**2-hydroxyestrone / 16-hydroxyestrone Ratio**

By Wendy L. Ellis, ND and Ronald Steriti, ND, PhD

© 2009

2-hydroxyestrone (2-OH estrone) and 16-hydroxyestrone (16A-OH estrone) are Phase I metabolites of Estrone (E1). Their ratio is of clinical significance in pre and peri-menopausal women. In post-menopausal women it does not have the same clinical significance. It is, however, hypothesized that the 2/16 ratio is important in menopausal women who are on hormone replacement therapy (HRT).

**Breast Cancer**

In one study, significantly lower values of the 2/16 ratio and higher levels of 16-alpha-hydroxyestrone were observed in tumor tissues, reinforcing the hypothesis that an imbalance of 2- and 16-alpha-hydroxylation may be implicated in breast cancer development. Additionally, 16-alpha-hydroxyestrone levels are observed in larger amounts in carcinogenic breast tumors, however, when the tumors have higher amounts it correlates to a prolonged survival of breast cancer patients. (Castagnetta, Granata et al. 2002)

Another study’s analysis of 16-alpha-hydroxyestrone in pre and post-menopausal women indicates that it is a strong risk factor for breast cancer. (Kabat, Chang et al. 1997) (Kabat, O'Leary et al. 2006)

The risk of breast cancer, in particular the estrogen receptor-positive type, was enhanced among postmenopausal women using estradiol-based HRT and among those who had a high 2-OHE concentration. (Wellejus, Olsen et al. 2005)

A common CYP1B1 polymorphism is associated with an increased 2/16 urinary estrone ratio. (Paracchini, Pedotti et al. 2005)

**Rheumatoid Arthritis And Systemic Lupus Erythematosus**

Patients with rheumatoid arthritis and systemic lupus erythematosus have increased renal excretion of mitogenic estrogens in relation to endogenous antiestrogens. In patients with RA and SLE, the magnitude of conversion to the mitogenic 16-alpha-hydroxyestrone is greatly upregulated, which likely contributes to maintenance of the proliferative state in these diseases. (Weidler, Harle et al. 2004)

**Bone Mineral Density**

Increased hydroxylation to relatively non-estrogenic metabolites 2-hydroxyestrone (2OHE1) and 2-methoxyestrone (2MeOE1) was associated with low bone mineral density (BMD), while increased hydroxylation to the potent 16-alpha-hydroxyestrone and weakly estrogenic estriol was associated with higher BMD. (Armamento-Villareal, Napoli et al. 2004)
Thyroid disorders

Increased 16alpha-hydroxyestrone activity compared to 2-hydroxyestrone activity appears to be associated with proliferative thyroid disease.

A case-control study of 49 subjects with proliferative thyroid disorders found that fifty-one percent (25 of 49) of the cases had a low 2/16 ratio compared to 31% (15 of 49) in the control group while 20% (10 of 49) of the control group had a high 2/16 ratio as compared to 8% (4 of 49) in the case group (P value < 0.05). (Chan, Sepkovic et al. 2006)

Improving the 2/16 ratio

Diindolylmethane

Dietary indoles, present in brassica plants such as cabbage, broccoli, and brussel sprouts, have been shown to provide potential protection against hormone-dependent cancers. 3,3'-Diindolylmethane (DIM) is under study as one of the main protective indole metabolites. DIM-treated subjects, relative to placebo, showed a significant increase in levels of 2-OHE1, DIM, and cortisol, and a non-significant increase of 47% in the 2/16 ratio from 1.46 to 2.14. The conclusion in this pilot study was that DIM increased the 2-hydroxylation of estrogen urinary metabolites. (Dalessandri, Firestone et al. 2004)

In another study, the percentage change in 2/16 urinary ratio, to a more favorable ratio, after indole treatment, was found to be significant. (Paracchini, Pedotti et al. 2005)

Indole-3-carbinol

One study found the ratio of urinary estrogens, 2OHE1/E3, was significantly increased in obese women following indole-3-carbinol (400 mg for two months), reflecting induction of 2-hydroxylation in these women. (Michnovicz 1998)

Flaxseed

Flaxseed is a rich source of dietary lignans. Forty-three postmenopausal women consumed 7.5 g/day of ground flaxseed for 6 wk, followed by 15 g/day for an additional 6 wk. The mean urinary level of 16alpha-hydroxyestrone (16alpha-OHE1) was higher at the end of 12 wk compared to baseline (change of 1.32 ug/day, P = 0.02). There was no significant change in 2-OHE1 excretion. Mean urinary excretion of 2-methoxyestradiol was also lower at 12 wk than at baseline (P = 0.03). (Sturgeon, Volpe et al. 2010)

Flax will interfere with hormone panels. Avoid flax for at least 5 days before testing.

Sesame

Sesamin, a sesame lignan, may be converted by intestinal microflora to enterolactone, a compound with estrogenic activity and also an enterometabolite of flaxseed lignans, which are known to be phytoestrogens. Whether sesame can be a significant source of phytoestrogens is unknown.

Twenty-six healthy subjects attended, and 24 completed, this randomized, placebo-controlled, crossover study. Half of them consumed 50 g sesame seed powder daily for 5 wk, followed by a
3-wk washout period, then a 5-wk 50-g rice powder placebo period. The other half received the 2 supplements in reverse order. Serum sex hormone-binding globulin and urinary 2-hydroxyestrone (n = 8) increased significantly by 15 and 72%, respectively, after sesame treatment. (Wu, Kang et al. 2006)

**Prozac**

A preliminary study of the effect of fluoxetine treatment on the 2:16-alpha-hydroxyestrone ratio in young women. In three of the four women who were nonsmokers, the 2OHE1:16OHE1 ratio was significantly higher after 5 weeks of fluoxetine therapy. (This is not an endorsement for prozac, purely informational) (Thompson, Kirshner et al. 2003)
References


