute to the protective effect that being pregnant has on bone mass (Nguyen et al. 1995; Streeten et al. 2005). Similarly, the duration, timing, and intensity of lactation all appear to influence bone density, although because of the variable nature of these factors

across females, exactly how that relationship shapes long-term bone health remains unclear. For example, some studies show a protective effect (Hreschchyshyn et al. 1988; Pearce 2006), while others document a negative influence of breastfeeding on bone density (Affinito et al. 1996; Drinkwater and Chestnut 1991; Kent et al. 1993; Lamke et al. 1977; Sowers 1996). The interaction between multiparity and lactation can further obscure how breastfeeding patterns might influence skeletal health in the short-term and especially long-term, a problem that is complicated by a reliance in many studies on retrospective self-report data. Despite these issues, there is an emerging consensus across several longitudinal studies that bone loss appears to be transient during the lactation cycle, and, upon weaning, bone integrity is restored to baseline, pre-pregnancy values (Pearce 2006; Sowers 1996).

As with lactation, menopause represents a hypoestrogenic state, and, therefore, bone loss among midlife women involves the same physiological trigger that prompts calcium mobilization and the loss of estrogens and progesterone. However, the hormonal preparation that permitted earlier accumulation of calcium during pregnancy is not present at menopause nor is the compensatory accretion that occurs at weaning (Galloway 1997). As a result, there is only progressive loss of bone mass during perimenopausal and postmenopausal life. Unsurprisingly, male reproductive patterns have less of an effect on skeletal health than among women, although men may be susceptible to increased bone resorption due to testosterone deficiency that occurs in the later stages of life (Snyder et al. 1999).

Evolutionary and Life History Explanations for High Risk Among Women

Broadly, female propensity for enhanced bone loss has been articulated as a trade-off between reproduction and skeletal health and, specifically, an example of antagonistic pleiotropy where there are positive effects at young, reproductive ages despite negative influences in later life (Galloway 1997). Successful reproduction during premenopausal life requires the enhanced ability to mobilize calcium in order to meet the ontogenic needs of the gestating and postnatal infant. Calcium is an essential mineral whose absorption and use by the body is facilitated by estrogens. These latter regulatory hormones fluctuate depending on the calcium requirements of the body with the greatest reduction or "cost" occurring during lactation. However, as noted earlier, this heightened mobilization of calcium during lactation which manifests as bone loss appears to be temporary, returning to baseline values within twelve months of parturition (Sowers et al. 1993).

As the most pronounced and permanent bone loss among females is experienced during the perimenopausal and postmenopausal years, selection to maintain bone during later life has been reduced. During midlife, bone physiology has been decoupled from direct fitness benefits, although bone mass may be maintained by other factors such as inclusive fitness benefits of somatic maintenance (e.g., Hawkes

et al. 1998). Therefore, postmenopausal bone loss has been framed as an example of antagonistic pleiotropy in which traits that are beneficial to early reproductive life, including highly effective mechanisms for the mobilization of calcium for offspring, become deleterious when coupled with other senescent-related physiological changes (Carter and Nguyen 2011; Galloway 1997; Kirkwood 2005).

While most commonly theorized within this framework, there have only been a few genes identified as examples of antagonistic pleiotropy. With regard to bone density, Cheung et al. (2008) noted that the presence of guanine instead of the more common adenine in the ALOX15 gene was associated with a reduced risk of low bone mineral density (BMD) among premenopausal women but a heightened risk in postmenopausal women. Here, the guanine allele appears to play a role in determining one's risk of developing osteoporosis although the function varies depending on the life stage. While other candidate genes for osteoporosis risk have been identified, empirical evidence of antagonistic pleiotropy is limited. So while this oft-employed model may be a theoretically sound explanation for bone loss in midlife women, with the exception of the ALOX15 gene, it remains one that has weak empirical support.

The nuances of female reproduction on postmenopausal bone density may be demonstrated through a comparison of two indigenous Amazonian populations: the Tsimane of Bolivia and Shuar of Ecuador, both forager-horticulturalist groups. Cross-sectional studies of these groups are among the only ones currently available that investigate maternal bone reserves in relation to reproduction in natural fertility, subsistence-based, non-industrialized populations (Madimenos et al. 2012; Stieglitz et al. 2015). Further, bone density data for both populations were gathered using the same calcaneal ultrasonometry device, and thus comparisons between the Tsimane and Shuar are not wrought with issues that arise with comparisons across differing technologies.

Among postmenopausal Tsimane women, higher parity, short birth spacing, and early age at first birth were found to be associated with reduced bone density, after adjusting for potential confounders. Greater cumulative reproductive burden among females seemed to be independently related to lower bone density and jointly related with other lifestyle, developmental, and heritable factors (Stieglitz et al. 2015). Results suggested that the maternal skeleton may serve to give vital nutrients to growing offspring, but at the expense of reduced maternal bone density. The "disposable soma" theory of aging was proposed as a theoretical framework to understand these findings (Kirkwood and Rose 1991). Disposable soma theory, an extension of antagonistic pleiotropy, contends that an organism invests only enough energy into somatic repair, including its bones, to maintain it in reasonable condition for as long as it has an opportunity to reproduce; hence, the body is "disposable." With regard to the Tsimane, greater lifetime reproductive effort among postmenopausal women was significantly associated with reduced calcaneal bone density, an indicator of somatic decline.

Among the Shuar, however, neither multiparity nor lactation duration appeared to be adversely related to bone density among women of postreproductive age (Madimenos et al. 2012). In fact, a main finding was that among postmenopausal

women, females who were younger at menarche (12–13 vs. 14–15 years old) exhibited significantly better bone health. Earlier menarcheal age may have a stimulating effect on bone development by enhancing bone formation that coincides with circulating estrogens, thereby establishing higher peak bone mass, which provides a foundation for better bone health in later adulthood. These results suggest that the timing of menarche and factors that influence its onset, including nutrition and disease burden, may be associated with postmenopausal bone density. It is proposed that postmenopausal Shuar women who experienced early menarche may be in better phenotypic condition than those who experienced first menses later (Madimenos et al. 2012). Although more studies are needed, the Shuar example provides support for the integral role of early life history stages in shaping one's later risk of bone loss.

Given the vastly different conclusions drawn from many clinical studies regarding reproduction and long-term bone health, the inconsistent findings between the Tsimane and Shuar studies are not surprising. Because of the complex interacting factors related to bone maintenance and loss that manifest across the life course, it is likely that a single explanatory evolutionary framework for understanding skeletal health is insufficient in the same way that a single behavioral mechanism of bone loss may not be identified. The Tsimane and Shuar findings do underscore three major points. First, with both disposable soma and early developmental origins of adult disease offered as possible interpretative frameworks, the classic antagonistic pleiotropy theory may be an oversimplified model for explaining female susceptibility to bone loss. Second, these findings emphasize a need for more robust datasets from small-scale societies in order to eliminate the need for controlling for the vast variation in physical activity levels and oral contraceptive use that are characteristic of Western, industrialized populations. Studies of these latter populations provide the basis for most current knowledge of bone health, leaving a major gap in the literature. Finally, these results highlight the extent to which evolutionary and life history approaches to bone loss can offer novel and complementary insight to augment clinical and epidemiological literature.

Clinical Recommendations

Osteoporosis is often referred to as the "silent" disease because bone loss progresses over time without any discernible symptoms. Many people are unaware that they have osteoporosis or that they are at risk of developing the condition until a bone densitometry test is administered or they experience a minor fall. Because of the higher risk of low bone density among women in general, the National Osteoporosis Foundation and the US Preventive Services Task Force recommend testing all women age 65 years and older regardless of clinical risk factors (NOF 2010; US Preventive Services Task Force 2011); for males, the minimum age recommendation is 70 years. Younger postmenopausal women between 50 and 65 years old should also be tested if there is cause for concern based on clinical

risk factors. Additionally, women who are undergoing the menopausal transition and have a specific factor associated with increased fracture risk (e.g., prior fracture, taking high-risk medication) should be tested. Although there are a number of available technologies that can indicate a person's risk of osteoporosis, diagnosis can only be established or confirmed by a measurement of bone density performed by a dual-energy absorptiometry (DEXA) scan.

Assessing Bone Health

Bone mineral density (BMD), the most important diagnostic parameter of bone health, is commonly used in clinical settings as an objective and reliable predictor of future fracture risk (Bartl and Frisch 2004; Levis and Altman 1998; Ross et al. 1995). BMD can be measured through a variety of means including DEXA and quantitative ultrasound (QUS), while other indicators of bone health can be assessed using biomarkers. Regardless of the technique employed, access to diagnostic tools will vary based on regional and local resources. Additional supplementary techniques, such as the computer-based fracture risk assessment tool (FRAX), may aid in more accurately predicting an individual's 10-year probability of a major osteoporotic fracture.

All available tools help to expose and assess individual-level bone health status and/or risk of developing osteoporosis and serve to increase the visibility of a largely cryptic disease. However, even with the relatively recent emergence and development of many of these technologies, osteoporosis status may continue to be obscured in places where diagnostic resources are limited. This issue is of notable concern in non-Western, non-industrialized regions where resources are generally allocated toward treatment and diagnosis of infectious diseases with limited funds apportioned for combating the rise in chronic disease. The extent of the global reach of this "silent" epidemic, therefore, remains unclear and undoubtedly underestimated (Madimenos et al. 2014).

It is important to recognize that even where access to health care is more expansive and diagnostic tools are available, individual-level fracture risk could remain unclear. While this point is expanded upon in the subsequent section, it is becoming increasingly apparent that a BMD value may not be sensitive and specific enough to predict risk. This limitation in the assessment of bone health status creates challenges when trying to make individuals cognizant of this "silent" condition.

Techniques and Tools for Assessing Risk

DEXA is the most widely used method for assessing BMD and diagnosing osteoporosis in clinical settings. The technique involves two X-ray beams positioned on a specific body site and the measurement of beam attenuation, a parameter related to

bone mineral content; this then allows the calculation of BMD expressed in absolute terms of grams of mineral per square centimeter scanned (g/cm^2). DEXA can measure central (hip and spine) and peripheral (forearm) sites, and also has the capacity to be used to perform a full body scan. It remains the only available technique that can confirm osteoporosis diagnosis (Schousboe et al. 2013).

For postmenopausal women and men aged 50 years and older, the World Health Organization (WHO) has established diagnostic T-score criteria (normal, low bone mass, and osteoporosis) based on measurements at the spine, hip, or forearm. T-scores compare an individual's BMD to that of the average healthy 30-year-old of the same sex and when possible, ethnicity. Broadly, ethnicity is a proxy for a variety of potentially shared cultural, religious, dietary, geographic, and genetic factors that affect bone mass, and for this reason, the interplay between ethnic background and sex is a more valuable determinant of osteoporosis risk than sex alone (Cauley 2011; Nelson and Villa 1999). Measured in standard deviation units (SD), osteoporosis is identified when a T-score is ≤ -2.5 SD while clinically low bone mass is confirmed at -1 to -2.5 SD (ISCD 2013). Z-scores or "age-matched" values may also be informative as they compare individual BMD with the average BMD for their age group, while accounting for sex and ethnicity. In younger populations, T-scores and Z-scores are usually similar; however, among older individuals, lower bone density values are more prevalent, thereby shifting the mean for these age cohorts. Age-matched comparisons can therefore be misleading because even if individual bone density falls within the average Z-score range, BMD may still be clinically low.

Although considered the "gold standard" in measuring bone density, DEXA scanners are expensive, not portable, and expose participants to ionizing radiation; these factors limit their use for non-clinical and screening purposes. Unfortunately, DEXA as a diagnostic tool is not universally available in many countries leading bone specialists to employ alternative technologies to predict risk of osteoporosis and fracture.

Quantitative ultrasound (QUS) techniques offer an alternative means of measuring skeletal health and are useful for screening individuals for osteoporosis risk. QUS provides information on both cortical and trabecular bone, and its measurements are influenced by several factors, including bone micro-architecture (Bartl and Frisch 2004). This technology has demonstrated utility both in research and in population-level screening, in part because QUS devices are portable and relatively inexpensive (Madimenos et al. 2014; Stieglitz et al. 2015). Moreover, validated calcaneal ultrasounds are highly correlated with DEXA and may predict fractures in postmenopausal women and in men 65 years and older (Langton and Langton 2000). While there is certainly variation in bone density among different skeletal regions, the calcaneus is a weight-bearing bone, similar to the femur, and therefore is an ideal single-site measure of bone density (Barkmann et al. 2000; Gerdhem et al. 2008; Nayak et al. 2006).

More recently, multiskeletal site ultrasonometers have gained popularity and a few studies have demonstrated their use in clinical and field-based settings (Barkmann et al. 2000). These devices typically operate using a hand-held probe to

generate and detect ultrasound waves. The probe is applied directly to the skin at multiple skeletal sites including the radius, tibia, phalanx, and metatarsal. Ultrasound is emitted by the generating transducers and transmitted along the bone. Multiskeletal site QUS devices have yet to be validated as extensively as the more established calcaneal devices but show promise for measuring skeletal fragility and monitoring bone changes that occur in the early years of the menopausal transition. Moreover, such devices are ideal for screening populations living in regions where diagnostic tools are limited.

While the screening benefits of QUS devices are notable, one must recognize that DEXA and ultrasonometry measure different aspects of bone quality and quantity. QUS uses sound waves to generate T-scores and Z-scores in addition to two primary measures of bone: broadband ultrasound attenuation (BUA; dB/MHz) and speed of sound (SOS; m/s). BUA is defined as the slope of attenuation versus frequency curve; SOS is the speed with which sound passes through bone, which is, in theory, related not only to the density of the bone, but also to bone size and quality (Bonnick 2010). Higher BUA and SOS values indicate greater bone density. BMD values generated by QUS devices are a composite parameter based on SOS and BUA, and while these devices may be used clinically for screening purposes, QUS-derived T-scores do not adhere to the same diagnostic cut-offs for low bone mass and osteoporosis as DEXA. A device-specific threshold for identifying individuals at higher risk of developing osteoporosis is necessary, although depending on the reference these thresholds may slightly vary (Frost et al. 2000). Values derived from ultrasound, therefore, may only identify whether individuals are at low or high risk for developing osteoporosis.

Additional methodological issues exist that are related to the value of T-scores as a measure for determining osteoporosis status and/or risk. Since populations used to establish reference standards for both DEXA and ultrasonometer devices are typically limited to specific ethnic groups (e.g., Caucasian-American, Chinese-American), this may pose issues in translating T-scores to an individual or population not represented in the device software. For example, employing ultrasonometer devices in remote, field-based settings for individuals who are not ethnically represented in the reference population database creates complexities for screening risk (Madimenos et al. 2014). One challenge then, for clinicians and health researchers globally, is to amass bone density data in order to establish reference standards and T-scores that are regionally and, moreover, population-specific.

FRAX Although BMD values are important for establishing the presence of osteoporosis and for tracking changes in bone density over time, documenting an individual's risk of fracture is necessary for informing treatment guidelines. Future fracture risk is difficult to predict using simply a BMD value derived from DEXA or QUS devices. Information about additional risk factors is needed. For this reason, the WHO created an easily accessible Web-based fracture risk algorithm called FRAX that is designed to calculate the 10-year probability of a major osteoporosis-related fracture based on easily obtained clinical risk factors (Lewiecki and Watts 2009). Risk factors including sex, weight, previous fractures, and family history of osteoporosis, can be used to assess fracture risk, with or without bone density

results. FRAX may be utilized for men and women and is validated globally, with output and utility of results adaptable to individual populations or regional/national standards. Models are now available in 39 countries and in 13 languages (Kanis et al. 2011; McClung 2012). While FRAX was devised to address limitations in BMD values for predicting individual-level fracture risk, the algorithm has some of its own limitations which restrict its universal use in clinical settings.

One major issue with FRAX is that not all risk factors are straightforward. For example, previous fractures are not clearly defined, and could include fracture sites not related to osteoporosis, such as fingers and toes (Lewiecki and Watts 2009). Additionally, fracture risk associated with corticosteroid use does not take into account dosage or treatment duration. Dose–response relationships in general are not a feature of FRAX which does not distinguish between single and multiple fractures, number, type, and severity of previous fractures or duration of alcohol use (Silverman and Calderon 2010). Another limitation is that not all potential risk factors are considered in the algorithm and in particular, measurements that are difficult to obtain by a primary care physician such as physical activity, vitamin D deficiency, or biomarkers of bone turnover, are excluded. Measures of frailty and risk of falls are also not incorporated in the FRAX model, and as a result, the risk for individuals with a history of multiple falls may be underestimated (Hans et al. 2011; McClung 2012). Despite these limitations, the use and interest in FRAX has continued to stimulate potential improvements to the model and aid in clinical interpretation (Kanis et al. 2011).

Biomarkers In recent years, attention has turned to the role of numerous biochemical markers of bone turnover to predict the rate of bone loss in postmenopausal women and to assess the risk of fractures. In osteoporosis treatment studies, markers of bone turnover may even appear more strongly associated with fracture risk reduction than BMD (Eastell and Hannon 2008). Biochemical markers of bone turnover, which can be measured in the serum and urine in untreated patients, are divided into two categories: markers of bone resorption [i.e., serum C-telopeptide (CTX), and urinary N-telopeptide (NTX)] and markers related to bone formation [i.e., serum bone-specific alkaline phosphatase (BSAP) and osteocalcin]. These biomarkers may predict bone loss and, when analysis is repeated after 3–6 months of treatment with antiresorptive therapies, may be predictive of fracture risk reduction (Eastell and Hannon 2008).

Menopause is marked by an increase in levels of markers of bone turnover, particularly markers of resorption. High bone turnover, in which bone resorption outpaces bone formation, is associated with low BMD. In postmenopausal women with osteoporosis, markers of bone resorption are significantly elevated while bone formation markers are less elevated and may be even reduced (Kushida et al. 1995).

Vitamin D has long been recognized as vital to the growth and development of bone because of its role in bone resorption and deposition. In general, this metabolite heightens calcium transport through cellular membranes, increases renal and intestinal absorption of calcium, and enables the mobilization of calcium from bones (Dawson-Hughes 2004). Vitamin D may also serve to improve muscle

strength, balance, and leg function, thereby decreasing the risk of falling and reducing risk of future fractures.

Vitamin D can be obtained through dietary sources (vitamin D_2; ergocalciferol) or endogenously synthesized via exposure to adequate amounts of sunlight (vitamin D_3; cholecalciferol). Vitamin D_2 and D_3 are carried by the bloodstream to the liver where they are converted into 25-hydroxyvitamin D, also known as calcidiol. With the influence of parathyroid hormone, vitamin D is also metabolized in the kidneys into the most active form, 1,25-dihydroxyvitamin D, or calcitriol (Holick and Chen 2008). This latter metabolite increases the active absorption of calcium through the gastrointestinal tract. Vitamin D deficiency develops when both the endogenous and exogenous (i.e., sunlight) sources are insufficient, thereby contributing to reduced bone mass. A diagnosis of vitamin D insufficiency and deficiency may be determined by assaying serum 25-hydroxyvitamin D levels (Hamdy and Lewiecki 2013).

Vitamin D has many beneficial effects across age groups and developmental stages. Sufficient levels of vitamin D are especially important during childhood growth as deficiencies can result in the childhood disease, rickets. During pregnancy, the serum concentration of vitamin D increases and remains elevated. This heightened presence appears to promote increased efficiency in transporting calcium into the circulation. In advanced age, absorption of vitamin D is reduced by as much as 40% compared to younger individuals (Gloth 1999). Beyond chronological age, additional factors that may contribute to vitamin D insufficiency in older individuals include reduced exposure to the sun, dietary deficiencies, decreased cutaneous synthesis of vitamin D, increased use of medications that interfere with vitamin D metabolism, and the greater likelihood of co-morbid conditions that can hinder vitamin D metabolism (e.g., fat malabsorption syndromes) (Holick 2006).

With its adverse effect on bone metabolism, vitamin D insufficiency has been recognized as an increasingly significant public health problem, particularly among midlife women (Malabanan and Holick 2003). In addition to senescent-related declines in vitamin D metabolism, estrogen deficiency that occurs during the perimenopausal and postmenopausal years may exacerbate hyperparathyroidism, likely due to a reduction in intestinal calcium absorption caused in part by decreased calcitriol levels (Malabanan and Holick 2003). The consequence of estrogen reduction and hyperparathyroidism include heightened bone resorption and accelerated bone loss which is most rapid during early menopause.

Across all ethnic backgrounds, vitamin D inadequacy appears to be particularly high among postmenopausal women, especially those with osteoporosis and history of fracture. A global assessment of vitamin D status in postmenopausal women with osteoporosis showed that 24% were deficient (<10 ng/ml), with the highest prevalence of low serum 25(OH)D in central and southern Europe (Lips et al. 2001). Given that populations living at latitudes above 37°N and 37°S have insufficient exposure to sunlight, particularly during the winter months, which in turn, affects vitamin D levels (Chen 1999; Webb et al. 1988), this finding is surprising. A number of potential explanations have been posited for the lower prevalence of low serum 25(OH)D levels in countries at higher latitudes. The high consumption of fatty fish and cod liver oil along with time spent outdoors were

postulated as contributing to the higher serum 25(OH)D levels observed in Norway and Sweden, in particular (Lips 2007; van Schoor and Lips 2011).

Additionally, cultural factors including clothing, sunscreen, and glass shielding can structure an individual's exposure to sunlight. For example, high rates of hypovitaminosis D are documented among Muslim women in the Middle East and the Indian subcontinent where many women maintain a conservative style of dress that covers most of their bodies, including hands and faces, and limits their exposure to sunlight (El-Hajj Fuleihan and Deeb 1999; El-Sonbaty and Abdul-Ghaffar 1996; Gannagé-Yared et al. 2000; Ghannam et al. 1999).

Dietary factors may also contribute to the high prevalence of hypovitaminosis D in Arab countries. Low milk consumption, especially among women, has been documented in Saudi Arabia (Elshafie et al. 2012), while vitamin D intake from all sources has been reported to be low in the Middle East (Bener et al. 2009; Lips 2007). The lack of vitamin D fortification in food further contributes to widespread low vitamin D levels (Badawi et al. 2012; Musaiger et al. 2011).

Connecting the Invisible with the Visible

Given the range of techniques available for assessing bone health status, it would seem that researchers and clinicians have shed much light on bone health in general, and specifically among midlife women, and indeed they have. With technological advancements in BMD measuring techniques, and increased understanding of the biochemical intricacies of bone formation and resorption, new research is refining our understanding of osteoporosis. However, there are unforeseen and emerging obstacles in the process of making visible the invisible condition that is osteoporosis. Some of these obstacles lie in the apparent disconnect between the biomarkers that are measured and their actual relationship to bone density. Additional unexpected barriers may arise when an individual's perception of their own health status conflicts with the reality of their measurement.

A Case Study: The Study of Women's Health in Qatar

The case study of vitamin D levels in Qatar highlights how self-reported vitamin D deficiency relates to serum levels of vitamin D and serves as an example of the occasional disconnection between the visible and the invisible (Gerber et al. 2016). The Study of Women's Health in Qatar was conducted in Doha, in the State of Qatar from July 2011 through May 2012. Participants in the study were recruited from nine primary health centers and were eligible for inclusion if they were between 40 and 60 years of age, were either of Qatari nationality or other Arab National, and were either Arabic or English speaking. Participants were excluded if they had a history of bilateral oophorectomy. Additional information has been

provided in earlier reports (Gerber et al. 2014, 2015). The protocol and consent form were approved by the institutional review committees at Weill Cornell Medical College-Qatar and at Hamad Medical Corporation, Qatar.

In the cross-sectional study, 523 women were asked, during face-to-face interviews, whether they suffered from any of a list of medical conditions, including vitamin D deficiency. Documented serum 25(OH)D levels measured within one year of the interview were also recorded and the level that was documented closest to the time of the interview was used. Vitamin D levels were categorized as vitamin D deficiency if serum 25(OH)D was less than 20 ng/ml and as insufficiency if less than 30 ng/ml.

The findings revealed that there was a high prevalence of low levels of serum 25 (OH)D. When using the cutpoint of <20 ng/ml, 53% of women were found to have these low levels. A higher, but still less-than-optimal level of serum 25(OH)D of <30 ng/ml, included 85% of the sample of women. Surprisingly, the mean measured level of serum 25(OH)D was very similar for those who reported vitamin D deficiency and for those who did not (19.7 ng/ml for those reporting vitamin D deficiency and 20.4 ng/ml for those not reporting deficiency). Similarly, women who reported taking vitamin D supplements had serum 25(OH)D levels that were not significantly higher than women who did not report taking supplements ($p = 0.37$).

Furthermore, agreement between self-report of vitamin D deficiency with measured serum 25(OH)D levels <20 ng/ml was very poor (kappa = −0.04, 95% CI = −0.10 to 0.02). Agreement was also poor when comparing self-report of vitamin D deficiency using the cutpoint of <30 ng/ml (kappa = −0.01, 95% CI = −0.04, 0.02). Even among women with levels $\geq$ 20 ng/ml, 82.4% believed that they were vitamin D deficient, while 13.3% who were below <20 ng/ml did not self-report deficiency. Among women who did not report vitamin D deficiency, 46.3% (37/80) had levels <20 ng/ml while 82.5% (66/80) had levels <30 ng/ml.

The implication of these findings is that what is visible, i.e., reported or believed to be correct, cannot always be taken at face value. Whether this lack of agreement between self-report and actual results can be attributed to women not knowing their laboratory results or simply their assumption that they were deficient is unclear. They may have expected that they were deficient because many reports exist in the literature, in both the scientific and lay press, that heighten awareness about the low levels of vitamin D found in Arab women generally (Ardawi et al. 2011; Kazmi 2005; Lips 2007), in the Gulf region (Dawodu et al. 1998; Fields et al. 2011), and in Qatar in particular (Alhamad et al. 2014; Badawi et al. 2012).

Many studies have reported on the strong relationship between levels of vitamin D and bone health. The Institute of Medicine (IOM 2011), the Endocrine Society (Holick et al. 2011), and the North American Menopause Society (NAMS 2010) have all recommended that vitamin D should be at sufficient levels in order to ensure optimal bone health. Yet the strength of the relationship between measured levels of vitamin D and bone mineral density, as measured by DEXA, is still unclear and under investigation.

For example, many studies have noted that blacks have lower vitamin D levels than whites yet, on average, BMD levels are higher in blacks than whites and their

risk of fragility fractures is lower. Women participating in The Study of Women's Health in Qatar, despite having a high prevalence of low serum 25(OH)D levels, had low levels of low bone mass and osteoporosis (Gerber et al. 2015). The prevalence of osteoporosis was 1.4% at the spine and 0.2% at the femur. This prevalence compares favorably to rates found among US women in the third NHANES, where 20% of women aged 50 years and older were diagnosed with osteoporosis (Looker et al. 1995).

One possible explanation for the disconnect between the high prevalence of low vitamin D levels among midlife women living in Qatar and the relatively low levels of low bone mass observed may be explained by what is being measured. There is a growing body of literature suggesting that it is the "bioavailable" vitamin D, vitamin D that is not bound to the vitamin D-binding protein, which is more closely related to bone metabolism than the total circulating levels of vitamin D (Powe et al. 2013). In contrast, vitamin D bound to the protein may be unavailable to many target tissues (Bhan 2014).

A study by Powe et al. (2013) found that, despite the fact that blacks had lower levels of 25-hydroxyvitamin D levels than whites, their levels of bioavailable 25-hydroxyvitamin D levels were similar to those of whites while their vitamin D-binding protein levels were lower than that of whites. In a previous study, these investigators found that bioavailable levels of vitamin D were more closely related to bone density as measured by DEXA than were total levels of vitamin D (Bhan et al. 2012).

Much of the variation in the levels of vitamin D-binding protein as well as its variability in function have been attributed to a few specific genetic polymorphisms (Bhan 2014). In particular, gene polymorphisms have been reported to be associated with serum vitamin D levels (Chun et al. 2014; Elkum et al. 2014). In a recent study conducted in Kuwait, two of the CRP2R1 SNPs and one GC SNP were found to be significantly associated with serum vitamin D levels only in people of Arab origin. The authors suggest that this exclusive association supports their potential roles related to the mechanisms of vitamin D deficiency in this population (Elkum et al. 2014).

Conclusions

Bone health is critically important to one's overall health and well-being. The promotion of skeletal health has been recognized as a public health issue, and there is growing concern that, as more people live to advanced ages, the prospects of declining bone health status across populations will only worsen (Office of the Surgeon General 2004). Skeletal health status is mostly invisible and osteoporosis is referred to as a "silent" disease because it is usually asymptomatic and often not detected unless a fracture occurs (Weston et al. 2011). For health researchers, it is often a challenge to translate bone health status to something that is "visible," or meaningful, to the individual. Great progress, however, has been made over the last

few decades toward the development of methods that measure and assess bone health. The methods used to uncover the underlying state of bone health among different individuals and populations often depend upon access to technology, resources, awareness, and cultural practices. These measures may very well change over time to enable us to more accurately predict, and hopefully, prevent, low bone mass. Future research may find that additional markers illustrate health differently in various populations as individualized or personalized medicine expands to the entire spectrum of health care.

While these techniques are not perfect and are continually developing, they do provide health researchers with a better means of contextualizing health status and arm them with information that helps guide hypotheses and expectations about health patterns in a population. At times, what clinicians and health promoters expect to observe does not align with reality. This is especially relevant regarding studies on bone health in midlife women because of the complexities of normal bone growth and development, the multiple interacting factors that contribute to cumulative bone loss and maintenance over the life course, and evolutionary and life history features that may predispose females to bone loss or mediate their risk of low bone density. These layers of complexity are exemplified in research from Tsimane and Shuar, the results of which highlight potential issues with searching for universal or singular behavioral and evolutionary risk factors affecting midlife bone health.

The case study of women in Qatar also highlights how it may be informative to not only report the observations of health researchers, but to also take into account an individual's perception of her own health. The lack of agreement between what women themselves think about their health status and what their measures actually reveal speaks to the importance of effective communication between healthcare providers and patients/individuals. Educational tools and furthering dissemination of osteoporosis-related health information may offer a means of shedding light on the obscurities of the silent epidemic.

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