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Review

The Role of Follicle-Stimulating Hormone in Bone Loss During Menopause Transition: A Narrative Review

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Abstract

For many years, menopause-related bone loss has been attributed solely to declining estrogen levels. Recently it has been suggested that bone loss accelerates during perimenopause, often preceding declines in estradiol (E_2), proposing that follicle-stimulating hormone (FSH), the levels of which are high during late perimenopause, may play a role in skeletal deterioration independently of E_2. The aim of this narrative review was to present aspects of bone health throughout the menopause transition with a focus on the relationship between FSH and bone-related outcomes. Epidemiological studies evaluating bone mineral density (BMD) and bone turnover markers (BTMs) were analyzed. Higher FSH levels were associated with reduced BMD, particularly at the spine and hip, as well as enhanced bone remodeling activity. In several longitudinal studies, FSH was found to be a more reliable predictor of bone loss than estrogen. In conclusion, FSH may serve as an early marker of perimenopausal bone health deterioration by identifying women at risk for bone loss and allowing for more personalized prevention strategies; however, further research is needed before its clinical use.

Keywords: follicle-stimulating hormone; bone health; bone mineral density; perimenopause

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1. Introduction

Throughout the perimenopause, women's hormone levels fluctuate, thus follicle-stimulating hormone (FSH) gradually rises while levels of circulating estrogen erraticly alternates and eventually decline [1,2]. It is increasingly recognized that this transitional state, which often lasts several years or even longer, is crucial for bone health [3–5]. Several cohort studies suggest that bone loss intensifies in the late perimenopausal stage, even before the onset of menopause and complete decline in estrogen levels [6–12].

Traditionally, menopause-associated bone loss has been attributed primarily to estradiol (E_2) deficiency [13,14]. However, this existing paradigm is being challenged as it is now speculated that low estrogen cannot adequately account for precipitous bone loss during the perimenopause since estrogen levels remain mostly unchanged, whereas FSH increases to sustain estrogen secretion from an otherwise failing ovary [15,16]. Emerging evidence points toward a potential direct role of FSH in bone metabolism, independent of E_2 [7,9,17–31]. In vitro and in vivo studies show that bone tissue contains FSH receptors (FSHR) [17,32–38] along with that FSH promotes osteoclast differentiation, activity and survival but has minimal impact on osteoblasts. This suggests that elevated FSH levels could be a contributing factor to enhanced osteoclast-mediated bone resorption [17,33,37].

Important insights of the role of FSH in bone metabolism are provided by animal studies as rodent models demonstrate that anti-FSH treatment appears to be osteoprotective independently of estrogen [34,38,39]. However, some findings of studies with mice remain contradictory [40,41]. Despite this, the specific role of FSH in menopause-related decrease in bone mineral density (BMD) remains underexplored.

Understanding whether elevated FSH levels contribute to early bone loss during perimenopause might have notable implications for clinical practice. Follicle-stimulating hormone may be a valuable biomarker for identifying women at high risk of osteoporosis at an earlier stage, when prevention strategies might be more effective [5,20,21,42].

This narrative review provides aspects of bone health throughout the perimenopause, with an emphasis on the relationship between FSH level and BMD as well as bone turnover markers (BTMs).

2. Hormonal Changes During Perimenopause

2.1. Definition and Stages of Perimenopause

Perimenopause, also called menopausal transition, is a transitory period surrounding the final years of a woman's reproductive life and characterized by complex and even unpredictable hormonal fluctuations [43,44]. According to the Stages of Reproductive Aging Workshop +10 (STRAW +10) [45], the menopausal transition is divided into two stages: early perimenopause and late perimenopause. In early perimenopause, the duration of consecutive menstrual cycles typically varies by at least seven days, while in late perimenopause cycles can last about 60 days or more. The final menstrual period (FMP) is predicted to occur one to three years from the beginning of the late menopausal transition stage. After a year from the FMP, the perimenopause ends, and this point in a woman's life is known as menopause.

2.2. Fluctuations in Hormone Levels During Perimenopause

The stages of perimenopause are associated with increased variability in levels of circulating hormones [46]. Female reproduction is regulated by the hypothalamic–pituitary–gonadal (HPG) axis [47]; therefore, fluctuation in the levels of hypothalamus, pituitary and ovarian hormones causes irregular ovulation during menopausal transition [48]. As ovarian follicular reserve decreases, the HPG axis enters a state of compensated failure, in which increased FSH levels are efficient to sustain relatively regular folliculogenesis and ovulation [48]. This state is achieved by declining inhibin B, a peptide that lowers pituitary FSH secretion via negative feedback inhibition [49,50]. Thus, an increase in FSH during the early stage of menopause transition is not caused by reduced E_2 but rather by diminished inhibin.

In terms of hormonal dynamics, perimenopause typically differs from the postmenopausal period as postmenopause is characterized by more stable low levels of E_2 and high levels of FSH [45]. During perimenopause, E_2 levels vary unpredictably, with periods of both lower and higher concentrations than in premenopausal women, until it is stabilized at a low level in the late perimenopause stage [46,50]. Because of irregular ovarian responsiveness during the menopausal transition, FSH levels fluctuate considerably, with periods of elevation alternating with returns to premenopausal ranges [46]; however, it is noted that the rise in FSH levels typically begins about six years before FMP and remains elevated afterward [50,51]. According to STRAW +10, elevated FSH values (>25 mIU/mL) in addition to a period of amenorrhea lasting 60 days or more defines late perimenopause [45]. The ovaries eventually lose the ability to produce functioning follicles because the state of compensated failure of the HPG axis cannot be maintained [48].

Changes in FSH and E_2 are the most noticeable hormonal changes during perimenopause; nevertheless, other hormones are also affected. Levels of luteinizing hormone (LH) typically rise in parallel with FSH elevation, though usually to a lesser extent [52]. Additionally, Anti-Müllerian hormone (AMH), produced by growing follicles of the ovary, declines progressively during perimenopause as the ovarian reserve diminishes [49]. Progesterone levels, similar to E_2, exhibit highly individual variability throughout the menopause transition, reflecting the irregularity of ovulatory cycles during this period [53]. Contrary to a common misconception, androgens do not decline sharply during the menopause transition. While testosterone secretion may drop slightly, decline in sex hormone-binding globulin (SHBG) values leads to stable or even increased free androgen levels, suggesting that androgen deficiency is not a typical aspect of perimenopause [49]. Taken together, these hormone changes create a complex perimenopausal endocrine milieu and may have a direct or indirect impact on bone health.

3. Bone Loss in Perimenopausal Women

3.1. Timing and Magnitude of BMD Loss

Since menopause-related bone loss begins even before the onset of menopause, perimenopause is a critical time for changes in women's bone strength [4]. Longitudinal studies indicate that decline in BMD accelerates during late perimenopause [7–9], at a time when menstrual irregularity and hormonal fluctuations are prominent, but estrogen levels may not yet be consistently low. On average, during the rapid bone-loss phase in menopause transition, women lose approximately 1.8 to 2.5% of BMD per year depending on the assessed bone site [9], and the average reduction in BMD over the menopausal transition period is about 10% [54]. It is proposed that during perimenopause, trabecular-rich skeletal locations, such as lumbar spine and hip, experience a greater decrease in BMD than cortical bone [9,54,55]. Hence it is important to recognize perimenopause as a crucial window for early skeletal deterioration.

3.2. Bone Mineral Density

Bone mineral density measurement by dual-energy X-ray absorptiometry (DXA) is the most widely used clinical indicator to assess bone strength and predict fracture risk [56]. It is most often performed on two sites: the lower spine (lumbar vertebrae L1–L4) and hips (femoral neck and total hips) [57]. These are sites most vulnerable to osteoporotic fractures [58,59]. The results of DXA are reported as T-scores, which compare an individual's BMD to that of the mean in the reference population [57]. According to the World Health Organization (WHO), a T-score of ≥ -1.0 is considered normal, between -1.0 and -2.5 indicates osteopenia (low bone mass), and ≤ -2.5 is diagnostic of osteoporosis [60]. Dual-energy X-ray absorptiometry screening in postmenopause is advised for women aged 65 and older or if they have clinical risk factors, such as low body weight, a history of fractures, an illness linked to bone loss, or use of medications that promote bone loss [61]. Even though studies demonstrate that BMD already begins to decline during perimenopause [5,7–11], recommendations for DXA testing for women going through menopause transition or in the early stages of postmenopause are not as clear [61].

3.3. Bone Turnover Markers

Although DXA is considered the gold standard for diagnosing osteoporosis, its limitations evaluating women in perimenopause or early postmenopause must be recognized as hormonal fluctuations may alter bone turnover and microarchitecture [3,4]. A single BMD measurement reflects bone that has already been lost but does not provide information about the rate of bone loss or the extent of microarchitectural deterioration [5]. Impor-

tantly, changes in bone strength and microarchitecture that occur during perimenopause are thought to be irreversible, so early identification may be critical to prevent long-term skeletal damage [12]. A dynamic evaluation of skeletal activity in addition to prediction of the risk of ongoing bone loss can be obtained using BTMs that are released into the bloodstream during bone production and resorption [5,12]. Commonly assessed BTMs that reflect bone formation are osteocalcin (OC), procollagen I N-propeptide (PINP), and bone alkaline phosphatase (BAP), whereas bone resorption markers are C-telopeptide of type I collagen (CTX) and urinary N-telopeptide of type I collagen (NTX) [62]. These markers may be used in identifying perimenopausal women at high risk of quickly declining bone mass as higher levels are linked to a greater rate of bone loss across menopause transition [5,12].

3.4. Factors Influencing Bone Loss

Multiple factors influence the extent and rate of bone loss during perimenopause. A pivotal cause of menopause-related loss in BMD is estrogen deficiency as it is an important regulator of bone remodeling—both formation and resorption [63,64]. Estrogen primarily inhibits bone resorption by affecting osteoclasts, in addition to indirectly impacting new bone formation by regulating the activity of osteoblasts [65,66]. Therefore, estrogen is able to change bone mass by altering the ratio of resorption and formation. Another sex hormone, testosterone, also plays a crucial role in bone remodeling by promoting osteoblast differentiation and proliferation while suppressing osteoclast maturation and activity [65]. Androgen deficiency may contribute to bone loss in both sexes; however, the findings of studies with females are controversial [67].

Other nonhormonal factors, including low body mass index (BMI), early menopause, genetic predisposition, sedentary lifestyle, insufficient vitamin D and calcium intake, smoking, or alcohol usage, are associated with greater bone loss [4,7,9,10,63,64,68]. Certain medications (e.g., glucocorticoids, aromatase inhibitors, and gonadotropin-releasing hormone agonists) may accelerate bone loss and increase the risk of fracture [63,69,70]. Various diseases, for instance, hyperparathyroidism, type 1 diabetes mellitus, hyperthyroidism, hypogonadism, chronic inflammatory diseases, etc., affect bone quality and are related to bone loss [69,71]. Thus, bone loss in perimenopause is complex and multifactorial.

4. The Potential Role of FSH Beyond Reproduction

Follicle-stimulating hormone is a gonadotropin hormone produced by the anterior pituitary and is well known for its role in regulating ovarian follicular development [72]. According to a 2019 study by Taneja et al., FSH may exert biological effects beyond the reproductive axis, such as regulating adipose tissue function, energy metabolism, cholesterol production, and bone mass [73]. Several non-reproductive diseases, such as osteoporosis, hypercholesterolemia, type 2 diabetes mellitus, obesity, cardiovascular disease, Alzheimer's disease, and some types of cancer, have been linked to elevated FSH levels [74].

Increase in FSH across menopause transition is associated with enhanced visceral adiposity [75] and reduced lean mass, reflected by higher waist circumference and waist–hip ratio [73,76]. These changes in fat distribution are possibly promoted through FSHR expressed on adipocytes and fat tissue [75], especially white adipose tissue and beige adipose tissue [74].

Moreover, FSH is associated with hypercholesterolemia by upregulating HMG-CoA reductase and reducing expression of low-density lipoprotein (LDL) receptors on hepatocytes, which subsequently lowers LDL cholesterol uptake [74]. Besides its role in cholesterol metabolism, FSH levels negatively correlate with the concentrations of triglycerides [77].

In the context of bone health, accumulating evidence suggests that FSH may have a direct role in bone mass regulation, independently of serum estrogen [3,19,21,25,27,37,73,78–80].

Molecular studies indicate that FSH promotes osteoclast formation, activity, and survival by directly acting on FSHR expressed in bone tissue [17,32–36,81]. It stimulates osteoclastogenesis through several pathways, including upregulation of osteoclastogenic cytokines, such as interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α), and interleukin-6 (IL-6) [82,83]. In addition, FSH enhances the expression of receptor activator for nuclear factor kappa-B (NF-κB) [84] and interacts with immune receptor complexes [85].

Evidence from animal studies supports an estrogen-independent role of FSH in bone regulation. In 2006, Sun et al. [17] reported that despite notable estrogen deprivation, neither the β-subunit of FSH (FSHβ) nor FSHR null mice had bone loss. A study by Zhu et al. [38] demonstrated that anti-FSH antibodies, titrated to a level that inhibits FSH's effect on osteoclasts while maintaining ovarian function, can stop bone loss and promote the production of new bone. In 2018, Ji et al. [34] demonstrated that monoclonal antibodies directed against FSHβ have osteoprotective effects in both ovariectomized and sham-operated mice, suggesting that blocking FSH's action may attenuate bone loss independently of estrogen and support the therapeutic potential of FSH blockade in bone-loss prevention. However, findings from rodent studies remain inconsistent. Notably, results from FSHβ or FSHR knockout mice are confounded by alterations in LH, androgens, and other ovarian factors, making it challenging to isolate the specific effects of FSH on bone metabolism [41].

Observational human studies showed that increased FSH levels promote the pathophysiological process of bone loss, especially during the menopausal transition. One of the most comprehensive and influential studies in this field is the Study of Women's Health Across the Nations (SWAN) [86], a large longitudinal and cross-sectional cohort of over 2000 ethnically diverse pre-, peri-, and postmenopausal women. According to SWAN findings, the fastest phase of bone loss begins two to three years before the last menstrual period, when FSH levels rise despite relatively stable estrogen concentrations. Importantly, even after menopause, estrogen therapy does not always normalize FSH levels, and bone loss may continue [87]. These findings imply a potential estrogen-independent role of FSH in bone homeostasis. It has been acknowledged that moderate FSH levels in healthy individuals help preserve bone mass, but perimenopausal elevations can stimulate additional differentiation of osteoclasts and disrupt bone remodeling balance [74]. Each doubling of FSH levels during menopause transition is associated with an additional 0.3% annual decline in BMD in the femoral neck and lumbar spine, mirroring the timing of hormonal shifts [4]. Thus, FSH potentially emerges as an important contributor to bone deterioration, as well as a predictive marker of bone loss during women's midlife.

5. Associations Between FSH and Bone Health During Perimenopause

A literature search was conducted to identify studies evaluating the relationship between FSH and bone health parameters during the menopause transition. The search was performed in PubMed up to May 2025 using terms related to FSH, perimenopause, and bone health. Studies including pre- and perimenopausal women and evaluating FSH in relation to BMD and BTMs were included [10,19,21,23–28,30,31]. Key characteristics and main findings of the included studies are summarized in Table 1.

Table 1. Epidemiological studies regarding the association between FSH and bone health.

Author (Year)	Study Design	Population	Mean Age (Years)	Mean FSH Level (IU/L)	Mean E_2 Level (pmol/L)	Measured Bone Outcome	Main Findings
Li et al. (2023) [21]	Cross-sectional	487 women in menopause transition	50 ± 8.5	23.2 ± 19.9	-	BAP, OC, CTX, NTX; BMD, LS & total hip	Higher FSH levels were independently associated with increased BTMs (r = 0.339–0.583, $p < 0.001$) and decreased BMD (r = −0.629 and −0.514, $p < 0.001$)
Uehara et al. (2022) [23]	Prospective	207 peri-menopausal women with endometriosis	45.02 ± 2.73	33.42 ± 41.84	341.36 ± 394.6	BMD, LS	High FSH levels were associated with decreased BMD (r = −0.3126, $p < 0.0001$)
Shieh et al. (2019) [24]	Longitudinal (SWAN data)	1559 pre- and peri-menopausal women	46.1 ± 2.6	-	-	BMD, LS & FN	Both lower E_2 and greater FSH values were associated with greater risk of imminent bone loss, independent of relevant clinical risk factors ($p < 0.0001$)
Ma et al. (2016) [25]	Cross-sectional	464 women in menopause transition	46.93 ± 0.30	57.68 ± 1.72	132.01 ± 11.12	CTX, PINP	Level of FSH was independently related to CTX (r = 0.380, $p < 0.01$) and PINP (r = 0.272, $p < 0.01$)
Crandall et al. (2013) [26]	Longitudinal (SWAN cohort)	720 pre- and early peri-menopausal women	46.21 ± 2.53	-	-	BMD, LS & FN	The only hormonal predictor significantly associated with FN bone loss was FSH
Wu et al. (2013) [19]	Cross-sectional	368 women in menopause transition	-	-	-	BMD, LS, left hip & left forearm	Decreased rate of BMD was significantly negatively correlated with FSH (r = −0.429 to −0.622, all $p = 0.000$)
Seifert-Klauss et al. (2012) [10]	Prospective observational	50 women in menopause transition	48.3 ± 5.4	74.1 ± 21.0	65.35 ± 90,7	BAP, OC, CTX; BMD, LS	Increased FSH levels were associated with accelerated BMD loss (r = 0.5; $p = 0.01$)
Cheung et al. (2011) [27]	Prospective	160 women in menopause transition	47.7 ± 2.2	27.73 ± 32	238.89 ± 306	BMD, LS, FN & total hip	Higher baseline FSH levels predicted more rapid bone loss; FSH was an independent predictor of BMD decline at FN ($p = 0.034$) and total hip ($p = 0.022$)
Sowers et al. (2006) [28]	Longitudinal (SWAN data)	2311 pre- and early peri-menopausal women	46.4 ± 2.7	21.4 ± 21.5	244.9 ± 200.8	BMD, LS, FN & total hip	Loss of BMD at the LS and hip was most strongly related to the interaction between baseline FSH and its longitudinal changes, rather than E_2 levels or changes
Vural et al. (2005) [30]	Cross-sectional	87 women before menopause	41.6 ± 3.9	-	-	NTX, OC; BMD, LS & FN	Higher gonadotropin levels, independent from age, were correlated with increased bone resorption ($p = 0.015$, $R^2 = 0.190$)
Sowers et al. (2003) [31]	Longitudinal (SWAN data)	2375 pre- and early peri-menopausal women	46.4 ± 2.7	24.1 ± 25.4	276.45 ± 280.12	OC, NTX; BMD, LS	Higher FSH levels, but not other reproductive hormones, were positively associated with higher NTX (partial r2 = 2.1%, $p < 0.0001$) and OC concentrations (partial r2 = 4.1%, $p < 0.0001$)

Laboratory values are presented as mean ± standard deviation or median (interquartile range). BAP—bone alkaline phospahatase, BTMs—bone turnover markers, CTX—C-telopeptide of collagen type 1, E_2—estradiol, FMP—final menstrual period, FN, femoral neck, LS, lumbar spine, NTX—N-telopeptide of collagen type 1, OC—osteocalcin, PINP—N-amino terminal propeptide of collagen type 1.

5.1. Studies Evaluating FSH and Bone Health

5.1.1. Association Between FSH and BMD

Numerous studies demonstrated a negative association between FSH levels and BMD during the menopausal transition. Li et al. [21] showed that FSH was negatively correlated with BMD in the lumbar spine ($r = -0.629$, $p < 0.001$), even after adjusting for age and BMI. The link between elevated FSH levels and reduced BMD in perimenopausal women was also reported in several other studies, including those by Wu et al. [19], Uehara et al. [23], Crandall et al. [26], and Cheung et al. [27]. According to Cheung et al. [27], women in the highest quartile of FSH lost bone 1.3–2.3 times faster compared with those in the lowest quartile. In 2003, Sowers et al. [31] reported that pre- and early perimenopausal women

with FSH levels above 26 IU/L had, on average, a 2.5% lower BMD compared to those with lower FSH levels (<10 IU/L).

Importantly, a four-year longitudinal analysis by Sowers et al. [28] showed that both baseline and annual FSH levels were predictive of bone loss, with greater increases in FSH associated with more pronounced declines in BMD in the spine and hip regions. These findings indicate that having at least two serial FSH measurements, rather than a single baseline value, may offer valuable prognostic information during the menopause transition. They also noted that serial FSH measurements may be more predictive of bone loss over time than E_2. Likewise, a study by Shieh et al. [24] examined whether baseline E_2 or FSH levels in pre- and perimenopausal women could predict bone loss over the following year. Results showed that both lower E_2 and higher FSH were associated with a greater risk of significant BMD decline. Specifically, in the lumbar spine, each halving of E_2 and each doubling of FSH was linked to a 10% and 39% higher risk of bone loss, respectively (both $p < 0.0001$). Similar associations were observed in the femoral neck (12% and 27% increased risk; $p = 0.01$ and $p < 0.001$, respectively). Importantly, FSH was a more informative predictor than E_2 at prospectively predicting bone loss by the next year.

In contrast, a study by Vural et al. [30] did not observe a significant association between FSH and bone mass in women aged 35–50 years.

5.1.2. Association Between BTMs

Elevated bone turnover activity has also been closely linked to higher FSH levels. Study by Li et al. [21] showed that FSH was a positive influential factor on BAP, OC, and NTX ($\beta = 0.188$–0.403, all $p < 0.001$) and a negative influential factor on CTX ($\beta = -0.183$, $p < 0.001$). Ma et al. [25] concluded that serum FSH levels were independently associated with BTMs. In their multiple linear regression analyses, FSH was the only independent predictor of CTX ($\beta = 0.45$, $p < 0.001$), and, together with age, it was significantly associated with PINP after adjustment for LH and E_2 ($\beta = 0.20$, $p = 0.036$). It was suggested that measuring FSH in mid-age women with irregular periods could be used in early diagnosis of postmenopausal osteoporosis. A study by Sowers et al. [31] showed that FSH was positively correlated with both bone resorption and formation markers, such as NTX ($\beta = 0.003$, partial r2 = 2.1%, $p < 0.0001$) and OC ($\beta = 0.216$, partial r2 = 4.1%, $p < 0.0001$). In addition, there was no significant correlation between these markers and sex steroids like E_2 and testosterone [31]. According to Vural et al. [30], higher gonadotropin (including FSH) levels were independently correlated with increased bone resorption (r = 0.403, $p = 0.000$) but not bone formation.

5.2. Summary of Findings

The studies summarized in Table 1 indicate a significant association between FSH levels and bone metabolic status during the menopause transition. Epidemiological studies [10,21,23,24,26–28] observed a link between elevated FSH and decreased BMD, specifically in the lumbar spine and hip, even after adjusting for age, E_2 levels, and other variables. Several longitudinal studies analyzing SWAN data [24,26,28], as well as a study by Shieh et al. [24], identified FSH as a more accurate predictor of bone loss than E_2. Additionally, multiple studies [10,21,25,30,31] demonstrated that FSH and BTMs were positively correlated, suggesting that FSH may contribute to increased bone remodeling activity. These results tend to support the hypothesis that FSH influences bone metabolism during menopause transition in a way that is clinically important.

6. Clinical Implications

Results from epidemiological studies support the hypothesis that FSH has an impact on bone metabolism throughout the menopause transition. It may be used for early identification of women at risk of accelerated bone loss, especially if measured simultaneously with BMD and BTMs [21]. Several longitudinal studies showed that increased FSH levels, even when E_2 concentrations stay within normal ranges, are linked to decline in BMD. It raises the possibility that FSH may be used to identify women who are at risk of rapid bone loss before the clinical onset of menopause, when DXA scans do not yet indicate osteopenia or osteoporosis. Although DXA scan is currently advised for postmenopausal women aged 65 and older, younger women with significantly elevated FSH levels, such as those in perimenopause or early postmenopause, may benefit from earlier DXA screening, especially if they have additional risk factors (e.g., low BMI, smoking, family history of osteoporosis).

It is important to note that FSH levels are highly variable throughout the menopause transition and can fluctuate within and between cycles; thus, serial evaluations of FSH may be more informative than a single measurement. However, this approach may be impractical in routine patient care. Moreover, FSH has not yet been proven to be a reliable indicator of bone loss or fracture risk; therefore, it should be considered only as a potential complementary tool rather than a standalone measure.

7. Limitations of Current Evidence and Future Direction

Although the reviewed studies suggest a possible role for FSH in perimenopausal bone metabolism, it is important to recognize several limitations when interpreting these findings. First, all the studies were observational in design, limiting the ability to prove causation. Some of the studies adjusted for confounding factors such as age, BMI, and E_2 levels; however, residual confounding cannot be excluded. Second, there is considerable heterogeneity among studies in terms of demographic characteristics, definitions of menopausal stage, FSH values, and measured outcomes (e.g., BMD site, BTMs). In several cases, E_2 was not measured, complicating efforts to determine whether observed associations are truly independent of estrogen status. Third, there is natural variability in the hormonal environment during the menopause transition. Levels of FSH vary greatly within and between individuals; therefore, a single measurement of FSH may not be sufficient to reflect long-term hormone exposure. This issue was addressed in a longitudinal study by Sowers et al. [28] by using serial FSH values, although such approaches may be difficult to apply in standard clinical practice. Lastly, there is a lack of data from human clinical trials that directly target FSH, despite strong biological plausability supported by molecular and animal studies. Most of the finding are based on indirect associations, and it is unknown how much FSH acts as an independent marker of bone loss or simply as an indicator of ovarian aging. Taken together, while current epidemiological evidence supports a possible role for FSH as an early indicator of changing menopause-related bone metabolic status, further studies are needed to confirm its definite role in human's bone health, as well as to validate its clinical utility.

8. Conclusions

Bone loss is accelerated during perimenopause, making it a crucial time for early detection of irreversible bone health deterioration. It has been hypothesized that FSH has a clinically relevant role in bone health during menopausal transition as higher levels of this hormone are linked to reduced BMD and increased bone turnover, potentially preceding declines in estrogen. Longitudinal studies suggest that FSH may be a predictor of bone loss in midlife women even better than E_2. While FSH has not been used in routine clinical practice, it may represent a useful early marker for identifying women at higher risk of

bone loss. Future research is essential to confirm its utility in bone health assessment, as well as in bone-loss screening strategies.

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Abbreviations

AMH	Anti-Müllerian hormone
BAP	Bone alkaline phosphatase
BMD	Bone mineral density
BMI	Body mass index
BTMs	Bone turnover markers
CTX	C-telopeptide of type 1 collagen
DXA	Dual-energy X-ray absorptiometry
E_2	Estradiol
FMP	Final menstrual period
FSH	Follicle-stimulating hormone
FSHR	FSH receptor
HPG	Hypothalamic-pituitary-gonadal
LH	Luteinizing hormone
NTX	N-telopeptide of type 1 collagen
OC	Osteocalcin
PINP	Procollagen I N-propeptide
SHBG	Sex hormone-binding globulin
SWAN	Study of Women's Health Across the Nations

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