

Menopausal Hormone Therapy Promotes Bone Health

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Clinical Context

Osteoporosis is characterized by increased bone fragility and susceptibility to fracture resulting from low bone mass and microarchitectural deterioration of bone tissue. Although bone mineral density (BMD) is a major determinant of bone strength and fracture risk, one-half of fragility fractures occur in persons with BMD values in the osteopenic or normal range, suggesting that bone microarchitecture also affects bone strength.

Menopausal hormone therapy (MHT) has been shown to benefit BMD, but it has not previously been determined whether MHT may also improve bone microarchitecture, as reflected in trabecular bone score (TBS). The goal of this cross-sectional analysis by Papadakis and colleagues was to describe the effect of MHT on TBS and BMD before and after treatment withdrawal.

Study Synopsis and Perspective

Hormone replacement therapy (HRT) can improve not only BMD but bone mass and structure, and the benefits of HRT on bone persist for at least 2 years after treatment is discontinued, a new cross-sectional analysis of a Swiss cohort indicates.

"We now know that almost half of all fragility fractures can occur in subjects who have either normal or osteopenic bone-mineral density," lead author Georgios Papadakis, MD, CHUV, Lausanne University Hospital, Lausanne, Switzerland, told *Medscape Medical News*.

"And bone microarchitecture has increasingly been recognized as an important factor in bone fragility, so used in the right context -- namely, in young postmenopausal women for whom the benefits outweigh the risks -- HRT is effective for both the prevention and treatment of osteoporosis," Dr Papadakis added.

The research was published online November 17 in the *Journal of Clinical Endocrinology & Metabolism*.^[1]

Half of Women Were Current or Past Users of HRT

A total of 1279 women between 50 and 80 years old who were part of the larger OsteoLaus study^[2] were available for the current analysis. They were divided into 3 groups: current HRT users, past HRT users, and women who had never taken HRT.

Current users had to have taken HRT for at least 6 months.

"Bone-mineral density was measured at the lumbar spine, femoral neck, and total hip with dual X-ray absorptiometry [DXA] while a trabecular bone score (TBS) of the spine was arrived at by evaluating pixel gray-level variations in the lumbar-spine DXA image," the investigators note.

As they point out, TBS provides an indirect index of trabecular bone microarchitecture and has been shown to predict fracture risk independently of BMD and the Fracture Risk Assessment tool.

Of the 1279 women included in the analysis, 282 (22%) were current users of HRT, 380 (30%) were past users, and 617 (48%) were nonusers.

It is important to note that past users were significantly older than the other 2 groups and had a higher prevalence of fractures. They also took calcium and vitamin D supplements more frequently than did current and never-users of HRT, although there were no between-group differences in body mass index (BMI) or dietary intake of calcium.

"Current-user group members had consistently higher values of TBS and BMD at all sites compared with never users and past users in both unadjusted and adjusted models," Dr Papadakis said.

Furthermore, after adjustment for age and BMI, past users had higher lumbar spine and total hip BMD than did never-users ($P = .017$ and $P = .026$, respectively), he added.

In addition, on multivariate analysis the investigators note that slopes for 10-year increments in TBS were significantly less steep in both current and past HRT users, "indicating that [HRT] slows down the age-associated loss of TBS," they observe.

In contrast, investigators found no differences in BMD based on duration of HRT use in either current or past users.

Table. Adjusted Mean BMD and TBS According to HRT Status

Age and BMI-Adjusted BMD and TBS	Current HRT Users	Past HRT Users	Never HRT Users
BMD lumbar spine	0.98	0.94	0.91
TBS lumbar spine	1.31	1.29	1.27
BMD femoral neck	0.76	0.73	0.72
BMD total hip	0.89	0.86	0.84

BMD, bone mineral density; BMI, body mass index; HRT, hormone replacement therapy; TBS, trabecular bone score.

Antiestrogenic Drugs and Microarchitecture

As Dr Papadakis observed, drugs used to prevent fragility fractures in women with osteoporosis really should improve both BMD as well as bone microarchitecture.

However, so far current drugs used to treat osteoporosis actually have less of an effect on bone microarchitecture than they do on BMD, he pointed out.

He thus speculates that agents that more favorably influence bone microarchitecture, such as HRT, may well have advantages over those that do not, although this idea is still hypothetical.

"The idea is not to prescribe HRT to all women," he emphasized, "and I don't think HRT should be prescribed indefinitely, either," he added.

"But at least in young postmenopausal women at increased risk of osteoporosis, HRT can be a very effective first-line treatment, provided the woman has no contraindications and it can be continued for at least 5 and maybe even 10 years."

However, he emphasized that once HRT has been discontinued, any positive gains from HRT on either BMD or bone microarchitecture will likely be gone 2 years later.

Dr Papadakis has disclosed no relevant financial relationships. Disclosures for the coauthors are listed in the original study.

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Study Highlights

- Of 1500 women 50 to 80 years old in the general Swiss community OsteoLaus cohort, 1279 were not treated with bone-modulating therapy and were categorized as current MHT users for 6 months or longer (22%), past users (30%), or never-users (48%).
- Participants underwent dual x-ray absorptiometry for measurement of spine TBS and BMD at the lumbar spine, femoral neck, and total hip (primary endpoints).
- After adjustment for age and BMI, TBS was higher in current MHT users (1.31 ± 0.01) vs past users (1.29 ± 0.01) or never-users (1.27 ± 0.01 ; $P < .001$ for both), as were all BMD values.
- Past vs never-users of MHT had higher BMD at the lumbar spine (0.94 ± 0.01 vs 0.91 ± 0.01 g/cm²; $P = .017$) and total hip (0.86 ± 0.01 vs 0.84 ± 0.01 g/cm²; $P = .026$), and a nonsignificant trend toward higher TBS ($P = .066$).
- Compared with never-users, current and past MHT users had significantly lower 10-year loss of TBS and BMD at the lumbar spine and total hip.
- In multivariate analysis, slopes for 10-year increments were significantly less steep in current and past MHT users vs never-users, suggesting that MHT slows down age-associated loss of TBS.
- The residual impact of MHT on TBS and BMD in past users was significantly greater in early discontinuers (<2 years).
- Early discontinuers had significantly higher BMD levels than did late discontinuers (>5 years), perhaps suggesting an eventual rebound effect after treatment withdrawal, with rapid loss of the previously acquired benefit.
- The investigators estimate that the inflection point, beyond which the BMD benefit disappears, is between 2 and 4 years.
- On the basis of their findings, the investigators concluded that MHT is associated with preservation of bone microarchitecture, as reflected in TBS, and that the effect of MHT on TBS and BMD persists at least 2 years after treatment withdrawal.
- They suggest that their findings can be reliably generalized to clinical practice because of the large sample including a wide age range of postmenopausal women.

- For optimal efficacy in the prevention of fractures, antiosteoporotic agents should ideally affect bone mass and bone microarchitecture, but the impact of antiosteoporotic drugs on TBS is smaller vs the impact on BMD.
- This study is the first to show an association of MHT with higher levels of TBS.
- The finding that current MHT use is associated with higher BMD values at all relevant sites is consistent with results of previous randomized trials and a meta-analysis.
- Because BMD and TBS are surrogate markers of osteoporotic fracture risk, the finding of a residual effect in present users suggests that fracture incidence would be lowered in present vs never-users of MHT.
- Nearly half of all fragility fractures occur in persons with normal or osteopenic BMD, highlighting the importance of bone microarchitecture in bone fragility.
- The investigators suggest that MHT is effective to prevent and treat osteoporosis in young postmenopausal women for whom the benefits outweigh the risks.
- Study limitations include reliance on self-report for beginning and end of MHT and for drug administration routes, and lack of data on estrogen dose.

Clinical Implications

- MHT may help preserve bone microarchitecture measured by TBS up to 2 years after MHT withdrawal, based on a cross-sectional analysis.
- MHT has a well-established positive effect on BMD, and preservation of bone microarchitecture may contribute to antifracture efficacy.
- Implications for the Healthcare Team: Healthcare providers should bear in mind that the protective effect of MHT on BMD and TBS seems to persist for at least 2 years after treatment withdrawal.

CME Test

To receive *AMA PRA Category 1 Credit™*, you must receive a minimum score of 75% on the post-test.

Questions answered incorrectly will be highlighted.

You are a member of the healthcare team for a 57-year-old menopausal woman with concerns about bone health. According to the cross-sectional analysis by Papadakis and colleagues, which of the following statements about the effect of MHT on TBS and BMD is *correct*?

- TBS was higher in current MHT users than in never-users but did not differ significantly from that of past MHT users
- Adjustment for age and BMI abolished the significance of the observed associations
- Current and past MHT users vs never-users had significantly lower 10-year loss of TBS and BMD at the lumbar spine and total hip

- Early MHT discontinuers (<2 years) had significantly lower BMD levels than did late discontinuers (>5 years)

According to the cross-sectional analysis by Papadakis and colleagues, which of the following statements about the clinical implications of the effect of MHT on TBS and BMD in young menopausal women is *correct*?

- The investigators suggest that MHT is effective to prevent and treat osteoporosis in young postmenopausal women, for whom the benefits outweigh the risks
- The impact of antiosteoporotic drugs on TBS is greater than the impact on BMD
- The effect of MHT on TBS and BMD persists for at least 5 years after withdrawal
- The findings cannot be reliably generalized to clinical practice