Estrogen Metabolism Plus 24hr Urine

Physician Copy

Parkgate House
356 West Barnes Lane
New Malden, Surrey KT3 6NB

63 Zillicoa Street
Asheville, NC 28801 USA

Patient:
DOB:
Sex: F
MRN:

Order Number:

Completed:
Received:
Collected:

Methodology: LC-MS/MS; Specimen: 24hr urine; Results normalized to creatinine

Estrogens

Estrogen Metabolites

Reference Range

2-Hydroxyestrone + 2-Hydroxyestradiol [2-OH(E1+E2)] * — 1.4 — 1.3-36.3 mcg/g Creat.

* Premenopause (luteal) reference range shown

	Reference Ranges
Premenopause	1.3-36.3 mcg/g Creat.
Menopause	0.9-43.8 mcg/g Creat.
Male	0.7-12.5 mcg/g Creat.

16α-Hydroxyestrone (16α-OH E1)* — <dl — 0.5-8.9 mcg/g Creat.

* Premenopause (luteal) reference range shown

	Reference Ranges
Premenopause	0.5-8.9 mcg/g Creat.
Menopause	0.4-7.7 mcg/g Creat.
Male	<=2.0 mcg/g Creat.

4-Hydroxyestrone+4-Hydroxyestradiol [4-OH(E1+E2)] * — <dl — <= 5.9 mcg/g Creat.

* Premenopause (luteal) reference range shown

	Reference Ranges
Premenopause	<=5.9 mcg/g Creat.
Menopause	<=8.8 mcg/g Creat.
Male	<=1.6 mcg/g Creat.

2-Methoxyestrone+2-Methoxyestradiol [2MeO(E1+E2)]* — 1.2 — 0.2-8.6 mcg/g Creat.

* Premenopause (luteal) reference range shown

	Reference Ranges
Premenopause	0.2-8.6 mcg/g Creat.
Menopause	0.3-5.9 mcg/g Creat.
Male	0.2-2.5 mcg/g Creat.

4-Methoxyestrone+4-Methoxyestradiol [4MeO(E1+E2)]* — <dl — <= 1.0 mcg/g Creat.

* Premenopause (luteal) reference range shown

	Reference Ranges
Premenopause	<=1.0 mcg/g Creat.
Menopause	<=1.0 mcg/g Creat.
Male	<=1.0 mcg/g Creat.

Methodology: LC-MS/MS; Specimen: 24hr urine; Results normalized to creatinine

Estrogens

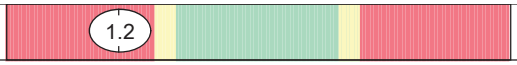
Ratios

	Reference Range
2-OH(E1+E2) / 16α-OHE1*	0.3-13.7

* Premenopause (luteal) reference range shown

	Reference Ranges
Premenopause	0.3-13.7
Menopause	0.3-15.1
Male	0.8-12.9

	Reference Range
2-OH(E1+E2) / 2-MeO(E1+E2)*	1.6-10.7



* Premenopause (luteal) reference range shown

	Reference Ranges
Premenopause	1.6-10.7
Menopause	0.4-11.6
Male	1.0-8.8

Lab Comments

The performance characteristics of all assays have been verified by Genova Diagnostics, Inc. Unless otherwise noted with ◆, the assay has not been cleared by the U.S. Food and Drug Administration.

<dl = Unable to calculate results due to less than detectable levels of analyte.

Please note analysis of estrogens and estrogen metabolites is now performed using LC/MS/MS. The reference ranges for these biomarkers have been updated.

Commentary

Commentary is provided to the practitioner for educational purposes, and should not be interpreted as diagnostic or treatment recommendations. Diagnosis and treatment decisions are the responsibility of the practitioner.

Estrogen Metabolites

Estrogens are metabolized by two main pathways: (1) formation of the catechol estrogens 2-hydroxyestrone/estradiol (2-OHE1/E2) via the CYP1A1 pathway and 4-hydroxyestrone/estradiol (4-OHE1/E2) via the CYP1B1 pathway; and (2) formation of 16α-hydroxyestrone (16α-OHE1) via the CYP3A4 pathway.

2/16 Ratio and Hydroxylation pathways

2/16 Ratio - The clinical utility of the ratio of 2-hydroxyestrone (2-OHE1) to 16α-hydroxyestrone (16α-OHE1) – the 2/16 ratio or Estrogen Metabolite Ratio (EMR) – historically reported lower 2/16 ratio levels among breast cancer cases compared to controls (particularly in premenopausal women). Recent studies have been mixed: there appears to be no strong evidence in the literature that a higher urinary 2/16 ratio protects postmenopausal women from breast cancer, and only weak evidence of a protective effect in premenopausal women.

Higher 2-OH (E1+E2)/16α –OH ratios in males have been associated with reduced risk of prostate cancer.

2-OH (E1+E2) - While traditional 2/16 ratio clinical utility may not be as robust as previously thought, a majority of findings indicate that metabolism of parent estrogens through 2-hydroxylation (independent of any relationship to 16α-OHE1) may be considered as a benign or even protective pathway. (Of note: one study found increased breast cancer risk with higher 2-OH levels, but only in a small subgroup of ER-/PR- cases.)

Studies suggest that women with predominant metabolism through the 2-hydroxyl pathway have accelerated postmenopausal bone loss and lower BMD compared to those with predominant 16α-hydroxylation who appear to have reduced risk of bone loss. Increased 2- hydroxylation has been noted in women with a positive family history of osteoporosis suggesting that increased risk of osteoporosis in those with a family history may be related to inherited differences in estrogen metabolism.

16α-OH - Recent findings in the peer-reviewed literature are mixed, with some studies finding an association with increased risk (cancers of the cervix, breast, endometrium, and head and neck, as well as in people with tumors related to the human papilloma virus), but many finding no significant association.

4-OH (E1+E2) - Research focus is shifting toward 4-hydroxyestrone which is thought to have greater estrogenic and genotoxic potential than either 2-hydroxyestrone or 16α-hydroxyestrone. Metabolites of 4-hydroxyestrone may induce DNA damage through redox cycling, which generates reactive oxygen species and form reactive semiquinones and quinones capable of forming adducts with glutathione and purines in DNA. However, studies demonstrate that when DNA is incubated with quinones in the presence of an antioxidant, the formation of the DNA adducts is reduced.
•In patients with a low 2-hydroxylation result, metabolism may be shifted toward this pathway by dietary interventions rich in cruciferous vegetables; flax; soy; rosemary and turmeric; exercise that increases lean body mass and decreases BMI; and supplementation with broccoli derivatives indole-3-carbinol (I3C) or diindolylmethane (DIM), as well as omega-3 fatty acids, and vitamins B6, B12 and folate.
•Support of antioxidant activity appears to be a reasonable proactive step for reducing risk of hormone-related disease. Several natural compounds have exhibited the ability to minimize DNA adduct formation/damage including, resveratrol, N-acetylcysteine, lipoic acid, and melatonin. Cruciferous and allium vegetables also demonstrate the ability to induce glutathione S-transferases.

Commentary

Methoxylated Estrogens

2-OH(E1+E2)/2-MeO(E1+E2) ratio - There is evidence that methoxylated estrogens, especially the 2-pathway methoxylated estrogens (E1 and E2), are associated with decreased breast cancer risk; 2-MeOE2, produced from 2-OHE2, has been described to have anti-proliferative, antiangiogenic, and pro-apoptotic activity in multiple types of cancer. A high 2-OH (E1+E2)/2-MeO (E1+E2) ratio may indicate less methylation activity and/or a robust amount of hydroxylated compared to methylated analytes.

4-MeO (E1+E2) - Most recent studies also find an increased breast cancer risk associated with the ratio of 4-pathway catechols to 4-pathway methylated catechols. This increased risk has been seen in cases with less extensive methylation of potentially genotoxic 4-hydroxylation pathway catechols; thus, increased relative levels of 4-methoxyestrogens would be considered favorable.

Catechol-O-methyltransferase (COMT) is the enzyme responsible for catalyzing methylation of catechol estrogens to methoxy estrogens, which simultaneously lowers the potential for DNA damage and increases the concentration of 2-methoxyestradiol (2-MeOE2), an anti-proliferative metabolite. Genetic polymorphisms (SNPs) may impact COMT catalytic activity, and as a result, may be associated with significant differences in catechol estrogen and methoxy estrogen levels – thereby contributing to differences in risk for estrogen-mediated breast cancer amongst individuals.
•Numerous factors support methylation including S-Adenosyl-l-Methionine (SAMe); methionine; magnesium; vitamins B2, B6 and B 12; folate (or folinic acid, 5-formyl THF or 5-methyltetrahydrofolate); trimethylglycine (TMG); glutathione; and stress management strategies that reduce catecholamine production.