the Baltimore Longitudinal Study of Aging demonstrate heterogeneity that might account for a lack of benefit in studies of treatment for subclinical hypothyroidism in older adults. At the same time, new data suggest the need for a more aggressive threshold for vitamin D in older adults, with a lower threshold associated with a drop in physical function compared to younger adults. Complexity in the regulation of hormonal pathways and the downstream effects on target tissues means multiple individuals with similar hormone levels may have different underlying physiology, with divergent clinical needs. Changes in activity and diet common during aging, and exacerbated by the pandemic, lead to physical and mood changes associated with hormonal dysfunction in popular culture and patient requests for evaluation. The ultimate goal should be personalized treatment decisions based on comprehensive evaluation and pathophysiology.

THE MANY FACES OF ELEVATED TSH: WHEN TO AVOID THYROID HORMONE THERAPY IN OLDER ADULTS

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We have previously demonstrated that hypothalamic-pituitary-thyroid axis aging is characterized by several distinct patterns. An elevated thyrotropin (TSH) level (mean 5.6mIU/L) with normal free thyroxine (FT4) was present in 75 BLSA participants with at least 3 visits. Twenty-one percent had an historical pattern consistent with primary gland failure, while 13% had a pattern consistent with an HPT response to stressors (aging-adaptation). The remainder had intermediate patterns of change. FT4 >0.92pg/ml identified those in whom TSH elevations occurred with aging-adaptation with a 90.0% sensitivity and 93.8% specificity, indicating no need for therapy. In addition, among 597 participants with stable TSH levels in the reference range, being on thyroid hormone therapy increased mortality risk (IRR=1.8; 95% CI 0.9-2.1). Thus, including FT4 in the diagnostic criteria for hypothyroidism in older adults could target therapy to avoid the potential harm of reversing the aging adaptations in those who do not have true early hypothyroidism.

SEX-SPECIFIC 25-HYDROXYVITAMIN D THRESHOLD CONCENTRATIONS FOR FUNCTIONAL OUTCOMES IN OLDER ADULTS

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25-Hydroxyvitamin D [25(OH)D] has extra-skeletal effects, but it is not known whether the minimum sufficient serum levels for such targets, like muscle, differ from those for bone health (typically recommended at 20 or 30 ng/dL). Therefore, we derived and validated sex-specific thresholds for serum 25(OH)D predictive of poor physical function using 5 cohorts comprising 16,388 community-dwelling older adults (60.9% women). Using a cohort-stratified random two-thirds sample, we found incident slow gait was best discriminated by 25(OH)D<24.0 versus 25(OH)D>=24.0 ng/mL among women (Relative Risk=1.29; 95% CI 1.10-1.50) and 25(OH)D<21.0 versus 25(OH)D >=21.0 ng/mL among men (RR=1.43; 95% CI 1.01-2.02). Estimates from the remaining one-third validation sample were similar. Empirically identified and validated sex-specific 25(OH)D thresholds from multiple well-characterized cohorts of older adults may yield more biologically meaningful definitions in important sub-populations. Such thresholds may serve as candidate reference concentrations or inform design of vitamin D intervention trials in older adults.

TESTOSTERONE THERAPY FOR MEN WITH AGE-RELATED LOW TESTOSTERONE: TEMPEST IN A TEACUP

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Serum testosterone concentrations decrease in men with age, but benefits and risks of raising testosterone levels in older men remain controversial. In the T-Trials, a total of 790 men, age 65 and older, with a serum testosterone concentration of < 275 ng/dL and symptoms of sexual dysfunction, fatigue or physical dysfunction were randomized to either testosterone gel or placebo gel for 1 year. Treatment in the testosterone arm increased serum testosterone levels to the mid-normal range for young men. Testosterone replacement was associated with a significant increase in sexual activity ($p < 0.001$), libido and erectile function. In contrast, there was no improvement in vitality or physical function. Adverse findings included increases in non-calcified plaque formation and a higher rate of prostate events. In sum, testosterone treatment in older men was associated with modest benefits, while the risk on prostate and cardiovascular health remain unclear.

ASSOCIATIONS BETWEEN ENDOGENOUS ESTROGEN, POSTMENOPAUSAL HORMONE THERAPY, AND COGNITIVE CHANGES IN OLDER WOMEN

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How markers of brain health are associated with endogenous estrogen and use of postmenopausal hormone therapy (HT) varies depending on women's years from menopause and metabolic health status, ranging from potential benefit to harm. The Women's Health Initiative (WHI) included 7,233 women age 65-80 who underwent a randomized clinical trial of various HT preparations for an average of 5.9 years. Over up to 18 years of post-trial follow-up, diabetes (DM2) increased the risk of dementia (hazard ratio [HR] 1.54 [95% CI 1.16–2.06]). Having DM2 and also treatment with unopposed conjugated equine estrogens increased the risk to HR=2.12 [1.47-3.06]. We hypothesize