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## **Hormonal and Cardiovascular Testing**

### **Estronex 2/16**

When a major study of hormone replacement therapy in women was recently discontinued, clinicians and patients alike were left with unanswered questions. Why are certain tissues, such as the breast, susceptible to estrogen-induced cancer? Why are some women at risk, but not others?

Researchers at Rockefeller University have found that the body metabolizes estrogens into several different metabolites that can impact cancer development. One metabolite, 2-hydroxyestrone (2-OHE1), tends to inhibit cancer growth. Another, 16-a-hydroxyestrone (16-a-OHE1), actually encourages tumor development. A woman's "biochemical individuality" determines which of these metabolites predominates. Studies have shown that measuring the ratio of these two metabolites provides an important indication of risk for future development of estrogen-sensitive cancers. Significantly, the studies also show that this risk is modifiable!

Scientists have recently developed a test for this ratio. Now available from Nutritional Medicine Associates, the Estronex<sup>TM</sup> 2/16 Test measures the ratio of these two critical estrogen metabolites from a single urine specimen. Estronex 2/16 ratios less than 2.0 indicate increasing long-term risk for breast, cervical, and other estrogen-sensitive cancers. Nutritional interventions can help raise Estronex 2/16 ratios and decrease long term risk.

### ***Total and Free Testosterone***

Free testosterone is included in both the male and female panels.

Testosterone is produced in the testes in men, in the ovaries in women, and in the adrenal glands of both men and women. In men, testosterone production is stimulated by luteinizing (LH), which is produced by the pituitary gland and by Leydig cells in the testes. Testosterone levels normally decline with age, dropping to approximately 65% of young adult levels by age 75. This drop in testosterone is partially responsible for the significant physiologic changes seen in aging men.

Less than 2% of testosterone is typically found in the "free" (uncomplexed) state in the serum of both men and women. Approximately 50% is bound to sex hormone-binding globulin (SHBG) and the remainder to albumin. In men, free testosterone (an androgen, or "male hormone") levels may be used to evaluate impotence or infertility.

In women, high levels of free testosterone may indicate hirsutism (excessive hair growth, especially on the face and chest), which is often indicative of polycystic ovaries and, less commonly, ovarian cancer. Increased testosterone in women also suggests low estrogen levels.

Total testosterone (complexed and uncomplexed) is useful for assisting with differential diagnosis in males (LH secretion and Leydig cell function, gonadal and adrenal function, diagnosis of hypogonadism, hypopituitarism, Klinefelter syndrome, and impotence) and in females (Stein-Leventhal syndrome, masculinizing tumors of the ovary, tumors of the adrenal cortices, and congenital adrenal hyperplasia).

### ***DHEA-S (dehydroepiandrosterone sulfate)***

DHEA, often used as a muscle-building supplement by bodybuilders, measures adrenal cortical function. Elevated levels of this hormone, which peaks during one's 20s, may be indicative of CAH (congenital adrenal hyperplasia), a group of disorders that result from the impaired ability of the adrenal glands to produce corticosteroids. DHEA is also being evaluated in clinical trials for its role in memory and Alzheimer's disease, though results are as yet inconclusive.

### ***Estradiol***

In non-pregnant women, estradiol is the most commonly measured type of estrogen; levels vary throughout the menstrual cycle, and are reduced to low but constant levels after menopause. Increased levels of estradiol in woman indicate an increased risk of breast or endometrial (lining of the uterus) cancer. In men, estradiol is produced in amounts far lower than in women, and indicates hypothalamic and pituitary function. Increased levels of estradiol along with decreased levels of testosterone may indicate decreased sex drive and ability to urinate. In men, estradiol and testosterone levels should be tested together.

### ***Homocysteine***

Elevated levels of the amino acid homocysteine have been shown to be an independent risk factor for development of coronary artery disease and thrombosis (stroke). Data also indicate that homocysteine levels may be elevated in patients with depression; if folic acid (which normally helps to break down homocysteine) levels are depressed, homocysteine levels increase

### ***C-Reactive Protein (CRP) and the Cardio CRP Test***

Inflammation is a key pathogenic mechanism for development and progression of atherosclerosis and heart disease. Atherosclerosis is essentially an inflammatory response to an injury, such as hypertension, cigarette smoking, a diet rich in low-density lipoproteins (LDL, the so-called "bad" cholesterol), and hyperglycemia, among others. These stimuli elicit secretion of molecules that, along with uptake of cholesterol lipoproteins, most likely form the basis for the atherosclerotic "fatty streak" along arterial walls.

While still present, these risk factors continue to facilitate the attraction and accumulation of inflammatory cells—macrophages, mast cells, and activated T-lymphocytes—within the atherosclerotic plaque. Disruption of this plaque, caused by chronic inflammation, may cause a heart attack as oxygen-deprived blood vessels become clogged with pieces of dislodged plaque material.

C-reactive protein is a very sensitive marker of systemic inflammation, and has emerged as a powerful predictor of coronary heart disease<sup>21</sup> and other cardiovascular diseases.

The highly sensitive cardio CRP test is able to measure the presence of C-reactive protein in the blood, even at very early stages of vascular disease, allowing for appropriate intervention with diet, supplements, or anti-inflammatory therapy.

Elevated levels of C-reactive protein have also been found to be associated with risk of developing diabetes Type II,<sup>22</sup> loss of cognitive ability in seemingly healthy people,<sup>23</sup> Alzheimer's disease, and depression in the elderly. Furthermore, risk factors for atherosclerosis and heart disease, such as smoking and high blood pressure, elevate blood levels of C-reactive protein that can be detected by the cardio CRP test.<sup>24</sup>

### ***PSA (prostate specific antigen); free and complexed***

Offered as part of the male testing panel, PSA is a very sensitive marker that may suggest prostate cancer. It may also be used to monitor efficacy of therapeutic regimens associated with the prostate.

PSA is normally found at million-fold lower concentrations in the serum than in the seminal fluid. In seminal fluid, PSA predominantly exists in the "free" (uncomplexed) state; in serum, it is generally found bound to inhibitors. Risk of prostate cancer may be assessed by determining absolute amounts of total PSA or by calculating the percent of free PSA compared to total PSA (complexed plus uncomplexed). A study in the *New England Journal of Medicine* found that 25% of patients with normal digital rectal exams (DRE) and total PSA levels of 4.0–10.0 ng/ml had prostate cancer.<sup>25</sup> In the same study group, researchers calculated that risk of prostate cancer increased with decreases in the percentage of free PSA in the serum. In other words, as the ratio of complexed to free PSA increased (concomitant with total increased levels of PSA), risk of prostate cancer increased dramatically.

It should be noted that elevated levels of PSA may not necessarily signal prostate cancer, and prostate cancer may not always be accompanied by expression of PSA. Levels may be elevated in the presence of a urinary tract infection and an inflamed prostate.

In another study recently published in the *New England Journal of Medicine*, investigators recommended lowering the PSA cutoff from 4.1 ng/ml (the threshold at which biopsy is currently recommended). At the current threshold, it was determined that "82 percent of cancers in younger men and 65 percent of cancers in older men would be missed."<sup>26</sup> But levels below the currently recognized cutoff of 4.1 ng/ml may not distinguish between prostate cancer and benign prostate disease. New tests looking at PSA precursor (proPSA) alongside PSA may aid in improving diagnosis. Clinical trials are currently under way.<sup>27</sup>

### ***Progesterone***

Progesterone levels, included in the female testing panel, may track menstrual/ovulation cycles (levels are highest during mid-cycle, the time of ovulation) and may be used as a marker for ovarian and adrenal tumors, and for luteal ovarian cysts (increased levels). Decreased levels are associated with amenorrhea (lack of menstruation), fetal death, and toxemia in pregnancy. Adelaide's Exercise Physiology Laboratory in Australia recently reported that women who exercised during times when progesterone and estrogen levels were at their highest (mid-month) had increased rates of fat metabolism as well as lower perceived exertion levels, suggesting more benefit from exercise during times of peak hormone levels.<sup>28</sup>

### **Cardiovascular**

#### **Fibrinogen**

Fibrinogen, a protein synthesized in the liver, is an important component in the normal process of blood clotting. As part of the coagulation cascade, fibrinogen is converted to fibrin and, along with platelets, helps to form a stable fibrin clot.

Fibrinogen is also an acute-phase protein reactant, meaning that it increases in response to disease processes involving tissue inflammation or damage. As

discussed in the C-reactive protein section, development of atherosclerosis and heart disease are products of inflammatory processes. As such, fibrinogen, which is a measure of inflammation, can help predict risk of heart disease and stroke, and can complement tests for serum cholesterol, cholesterol lipoproteins, lipids, C-reactive protein, and inflammatory cytokines.

High fibrinogen levels may indicate a risk of heart disease. Levels are also increased in other inflammatory disorders, in pregnancy, and in women taking oral contraceptives. Decreased levels are seen in patients with hereditary afibrinogenemia, intravascular coagulation, primary and secondary fibrinolysis, and liver disease. An increase in dietary fish oils may result in decreased fibrinogen levels,<sup>40</sup> which has important implications for patients at risk for heart disease and stroke.