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Anti-Mullerian Hormone as Predictor of Future and Ongoing Bone Loss During the Menopause Transition

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Abstract

The menopause transition in women is a period of significant bone loss, with rapid declines in bone mineral density (BMD) commencing a year before the final menstrual period (FMP). Changes in menstrual bleeding patterns cannot reliably tell us if this rapid bone loss has begun or is imminent. We hypothesized that low circulating levels of Anti-Mullerian Hormone (AMH), which decline as women approach the FMP, would be associated with future and ongoing rapid bone loss. We used data from The Study of Women's Health Across the Nation, a multi-site, multi-ethnic, prospective cohort study of the menopause transition to test this hypothesis. Adjusted for age, body mass index, race/ethnicity, and study site, every 50% decrement in AMH level in premenopause and early perimenopause was associated with 0.14% per year faster decline over the following 3–4 years in lumbar spine BMD and 0.11% per year faster decline in femoral neck BMD ($p<0.001$ for both). AMH in late perimenopause was not associated with the rate of future BMD decline. AMH was also associated with the magnitude of ongoing bone loss, measured as

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Disclosures

Anthony Morrison was an employee of Ansh Labs (Webster, TX) at the time this study was started; Ansh Labs performed AMH assays for the SWAN study free of charge. Mr. Morrison is currently with Motive Biosciences. The authors declare that there are no other potential conflicts of interest.

percent of peak BMD lost by the end of the next 2–3 years. Every 50% decrement in AMH level was associated with 0.22% additional loss in spine BMD in premenopause, 0.43% additional loss in early perimenopause, and 0.50% additional loss in late perimenopause ($p<0.001$ for all three). If a woman will lose more of her peak BMD than the site-specific least significant change (LSC) at either the lumbar spine or femoral neck by the next 2–3 years, then AMH below 100 pg/mL will detect it with sensitivity of 50% in premenopause, 80% in early perimenopause, and 98% in late perimenopause. These findings suggest that AMH measurement can help flag women at the brink of significant bone loss, for early intervention.

Keywords

Menopause; Osteoporosis; DXA; Epidemiology; General population studies

Introduction

The transition from premenopause to postmenopause is a time of rapid bone loss in women, with average declines in bone mineral density (BMD) of 6 and 7%, respectively, in the femoral neck and lumbar spine, over 3 years bracketing the final menstrual period (FMP) date (1). This decline in BMD is accompanied by deleterious changes in bone microarchitecture, possibly further compromising bone strength, and increasing susceptibility to fragility fracture in later years (2,3). Not surprisingly, the incidence of fractures of the vertebra, radius, ulna, and humerus starts to increase sharply after the menopause transition (MT) (4,5); thus, the rationale for intervening early to attenuate MT-related loss in bone strength and reduce future fracture risk. In order to do so however, we need to be able to determine if the woman is about to start, or has already started, to rapidly lose bone mass. The large coefficient of variation in BMD measurements by dual x-ray absorptiometry (DXA) precludes the possibility of using serial BMD measurements in an individual as an early warning that MT-related bone loss has begun (6); several years of BMD decline will have already occurred before the cumulative loss is large enough to be reliably detected.

Since MT-related bone loss starts 1 year before the FMP, and the FMP can be dated only after 12 months of amenorrhea, the onset of bone loss can be determined from clinical menstrual bleeding information only retrospectively, 2 years after rapid loss has commenced. Recognizing the onset of MT-related rapid bone loss in real time, however, requires being able to reliably determine, *before* it has occurred, that the FMP will be within the next 12 months. Several recent studies have demonstrated the potential of serum anti-Mullerian hormone (AMH) level, a marker of ovarian reserve, to predict if the FMP is imminent vs. distant (7,8,9). This has been made possible by the development of new high-sensitivity AMH assays that can quantify AMH levels in the pg/mL range (). We therefore, hypothesized that low serum levels of AMH would be strongly associated with future and ongoing bone loss during the MT, and could be used to determine whether a premenopausal or perimenopausal woman has begun, or is about to begin, experiencing MT-related bone loss. We used longitudinal data collected from premenopause, through the MT, and into the postmenopause, from the Study of Women's Health across the Nation

(SWAN) to answer the following question: **Q1**. Does the serum level of AMH in a pre- or perimenopausal woman predict her *rate of future BMD decline over the next 3 to 4 years*?

In clinical practice, measurement of AMH is likely to occur only after menstrual bleeding becomes irregular, at which point MT-related bone loss will already have commenced in some women. To include the possibility that BMD decline may be ongoing at the time of AMH measurement, we address a second question: **Q2**. Is the current level of serum AMH associated with *the fraction of peak BMD that will have been lost after a few years, including both ongoing and imminent loss*? If the answer to these questions is yes, then serum AMH levels may be clinically useful indicators of whether or not MT-related bone loss has already begun (i.e., is ongoing) or is about to commence (i.e., is imminent). Longitudinal cohort data from SWAN were used to address both questions.

Methods

SWAN is a prospective cohort study of the menopause transition in community-dwelling women who, at baseline, were between 42 and 52 years of age, had intact uterus and at least 1 ovary, were in premenopause (regular menstrual bleeding in the past year) or early perimenopause (less predictable menstrual bleeding at least once every 3 months), and were not on sex steroid hormone therapy. The cohort of 3,302 participants was recruited at seven study sites (Boston, MA; Chicago, IL; Detroit, MI; Pittsburgh, PA; Los Angeles, CA; Newark, NJ; Oakland CA); every site recruited non-Hispanic White women and women from one other race/ethnicity group. Four sites (Boston, Chicago, Detroit, and Pittsburgh) recruited Black women, the Newark site recruited Hispanic women, the Los Angeles site recruited Japanese women, and the Oakland site recruited Chinese women (12). Two study sites (Chicago and Newark) did not measure bone density; the SWAN Bone Cohort is composed of the 2,365 participants from the other 5 study sites.

Follow up visits occurred at intervals of 1–2 years, and included both repeat bone density measurements and fasting blood draws. At each study visit, a fasting blood draw between 8:00 and 10:00 AM was obtained in the early follicular phase (days 2–5) of a spontaneous menstrual cycle. As women progressed through the MT, it became increasingly difficult to schedule a day 2–5 blood draw within 60 days of the expected visit date, because of cycle irregularity. If 60 days had passed, the visit was scheduled at any convenient date in the next 30 days. Serum was processed promptly, frozen, and stored at −80° C until thawed for measurements. Participants also provided a fasting, non–first-void urine sample. Urine specimens were stored at −80°C until assays were performed. All SWAN participants have completed the MT, but not everyone had a natural (non-surgical) transition with known FMP date.

Study Samples.

Of the 2,365 women in the SWAN Bone Cohort, 1073 had a natural (non-surgical) MT with known FMP date and at least one AMH measurement before becoming postmenopausal (defined as one year after the FMP). Women were excluded for not having a follow-up BMD in the specified time period after the AMH measurement (3–4 years after AMH measurement for Analysis 1 to address Q1: 118 women, and 2–3 years after AMH

measurement for Analysis 2 to address Q2: 96 women), for use of bone-beneficial medications prior to the follow up BMD measurement (menopausal hormone therapy, calcitriol, calcitonin, bisphosphonates, denosumab, and parathyroid hormone: 31 women for Q1 analysis and 26 women for Q2 analysis), and for use of bone-detrimental medications prior to the follow up BMD measurement (oral or injectable glucocorticoids, aromatase inhibitors, selective estrogen receptor modulators, gonadotropin releasing hormone agonists, and anti-epileptic agents: 36 from Q1 analysis and 27 from Q2 analysis). This left us with 3,013 AMH observations from 888 women in Study Sample 1 (for Q1 analysis) and 3,211 AMH observations from 924 women in Study Sample 2 (for Q2 analysis). All AMH measurements before postmenopause were included in the analyses; most women contributed multiple observations to the analyses. Mean number of observations per woman was 3.4 for Analysis 1 and 3.5 for Analysis 2.

Measurements – Primary Predictor.

AMH was measured using a 2-site ELISA (MenoCheck picoAMH ELISA, Ansh Labs (10)) with intra- and inter-assay coefficients of variation ranging from 2.5% to 5.1% and 3.4% to 4.9%, respectively, at levels of 91 and 290 pg/mL. The lower limit of detection was 1.85 pg/mL.

Measurements – Outcomes.

At each study visit, femoral neck (FN) and lumbar spine (LS) BMD were measured using Hologic DXA scanners (Hologic, Inc., Waltham, Massachusetts). An anthropomorphic spine phantom was circulated to create cross-site calibration. The Boston, Detroit, and Los Angeles sites began SWAN with Hologic 4500A models and subsequently upgraded to Hologic Discovery A instruments. The Davis and Pittsburgh SWAN sites initially used Hologic 2000 models and later upgraded to Hologic 4500A machines. When a site upgraded hardware, it scanned 40 women on both its old and new machines to develop cross-calibration regression equations. A standard quality control program included daily phantom measurements, local site review of all scans, central review of scans that met problem-flagging criteria and central review of a 5% random sample of scans. Short-term *in vivo* measurement variability was 0.014 g/cm^2 (1.4%) for the LS and 0.016 g/cm^2 (2.2%) for the FN.

The dependent variable for our first analysis (designed to answer Q1) is the *annualized rate of BMD decline* in the years following the AMH measurement, and was calculated as the percentage of BMD lost between the AMH measurement visit and the follow-up visit 3–4 years later, divided by the number of years between the two visits. Separate rates of decline (in % per year) were calculated for the LS and the FN. The dependent variable in the second analysis (designed to address Q2) is the *percentage of peak BMD* (measured at the SWAN baseline visit when women were either premenopausal or early perimenopausal) *lost by the follow-up visit* 2–3 years *after* the AMH measurement. Here, the interval of bone loss brackets the date of AMH measurement - the baseline (pre- or early perimenopausal) BMD precedes AMH measurement, and the follow-up BMD is measured 2–3 years after AMH. This allows for bone loss to be ongoing at the time of AMH testing. See Figure 1

for the timeline of AMH and BMD measurements used in the calculations of the dependent variables for both Q1 and Q2.

Measurements – Covariates.

Race/ethnicity, age, and MT stage (premenopause, early perimenopause, or late perimenopause – defined as one or more menstrual bleeding gaps 3 or more months long but no gap of 12 or more months) were ascertained at every SWAN visit using standardized self-report or interview forms. Body height and weight were measured using standardized and quality-controlled protocols, and used to calculate body mass index (BMI). Serum level of follicular stimulating hormone (FSH) was measured in fasting blood samples using with a two-site chemiluminometric immunoassay; inter- and intra-assay coefficients of variation were 12.0 and 6.0%, respectively, and the lower limit of detection was 1.1 IU/L. Serum level of inhibin B was measured using an ELISA (Ansh Labs) with intra- and inter-assay CVs of <4% and lower limit of detection of 1.6 pg/mL. Urinary N-terminal telopeptide (NTx) – a marker of bone resorption, was measured using an automated immunoassay. The lower limit of detection of NTX was 10 nmol of bone collagen equivalents (BCE); intra- and inter-assay coefficients of variation were 2.8% and 4.8%, respectively. Urine creatinine (Cr) was measured using the Jaffé reaction. The lower limit of detection was 0.014 mmol, and the intra- and inter-assay coefficients of variation were 0.6% and 4.1%, respectively. Urine NTX was indexed to urine Cr, and resulting values are in nmol BCE / mmol Cr units.

Statistical Analysis.

We used multivariable, mixed effects, linear regression to estimate the association of log-transformed serum AMH level with BMD decline, in repeated measures, longitudinal data, and adjusted for age (continuous), MT stage, BMI, race/ethnicity, and study site. We used base-2 log transformed AMH as the primary predictor, so that a unit increment (or decrement) in the predictor translates to doubling (or 50% decrement) in AMH level. All time-varying covariate values were from the same visit as the AMH measurement. We included a random intercept at the participant level, to account for within-woman correlations across repeated measures over multiple study visits. Separate models were run for BMD at the LS and at the FN.

We tested for the possibility that AMH may have stronger associations with BMD decline in some MT stages than in others, by including interaction terms for clinical MT stage (premenopausal, early perimenopausal, late perimenopausal, or postmenopausal) at the time of the AMH measurement, with AMH. Results of interaction testing dictated that further analyses be stratified by MT stage. In MT-stage-stratified models, we tested for additional interactions with race/ethnicity and with BMI categories (<25, 25–30, 31–40, >40 kg/m^2). These interactions were not consistently significant across MT stages and across bone sites (LS and FN) and there was no discernible pattern of effect. Because of the distinct possibility that these interaction findings represent false discovery from multiple testing, we did not further stratify models by race/ethnicity or obesity.

To the MT-stage-stratified models, we added serum FSH, serum inhibin B, and urine NTx (measured at the same visit as AMH) to the models to determine if the prediction ability

of AMH was independent of these markers of proximity to FMP and bone resorption. Both FSH and urinary NTx have been shown to predict BMD decline during the MT (13,14). Because not all FSH measurements were obtained in the early follicular phase, we included a binary indicator variable that flagged FSH measurements that were outside the days 2–5 window of a menstrual cycle.

This modeling strategy was used for analysis of both future BMD decline rate (to address Q1) and of ongoing BMD loss in an interval that brackets the date of AMH measurement (to address Q2). For the latter analysis, we went one step further, and examined the sensitivity and positive predictive value (PPV) of AMH level below discrete thresholds for detecting significant ongoing bone loss. Bone loss was deemed to be significant if the cumulative decline in BMD exceeded the DXA machine's least significant change (LSC). The coefficient of variation (CV) for BMD measurements in SWAN was 1.4% at the LS and 2.2% at the FN; the LSC (which is 2.8 times the CV) is thus 3.9% for LS BMD and 6.2% for FN BMD. Significant bone loss was therefore deemed present if the proportion of bone lost from the baseline visit to the visit 2–3 years after AMH measurement (See Figure 1) exceeded these site-specific thresholds of 3.9% and 6.2% for the LS and FN, respectively.

Results

At SWAN baseline, in both study samples, mean age was 47 years, and two thirds of the participants were in early perimenopause; 3% were in late perimenopause, and the rest were premenopausal. Forty four percent of participants in each sample were non-Hispanic White, 25% were Black, and nearly one third were either Chinese or Japanese (Table 1). In the longitudinal, repeated measures data, with multiple AMH measurements from each woman before she became postmenopausal (up to 8 AMH measurements, median 3 in both samples), mean age was 49 years. Two thirds of the AMH measurements were in early perimenopause; median and geometric mean of AMH over repeated observations were 67 and 45 pg/mL in Study Sample 1 and 58 and 39 pg/mL in Study Sample 2, respectively. Mean annualized BMD decline rate over the 3–4 years following AMH measurement (Figure 1) was 1.1% per year in the LS and 0.9% per year in the FN; mean percentage of peak BMD lost within 2–3 years after the AMH measurement (Figure 1) was 2.8% in the LS and 2.3% in the FN (Table 1).

AMH as Predictor of Future BMD Decline Rate:

Adjusted for age (continuous), MT stage, BMI (continuous), race/ethnicity, and study site (with all time-varying covariates measured at the time of AMH measurement), women with 50% less serum AMH experienced 0.14% and 0.11% per year faster decline in LS and FN BMD, respectively, over the next 3–4 years ($p<0.001$ for both outcomes) – data not tabulated.

In interaction testing, we found a statistically significant interaction of AMH with MT stage. While the association of AMH with future BMD decline rate was statistically no different in premenopause relative to early perimenopause (interaction $p=0.4$ for both LS and FN), it was statistically significantly different in early perimenopause relative to late perimenopause (interaction $p< 0.0001$ for LS, $p=0.002$ for FN). We therefore, stratified the analyses by MT

stage, with premenopausal and early perimenopausal AMH measurements in one stratum, and late perimenopausal observations in a second stratum.

In MT-stage-stratified analyses, adjusted for the same covariates, a lower AMH level was associated with faster decline in BMD at both bone sites (0.14% and 0.11% faster per year at the LS and FN respectively, per 50% decrement in AMH) in premenopause and early perimenopause, but was *not* associated with BMD decline rate at either bone site (LS or FN) in late perimenopause (See Table 2). BMI and race/ethnicity modified the associations of AMH with future BMD decline rate differently by bone site (LS vs. FN) and MT stage. In premenopause and early perimenopause, effect modification was observed by both race and BMI at the LS but not the FN; in late perimenopause, race and BMI modified AMH associations only at the FN (data not tabulated). Because of the inconsistency of these effect modification findings and the concern for false positive discoveries from multiple testing, we did not further stratify models beyond MT-stage stratification.

Additional adjustment for FSH, inhibin B, and U-NTx in the MT-stage-stratified models marginally reduced the strength of the association at each bone site, but it remained strongly statistically significant in pre- or early perimenopause (Table 2).

AMH as Predictor of Magnitude of Ongoing BMD Loss:

Adjusted for age (continuous), MT stage, BMI (continuous), race/ethnicity, and study site (with all time-varying covariates measured at the time of AMH measurement), women with 50% less serum AMH experienced an additional 0.37% and 0.27% loss in LS and FN BMD (relative to baseline BMD), respectively, by 2–3 years after the AMH measurement ($p<0.001$ for both outcomes) – data not tabulated.

There was a statistically significant interaction of AMH with MT stage: The associations of serum AMH with magnitude of BMD loss were statistically different from each other in the three MT stages: interaction $p<0.001$ for premenopause vs. early perimenopause (for both FN and LS), and $p=0.02$ (LS) and 0.04 (FN) for early vs. late perimenopause. We therefore, proceeded to conduct analyses separately in each of the three MT stages.

In stratified analyses, adjusted for the same covariates, lower AMH was associated with greater loss in LS BMD in each of the 3 MT stages: 0.22%, 0.43%, and 0.50% more loss in premenopause, early perimenopause, and late perimenopause, respectively, per 50% decrement in AMH ($p<0.001$ in each stage). Every 50% decrement in AMH was also associated with 0.32% and 0.37% greater loss in FN BMD in early perimenopause ($p<0.001$) and late perimenopause ($p=0.006$), respectively, but not in premenopause (See Table 3). BMI and race/ethnicity inconsistently modified the associations of AMH with the magnitude of ongoing BMD loss across MT stages and bone sites (LS vs. FN) – data not tabulated. Given the lack of a discernible pattern in the effect modifications detected, suggestive of false discovery from multiple testing, we did not further stratify models beyond MT-stage stratification.

After additional adjustment for FSH, inhibin B, and U-NTx in the MT-stage-stratified models, lower AMH continued to be significantly associated with more loss in LS BMD in

premenopause and with more loss in both LS and FN BMD in early perimenopause, but not associated with BMD loss at either LS or FN in late perimenopause (Table 3).

Given the strong associations of AMH with magnitude of ongoing BMD loss, we quantified the sensitivity and PPV of AMH levels below select thresholds for detecting significant bone loss (defined as cumulative BMD decline exceeding site-specific LSC) at the LS, at the FN, and at either bone site (Table 4). For each AMH threshold, PPV can be interpreted as the probability that a woman with AMH below that threshold is experiencing significant bone loss.

The prevalence of significant bone loss increases with advancing MT stage, from 17% for significant loss at one or both bone sites (LS and FN) in premenopause, to 42% in early perimenopause, and 81% in late perimenopause. As expected, in each MT stage, sensitivity of low AMH for significant bone loss is greater at higher AMH thresholds, but PPV is larger at smaller thresholds (Table 4). Also, as expected, just as sensitivity is greater at higher AMH thresholds, so is the negative predictive value, NPV - the probability that a woman with AMH *above* the threshold is *not* experiencing significant bone loss (data not shown).

Comparing across MT stages, both sensitivity and PPV increase with advancing MT stage. Thus, AMH less than 100 pg/mL has sensitivity for significant bone loss (at one or both sites) of 50% in premenopause, 80% in early perimenopause, and 98% in late perimenopause. Similarly, AMH less than 50 pg/mL has PPV for significant bone loss of 33% in premenopause, 62% in early perimenopause, and 82% in late perimenopause (Table 4). As the prevalence of significant bone loss increases with advancing MT stage, NPV falls: In premenopause, the PPV at the 50 pg/mL threshold is 33% and NPV is 86%; in early perimenopause, PPV at the 25 pg/mL threshold is 59% and NPV is 73%; in late perimenopause, PPV at the 10 pg/mL threshold is 83% and NPV falls to 28% (NPV data not tabulated).

In late perimenopause, the PPV (which is the post-test probability of significant bone loss) at the different AMH thresholds is not much higher than the prevalence of significant bone loss (81% in late perimenopause), implying that AMH does not provide much additional information about bone loss in this late MT stage (Table 4). In contrast, in both premenopause and early perimenopause, PPV is substantially higher than the prevalence of significant bone loss in the MT stage (Table 4), and especially so for lower AMH thresholds.

Discussion

The MT is a critical period for bone health in women, with rapid losses in bone strength occurring over an approximately 3-year window bracketing the date of the last menstrual period, and fracture incidence rising sharply thereafter (4,5). Not surprisingly, researchers have often suggested that the MT may be an opportune time to intervene to prevent or delay the onset of osteoporosis in women and reduce the risk of debilitating fractures in later years (15,16,17). To date, however, our ability to intervene (and to test the efficacy of interventions) has been hampered by our inability to determine whether MT-related bone loss has begun or is imminent, and to identify the women who will lose the most bone

mass during the MT. Although the rapid bone loss phase starts 1 year before the FMP when menstrual bleeding patterns are changing, changes in bleeding patterns alone *cannot* be used to time the onset of the bone loss, because of substantial variability in how long different women experience menstrual irregularity before their FMP (1). There is also substantial variability in the amount of bone lost over the MT, and not all women lose large amounts of bone mass during this period. Subsequent fracture risk is linked to the magnitude of bone loss: the greater the loss, the greater is the subsequent fracture risk. Recent data from SWAN documented that each 0.5% per year faster decline in BMD at the lumbar spine during and immediately after the MT is associated with a 22% greater hazard for incident fracture, independent of pre-MT bone density (18). Effective and efficient early intervention is therefore predicated on being able to both identify the women who are slated to lose the most bone mass and determine when the bone loss has begun or is imminent.

The availability of high-sensitivity AMH assays that can quantify AMH levels in the pg/mL range has opened the possibility of reliably making these determinations. Consistent with our hypotheses, in answer to our first question Q1, we found that in pre- and early perimenopausal women, low levels of serum AMH are indeed predictive of fast declines in BMD over the next 3–4 years in both the hip and the spine. A 50% smaller serum AMH level is associated with 0.14% per year faster decline in LS BMD and 0.11% per year faster decline in FN BMD. Thus, a woman with 8-fold smaller AMH level (e.g., 25 compared to 200 pg/mL) will lose 0.42% and 0.33% more per year at the LS and FN, respectively, over the next 3–4 years. These are large differences relative to the mean BMD decline rate in the study of 1.1% per year at the LS and 0.9% at the FN. The prediction ability of low AMH for future fast BMD decline was independent of serum FSH, serum inhibin B, and U-NTx.

Measurement of serum AMH level early in the MT can potentially be useful to clinicians for determining whether MT-related bone loss has begun or is about to begin. In answer to our second question Q2, we found that lower levels of serum AMH in early perimenopause were strongly associated with more ongoing or imminent bone loss, specifically larger percentage of bone density decline relative to baseline BMD, in 2–3 years after AMH measurement. Only 17% of women in premenopause and 42% of women in early perimenopause were experiencing significant bone loss, i.e., bone density decline that exceeded the site-specific least significant change (1.4% decline at the LS, 2.2% decline at the FN). An AMH level smaller than 250 pg/mL would pick out 71% of the premenopausal and 90% of the early perimenopausal women experiencing significant bone loss. Clinicians can interpret the positive predictive values listed in Table 4 as the post-test probability of significant ongoing (or imminent) MT-related bone loss at different AMH thresholds. Thus, a finding of AMH smaller than 50 pg/mL increases the post-test probability of significant bone loss from pre-test levels of 17% and 42% in premenopause and early perimenopause, respectively, to 38% and the 69%. AMH measurement is less informative in late perimenopause; 81% of late perimenopausal women have significant bone loss, and a low level of AMH does not increase their post-test probability for significant bone loss.

Even with the high-sensitivity 2-site ELISA assay for AMH, the majority of women in late perimenopause have AMH levels below the assay's lower limit of detection, which may have limited its usefulness in indicating ongoing bone loss. AMH was more useful

earlier in the MT when levels are still mostly above the lower limit of detection. Of note, bone resorption marker, U-NTx is not useful for detecting MT-related bone loss in premenopause (14), and although FSH has discriminatory ability for MT-related bone loss in both premenopause and early perimenopause (13), its 10-fold variation across the menstrual cycle means that it requires blood draw within a narrow 3-day window in the early follicular phase. This issue with FSH becomes less of a concern later in the MT, and both FSH and U-NTx may be better at detecting MT-related bone loss in late perimenopause, as the woman gets closer to and passes the FMP date. Serum levels of inhibins, which are present in ovarian follicular fluid and suppress pituitary FSH secretion (19), also decrease during the MT, and are correlated with increases in bone turnover markers (20). Combining AMH, FSH, inhibins, and bone turnover markers may strengthen our ability to detect ongoing or imminent MT-related bone loss both early and late in the MT.

Our findings in this study are consistent with a recent cross-sectional analysis that found inverse associations between serum AMH level and BMD in premenopausal women with ovarian insufficiency (21). To our knowledge, ours is the first longitudinal study of AMH as a predictor of bone loss over the MT, and the first to show that AMH measurements during the MT can be used to predict the magnitude of future bone loss and to determine that significant MT-related bone loss is ongoing. These findings make feasible the designing and testing of midlife interventions to prevent or delay osteoporosis in women. Bisphosphonates have been shown to prevent BMD decline in women under 60 years of age (22), and zoledronic acid, in particular, is an intriguing option for an intervention trial because a single dose of zoledronic acid stabilizes BMD for at least 36 months (23).

It should be noted that women had to be at least 42 years old at baseline to be in the SWAN study, so our findings do not apply to women younger than age 42 and to women who have premature or early menopause. Because we excluded women who were already taking osteoporosis medications while in the menopause transition, our findings cannot be applied to such women. It should also be noted that the study cohort was limited to four race/ethnicity groups, and did not include Hispanic women. The cohort does however, include a large number of women from low socio-economic backgrounds. A second limitation, unavoidable in multi-decade longitudinal studies, is changes in DXA scanning equipment. When study sites upgraded their Hologic scanners, in vivo cross-calibration protocols permitted within-site and cross-site longitudinal standardization of BMD measurements. A third limitation is that many women in the SWAN Bone Cohort did not have a natural menopause with dateable FMP because of a variety of reasons that masked the actual FMP date, such as hysterectomy before the FMP and use of exogenous sex hormones; they were excluded from our study sample. Serum AMH may potentially be useful for detecting and quantifying bone loss in these women also, provided they did not lose their ovaries; further research is needed to test this, and to confirm the findings of this study.

Signal strengths of this work include the long follow up over the MT in four race/ethnicity groups with serial measurements of AMH and BMD, use of mixed effects modeling of repeated measurements data, analyses stratified by MT stage, demonstration of AMH prediction ability independent of FSH, inhibin B, and urinary NTx, and the creation of

probability tables for significant ongoing/imminent bone loss at various AMH thresholds for ease of use in clinical settings.

In conclusion, this study demonstrated that serum AMH levels in pre- or early perimenopausal women can be used to predict the rate of BMD decline over the next 3–4 years and to determine if a midlife woman is experiencing or about to experience MT-related bone loss. Future work will determine if predictions of the magnitude and timing of MT-related declines in BMD can be improved by combining serial measurements of AMH, FSH, inhibins, and markers of bone resorption.

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Data Availability

Data from the Study of Women's Health Across the Nation (SWAN) cohort analyzed in this study are publicly available, and can be accessed at the following websites:

https://www.swanstudy.org/

https://www.icpsr.umich.edu/web/ICPSR/series/00253

https://agingresearchbiobank.nia.nih.gov/studies/swan/?search_term=SWAN

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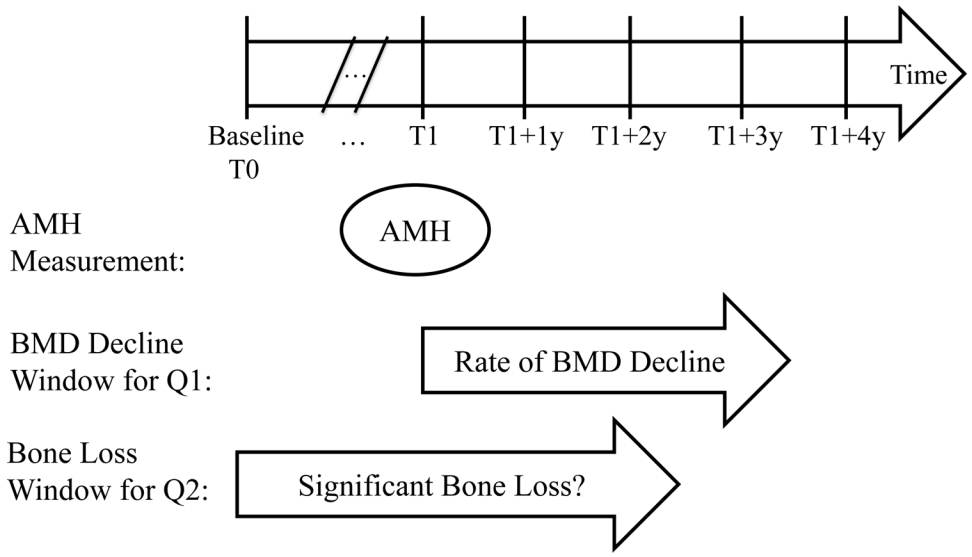

Figure 1.

Timing of anti-Mullerian hormone (AMH) measurement and bone assessment windows for analysis of AMH as predictor of future bone mineral density (BMD) decline rate (Q1), and as predictor of ongoing or imminent bone loss (Q2). **T0** refers to the Study of Women's Health (SWAN) baseline visit, and **T1** to the SWAN visit at which AMH is measured. All AMH measurements up to one year after the final menstrual period (FMP) were used in analyses (multiple measurements per woman); ellipsis depict variable lengths of time between baseline visit T0 and AMH measurement T1. The BMD decline rate for Q1 was determined from BMD measured at T1 and a follow up visit 3–4 years after T1. Bone loss for Q2 was determined from BMD measured at baseline (T0) and a follow up visit 2–3 years after T1.

Table 1.

Descriptive Statistics[1] of Study Samples' Characteristics at Study Baseline and over Repeated Observations

At Study Baseline	**SWAN Bone Cohort (N=2,365)**	**Study Sample 1 (N=888)**	**Study Sample 2 (N=924)**
Age (years)	46 (3)	47 (3)	47 (3)
MT Stage Premenopause	1,273 (54%)	272 (31%)	269 (29%)
Early perimenopause	1,070 (45%)	587 (66%)	621 (67%)
Late perimenopause	3 (0.1%)	0 (0%)	0 (0%)
Race/Ethnicity Black	665 (28%)	219 (25%)	230 (24%)
Chinese	250 (11%)	132 (15%)	133 (14%)
Japanese	273 (12%)	150 (17%)	153 (17%)
White	1,176 (50%)	387 (44%)	408 (44%)
Lumbar Spine BMD (gms/cm^2)	1.08 (0.14)	1.07 (0.14)	1.07 (0.14)
Femoral Neck BMD (gms/cm^2)	0.85 (0.14)	0.83 (0.14)	0.8 (0.14)
Over Repeated Visits Before Postmenopause[2]		Study Sample 1 (n=3,060)	Study Sample 2 (n=3,256)
Age (years)	-	49 (3)	49 (3)
MT Stage Premenopause	-	630 (21%)	613 (19%)
Early perimenopause	-	2,046 (67%)	2,202 (67%)
Late perimenopause	-	384 (12%)	441 (14%)
Body mass index (kg/m^2)	-	27.3 (6.5)	27.3 (6.6)
Obesity categories < 25 kg/m^2	-	1,398 (46%)	1,478 (45%)
25 – 30 kg/m^2	-	897 (29%)	960 (29%)
31 – 40 kg/m^2	-	597 (20%)	634 (19%)
> 40 kg/m^2	-	168 (5%)	184 (6%)
Serum AMH (pg/mL)	-	67 (4, 299)	58 (3, 294)
Serum FSH (IU/L)	-	22 (13, 49)	23 (13, 53)
Serum Inhibin B (pg/mL)		22 (2, 79)	21 (2, 76)
Urinary NTx	-	32.3 (23.8, 42.6)	32.6 (24.1, 43.2)
Future BMD Decline Rate[3] Lumbar Spine	-	1.1 (1.8)	-
Femoral Neck	-	0.9 (1.7)	-
Ongoing BMD Loss (%)[4] Lumbar Spine	-	-	2.8 (5.5)
Femoral Neck	-	-	2.3 (5.2)

AMH = Anti-Mullerian Hormone; MT = Menopause Transition; N = Sample size; n = Number of repeated observations; NTx = N-terminal telopeptide (nmol BCE /mmol Cr); SWAN = Study of Women's Health Across the Nation;

[1]Mean (standard deviation) or median (interquartile range) or number (%)

[2] Characteristics measured at the time of AMH measurement; repeated observations data

[3] Annualized rate of decline (% per year) over 3–4 years following the AMH measurement

[4] Proportion of prior peak BMD lost within 2–3 years after AMH measurement

Table 2.

Adjusted Association of Serum AMH[1] with Rate of Future BMD Decline (over the Following 3–4 Years)[2], Stratified by MT Stage at Time of AMH Measurement[3,4]

	Increment in BMD decline rate (% per year) per 50% decrement of AMH					
	Lumbar Spine			Femoral Neck		
MT stage	Estimate	95% CI	p value	Estimate	95% CI	p value
Pre- or early perimenopause						
Model 1:	**0.14**	0.12, 0.16	<0.001	**0.11**	0.09, 0.13	<0.001
Model 2:	**0.12**	0.10, 0.14	<0.001	**0.11**	0.09, 0.13	<0.001
Late perimenopause						
Model 1:	0.03	−0.05, 0.11	0.5	0.01	−0.08, 0.09	0.9
Model 2:	0.05	−0.05, 0.15	0.3	−0.00	−0.11, 0.10	0.8

AMH = Anti-Mullerian Hormone; BMD = Bone Mineral Density; CI = Confidence Interval; FSH = Follicular Stimulating Hormone; MT = Menopause Transition; SWAN = Study of Women's Health Across the Nation

[1]Median AMH in pre- and early perimenopause combined was 106 pg/mL and interquartile range (IQR) was (13, 362) pg/mL. In late perimenopause, median AMH was below the lower limit of detection (1.85 pg/mL), third quartile was 5 pg/mL.

[2]Mean BMD decline rate in pre- and early perimenopause combined was 0.9% per year (standard deviation, SD 1.4% per year) in the lumbar spine and 0.7 (SD 1.4) % per year in the femoral neck. In late perimenopause, mean decline rate was 1.5 (SD 1.4) % per year in the lumbar spine and 1.3 (SD 1.4) % per year in the femoral neck.

[3]Model 1 adjusts for age (continuous), MT stage (pre vs. early perimenopause), body mass index (continuous), SWAN study site, and race/ethnicity. Time-varying covariates were measured at the time of AMH measurement.

[4]Model 2 adjusts for all covariates in Model 1 plus serum levels of FSH and inhibin B, indicator flag for FSH measured outside the early follicular phase window, and bone resorption marker, urinary N-telopeptide. All time-varying covariates were measured at the time of AMH measurement.

Table 3.

Adjusted Association of Serum AMH[1] with Magnitude of Ongoing BMD Decline (from Study Baseline to Study Visit 2–3 Years after AMH Measurement)[2], Stratified by MT Stage at Time of AMH Measurement[3,4]

	Increment in BMD loss (% of baseline) per 50% decrement of AMH					
	Lumbar Spine			Femoral Neck		
MT stage	Estimate	95% CI	p value	Estimate	95% CI	p value
Premenopause						
Model 1:	**0.22**	0.10, 0.34	<0.001	*0.11*	−0.01, 0.24	0.08
Model 2:	**0.20**	0.07, 0.32	0.002	*0.13*	−0.01, 0.26	0.07
Early perimenopause						
Model 1:	**0.43**	0.37, 0.49	<0.001	**0.32**	0.26, 0.39	<0.001
Model 2:	**0.23**	0.16, 0.31	<0.001	**0.20**	0.12, 0.27	<0.001
Late perimenopause						
Model 1:	**0.50**	0.25, 0.75	<0.001	**0.37**	0.11, 0.63	0.006
Model 2:	0.17	−0.11, 0.46	0.2	0.05	−0.25, 0.35	0.7

AMH = Anti-Mullerian Hormone; BMD = Bone Mineral Density; CI = Confidence Interval; FSH = Follicular Stimulating Hormone; MT = Menopause Transition; SWAN = Study of Women's Health Across the Nation

[1]Median AMH in premenopause was 250 pg/mL and interquartile range (IQR) was (66, 697) pg/mL. In early perimenopause, median (IQR) of AMH was 66 (6, 283) pg/mL. In late perimenopause, median AMH was below the lower limit of detection (1.85 pg/mL), third quartile was 6 pg/mL.

[2]Mean BMD loss in premenopause was 0.2% (standard deviation, SD 4.1%) in the lumbar spine and 0.4 (SD 4.3) % in the femoral neck. In early perimenopause, mean (SD) of BMD loss was 2.6 (5.2) % in the spine and 2.2 (5.1) % in the femoral neck. In late perimenopause, it was 7.7 (5.5) % in the spine and 5.5 (5.3) % in the femoral neck.

[3]Model 1 adjusts for age (continuous), body mass index (continuous), SWAN study site, and race/ethnicity. Time-varying covariates were measured at the time of AMH measurement.

[4]Model 2 adjusts for all covariates in Model 1 plus serum levels of FSH and inhibin B, indicator flag for FSH measured outside the early follicular phase window, and bone resorption marker, urinary N-telopeptide. All time-varying covariates were measured at the time of AMH measurement.

Table 4.

Sensitivity and Positive Predictive Value (*PPV*) of Low Serum AMH for Ongoing Bone Loss, Stratified by MT Stage at Time of AMH Measurement

AMH *(n)*	MT stage	Lumbar Spine		Femoral Neck		Either Bone Site	
		Estimate	**95% CI**	**Estimate**	**95% CI**	**Estimate**	**95% CI**
	Premenopause *(n=613)*						
	Prevalence *	14%		7%		17%	
<50 (*125*)	Sensitivity	0.41	0.31, 0.52	0.43	0.28, 0.59	0.38	0.29, 0.48
	PPV	*0.28*	*0.20, 0.37*	*0.15*	*0.09, 0.23*	***0.33***	*0.25, 0.42*
<100 *(100)*	Sensitivity	0.54	0.43, 0.65	0.48	0.33, 0.63	0.50	0.39, 0.59
	PPV	*0.25*	*0.19, 0.32*	*0.12*	*0.07, 0.17*	***0.29***	*0.23, 0.36*
<250 *(307)*	Sensitivity	0.73	0.62, 0.82	0.70	0.55, 0.83	**0.71**	0.62, 0.79
	PPV	*0.20*	*0.16, 0.25*	*0.10*	*0.07, 0.14*	***0.25***	*0.20, 0.30*
<500 *(418)*	Sensitivity	0.87	0.78, 0.93	0.82	0.67, 0.92	**0.86**	0.78, 0.92
	PPV	*0.18*	*0.14, 0.22*	*0.09*	*0.06, 0.12*	*0.22*	*0.18, 0.26*
	Early perimenopause *(n=2202)*						
	Prevalence	35%		20%		42%	
<25 *(835)*	Sensitivity	0.62	0.58, 0.65	0.61	0.56, 0.66	0.59	0.56, 0.62
	PPV	*0.58*	*0.54, 0.61*	*0.32*	*0.29, 0.36*	***0.65***	*0.61, 0.68*
<50 *(1028)*	Sensitivity	0.73	0.69, 0.76	0.60	0.65, 0.74	**0.69**	0.66, 0.72
	PPV	*0.54*	*0.52, 0.58*	*0.30*	*0.27, 0.33*	***0.62***	*0.59, 0.65*
<100 *(1250)*	Sensitivity	0.83	0.80, 0.86	0.80	0.76, 0.83	**0.80**	0.77, 0.82
	PPV	*0.51*	*0.49, 0.54*	*0.29*	*0.26, 0.31*	***0.58***	*0.55, 0.61*
<250 *(1599)*	Sensitivity	0.92	0.90, 0.94	0.90	0.87, 0.93	**0.90**	0.88, 0.92
	PPV	*0.45*	*0.42, 0.47*	*0.25*	*0.23, 0.27*	*0.52*	*0.59, 0.54*
	Late perimenopause *(n=441)*						
	Prevalence	77%		47%		81%	
<10 *(362)*	Sensitivity	0.84	0.79, 0.88	0.86	0.80, 0.90	**0.84**	0.80, 0.88
	PPV	*0.79*	*0.74, 0.83*	*0.49*	*0.44, 0.54*	*0.83*	*0.79, 0.87*
<25 *(409)*	Sensitivity	0.95	0.92, 0.97	0.94	0.90, 0.97	**0.94**	0.92, 0.97
	PPV	*0.79*	*0.74, 0.82*	*0.48*	*0.43, 0.53*	*0.83*	*0.79, 0.82*
<50 *(421)*	Sensitivity	0.97	0.94, 0.98	0.95	0.91, 0.98	**0.96**	0.94, 0.98
	PPV	*0.78*	*0.73, 0.82*	*0.47*	*0.42, 0.52*	*0.82*	*0.78, 0.86*
<100 *(432)*	Sensitivity	0.99	0.97, 0.99	0.98	0.95, 0.99	**0.98**	0.96, 0.99
	PPV	*0.77*	*0.73, 0.81*	*0.47*	*0.42, 0.52*	*0.82*	*0.78, 0.85*

AMH = Anti-Mullerian Hormone (pg/mL); BMD = Bone Mineral Density; CI = Confidence Interval; LSC = Least Significant Change; MT = Menopause Transition; n = number of observations; PPV = Positive Predictive Value; SWAN = Study of Women's Health Across the Nation

Ongoing bone loss defined as BMD decline (from study baseline to study visit 2–3 years after AMH measurement) exceeding the site-specific LSC (3.9% at lumbar spine, 6.2% at femoral neck)

* Prevalence = Proportion of women in the MT stage who are experiencing ongoing or imminent bone loss

Bold font (in last column): Sensitivity estimates for ongoing bone loss at one or both bone sites that are better than 2 in 3 (≥ 67%) and PPV figures that are at least one third better than stage-specific prevalence are bolded.