

Cardiovascular CORNER

Can Blood Hormone Levels Guide Menopausal Hormone Therapy?

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Age and obesity are two important risk factors for venous thromboembolism (VTE) and stroke in the general population. Additionally, VTE and stroke have been linked with menopausal hormone therapy (HT). The role that age and obesity play in the risk for VTE and stroke is multifactorial, with increased estrogenicity a likely important component. Obesity is of particular significance for postmenopausal women since peripheral fat tissue is the major source of estrogen after menopause. However, the influence of age and

obesity on achieved serum estrogen levels among HT users was not known until recently. We compared the serum levels of estrogens and sex hormone-binding globulin (SHBG) across body mass index (BMI) and waist-to-hip ratio (WHR) categories in 91 postmenopausal women receiving 1 mg of micronized oral estradiol over 2 years in a randomized controlled trial.¹

As shown in the Table, there is a significant influence of obesity on serum estrogen concentrations among postmenopausal women randomized to estradiol therapy (ET); overweight and obese women had higher concentrations of total and free estradiol compared to women with BMIs <25kg/m². Serum levels of SHBG were lower in women with higher WHRs.

Age-associated altered pharmacokinetics can result in higher circulating concentrations of drugs, which may also be true for HT.^{2,3} Although we did not find a significant trend of serum estrogen levels with age among ET-treated women, there was a significant increasing trend in serum concentrations of estrone, total estradiol and free estradiol with higher BMI among ET-treated women ≥65 years (Figure).

These results suggest that the increased risk of VTE or stroke observed in older and heavier women taking HT may be partially explained by

Table. Levels of Estrogens and SHBG by Age, BMI and WHR among Estradiol-Treated Women

	BMI categories (kg/m ²)				WHR categories			
	<25	25-29	≥30	P for trend	<0.80	0.80-0.83	>0.83	P for trend
	Mean (SE)* n=26	Mean (SE) n=31	Mean (SE) n=34		Mean (SE) n=29	Mean (SE) n=28	Mean (SE) n=34	
E2	60.6(5.6)	64.4(4.7)	78.3(4.8)	0.01	70.7(5.4)	70(5.4)	65.1(5.0)	0.46
FE2	1.4(0.1)	1.5(0.1)	1.8(0.1)	0.002	1.59(0.1)	1.60(0.1)	1.59(0.1)	0.92
E1	316(34.9)	291(29.3)	334(29.0)	0.62	345(31)	322(31.7)	278(29.6)	0.11
SHBG	66.9(4.9)	55.9(4.1)	56.3(4.0)	0.12	67.9(4.3)	58.4(4.3)	51.5(4.1)	0.005

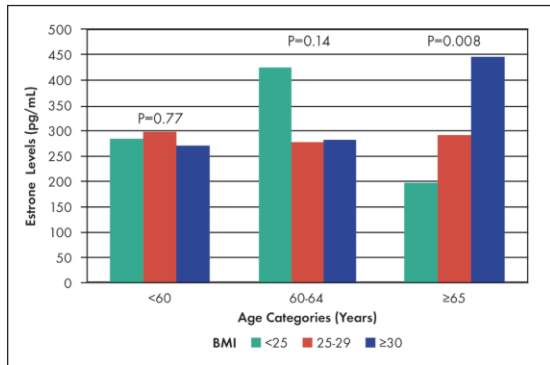
BMI=body mass index; WHR=waist-to-hip ratio.

E2=total estradiol; FE2=free estradiol; E1=estrone; SHBG=sex hormone-binding globulin

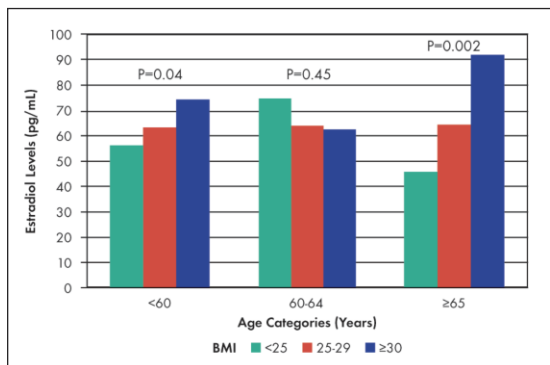
Models adjusted for age.

* Average of multiple assessments taken every six months during the trial.

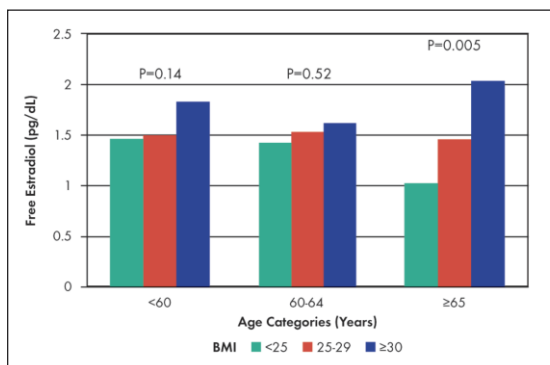
Figure.



A. Association of serum estrone levels with BMI stratified by age among women taking estradiol therapy



B. Association of serum total estradiol levels with BMI stratified by age among women taking estradiol therapy



C. Association of serum free estradiol levels with BMI stratified by age among women taking estradiol therapy

higher circulating estrogen and lower SHBG concentrations in this group of women. These results have important clinical implications in that it may be useful to consider both age and obesity when prescribing HT.

Circulating estrogen levels also can be influenced by polymorphisms of genes involved in steroid metabolism. Polymorphisms in the CYP17 and CYP19 genes have been shown to be associated with serum estradiol concentrations in postmenopausal women⁴⁻⁷ and have been linked with breast cancer. In a recent study, HT-treated women with a T>C polymorphism in the CYP17 gene were at greater risk for breast cancer than HT-treated women without the polymorphism.⁸ It is not known whether these genetic variants relate to risk of VTE or stroke. Studies are needed to test the possible modifying effect of these genetic polymorphisms on HT-related VTE and stroke risk among postmenopausal women. Such genetic variants may one day be useful in personalizing HT.

Although HT prescription rates declined dramatically after the initial WHI 2002 publication, a very large number of postmenopausal women continue to use HT. According to a recent survey approximately 14% of 50- to 59-year-old and 12% of 60- to 69-year-old postmenopausal women in the US used HT in 2005.⁹ The position statement of The North American Menopause Society (NAMS) states that the risk-benefit ratio of menopausal HT is favorable if initiated around the time of menopause.¹⁰ The NAMS expert panel took this position based on the accumulating data indicative of a favorable impact of early initiation of HT. While evidence continues to mount for the timing theory showing a reduction in the risk for the majority of outcomes associated with HT when initiated in young postmenopausal women, vigilance needs to continue concerning VTE. Personalizing the dose of HT guided by serum estrogen concentrations is one attractive option to possibly maximize the benefits from HT while mitigating untoward outcomes.

In conclusion, while supportive research is required, it may be useful to consider age and obesity to minimize HT-related VTE and stroke risk

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Seattle, WA.

Both authors disclose funding from the National Institutes of Health.

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when using HT in postmenopausal women. However, further studies are warranted to determine whether serum hormone concentrations underlie the potential mechanism for increased risk of VTE/stroke in older and heavier postmenopausal women treated with HT. In particular, researchers should investigate associations of HT-associated estrogen concentrations with VTE and stroke risk, and should further investigate clinical determinants (including age and obesity) of HT-related hormone levels. If such associations are supported, monitoring of hormone concentrations among higher-risk women may be warranted for reducing HT-related VTE and stroke risk. ■

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Drs. Karim and Stanczyk have disclosed no potential conflicts related to the content of this article.

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