Nordic Laboratories

PATIENT:	**Sample Report**			TEST REF:	**TST-##-#####**
TEST NUMBER:	##########	RECEIVED:	d-mm-yyyy	PRACTITIONER:	**Nordic Laboratories**
PATIENT NUMBER:	##########	TESTED:	d-mm-yyyy		
GENDER:	Female	COLLECTED:	d-mm-yyyy h:m	ADDRESS:	
AGE:	46				
DATE OF BIRTH:	d-mm-yyyy				

TEST NAME: Urinary Hormone Metabolites Estrogen Elite

Test Name	Result		Range
Urinary Estrogens			
Estradiol	**3.71**	**H**	0.78-1.79 µg/g Cr Premeno-luteal or ERT
Estrone	**10.95**	**H**	2.27-5.22 µg/g Cr Premeno-luteal or ERT
Estriol	**3.19**	**H**	0.78-1.98 µg/g Cr Premeno-luteal or ERT
E3/(E1+E2)	**0 22**	**L**	>0.3 (> median value)
2-OH Estradiol	**0.77**	**H**	0.17-0.70 µg/g Cr Premeno-luteal or ERT
2-OH Estrone	**2.49**		0.70-2.54 µg/g Cr Premeno-luteal or ERT
4-OH Estradiol	**0.45**	**H**	0.10-0.18 µg/g Cr Premeno-luteal or ERT
4-OH Estrone	**0.64**	**H**	0.17-0.47 µg/g Cr Premeno-luteal or ERT
16α-OH Estrone	**2 25**	**H**	0.35-1.07 µg/g Cr Premeno-luteal or ERT
2-OH (E1 + E2)/16-α-OH E1	**1.45**		1.29-5.49 Premeno-luteal or ERT
2-MeO Estradiol	**0.11**	**H**	0.03-0.08 µg/g Cr Premeno-luteal or ERT
2-MeO Estrone	**0.83**	**H**	0.26-0.68 µg/g Cr Premeno-luteal or ERT
2-MeO E1/2-OH E1	**0.33**		0.21-0.38 Premeno-luteal or ERT
4-MeO Estradiol	**0.02**		<0.04 µg/g Cr
4-MeO Estrone	**0.05**	**H**	<0.04 µg/g Cr
4-MeO E1/4-OH E1	**0.08**		0.05-0.13 Premeno-luteal or ERT
4-MeO E2/4-OH E2	**0.04**	**L**	0.10-0.29 Premeno-luteal or ERT
Bisphenol A	**1.61**		1.11-3.74 µg/g Cr Premeno-luteal
Urinary Progestogens			
Pregnanediol	**201**	**L**	465-1609 µg/g Cr Premeno-luteal or PgRT
Allopregnanolone	**2.05**	**L**	2.23-14.87 µg/g Cr Premeno-luteal or PgRT
Pgdiol/E2	**54.18**	**L**	1000-1500 (Optimal Luteal Only)
Urinary Androgens			
DHEA	**50.43**		15.82-129.17 µg/g Cr Premeno-luteal or DHEAT
Androstenedione	**5.18**		3.93-13.53 µg/g Cr Premeno-luteal or ART
Testosterone	**0.44**	**L**	1.22-3.97 µg/g Cr Premeno-luteal or ART
Epi-Testosterone	**2.57**		2.01-4.66 µg/g Cr Premeno-luteal
T/Epi-T	**0.17**	**L**	0.5-3.0
5α-DHT	**0.12**	**L**	0.28-1.52 µg/g Cr Premeno-luteal or ART
Urinary Creatinine			
Creatinine (pooled)	**1 26**		0.3-2.0 mg/mL

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TEST NAME: Urinary Hormone Metabolites Estrogen Elite

Test Name	Result	Range

<dL = Less than the detectable limit of the lab.
N/A = Not applicable; 1 or more values used in this calculation is less than the detectable limit.

Therapies
oral Vitamin D3 (OTC) (1 Days Last Used); Maxalta; Zinc; Magnesium

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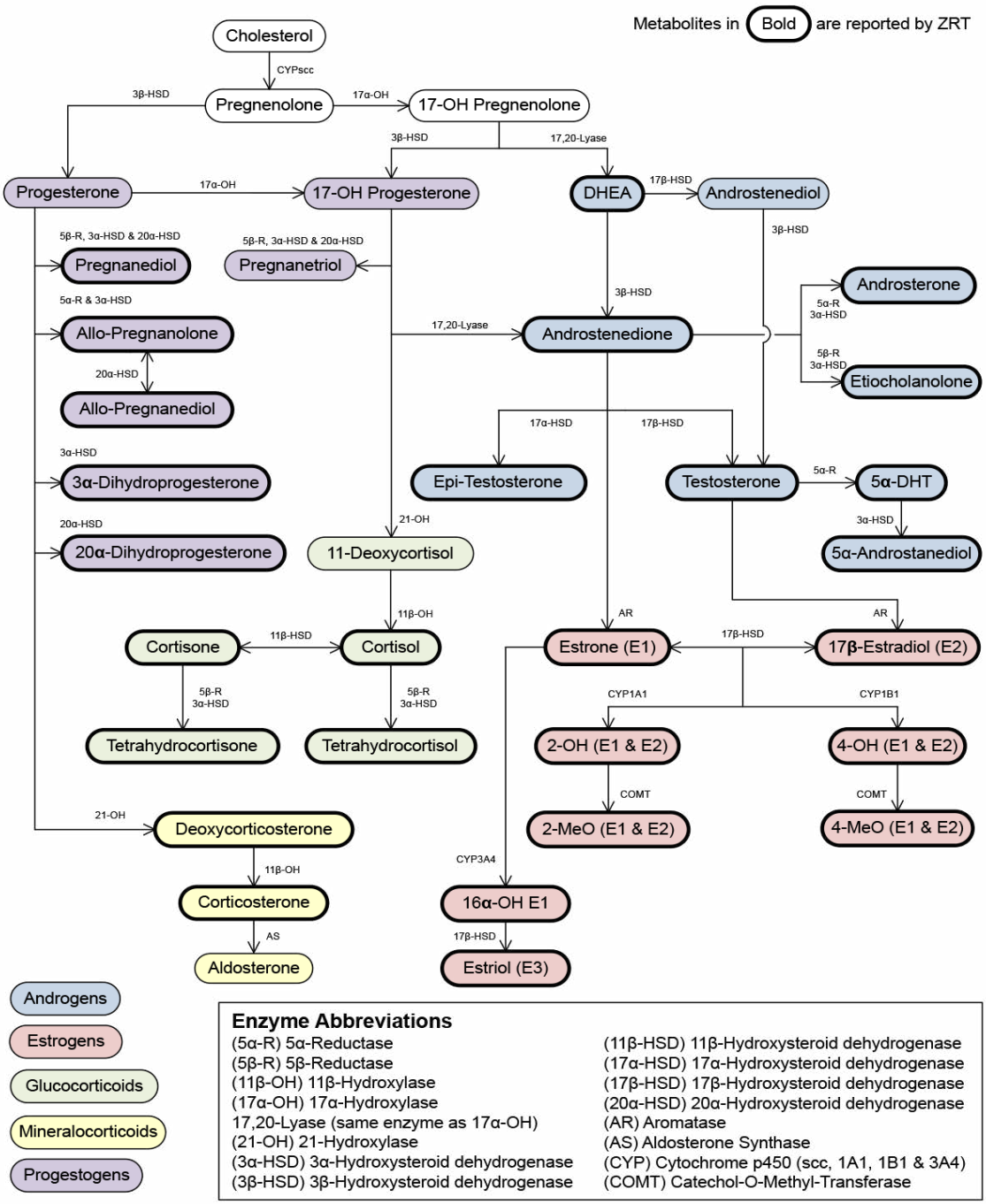
The Steroid Hormone Cascade



Enzyme Abbreviations

(5α-R) 5α-Reductase	(11β-HSD) 11β-Hydroxysteroid dehydrogenase
(5β-R) 5β-Reductase	(17α-HSD) 17α-Hydroxysteroid dehydrogenase
(11β-OH) 11β-Hydroxylase	(17β-HSD) 17β-Hydroxysteroid dehydrogenase
(17α-OH) 17α-Hydroxylase	(20α-HSD) 20α-Hydroxysteroid dehydrogenase
17,20-Lyase (same enzyme as 17α-OH)	(AR) Aromatase
(21-OH) 21-Hydroxylase	(AS) Aldosterone Synthase
(3α-HSD) 3α-Hydroxysteroid dehydrogenase	(CYP) Cytochrome p450 (scc, 1A1, 1B1 & 3A4)
(3β-HSD) 3β-Hydroxysteroid dehydrogenase	(COMT) Catechol-O-Methyl-Transferase

TEST NAME: Urinary Hormone Metabolites Estrogen Elite

Lab Comments

PARENT ESTROGENS (ESTRADIOL-E2, ESTRONE-E1, ESTRIOL-E3)

The parent estrogens are much higher than the reference ranges seen in premenopausal women. This is more common in peri-menopausal women (age range 45-55, but younger in some women with premature ovarian failure) and is caused by high production of FSH and luteal insufficiency (low progesterone produced by the corpus luteum following ovulation). Symptoms of both estrogen dominance and deficiency are common at this transition as estrogens fluctuate erratically from high to low in the absence of progesterone.

Consider means to lower the estrogen burden (diet consisting of more fiber and cruciferous vegetables, less red meat, weight reduction if problematic) and balance the estrogen with adequate progesterone (note: topical progesterone therapy, while it is effective for countering estrogens, is not well detected by urine testing and ratio of PgDiol/E2 is not accurate with this form of therapy).

High estrogens can increase blood circulating levels of many different steroid and thyroid binding globulins such as SHBG (Sex Hormone Binding Globulin), CBG (Cortisol Binding Globulin) and TBG (Thyroid Binding Globulin). This effectively reduces the tissue/cellular bioavailability of circulating estrogens and androgens (SHBG), progesterone and cortisol (CBG) and the thyroid hormones T3 and T4 (TBG). Thus, high estrogens can lead to lowered bioavailable levels of progesterone, testosterone, and cortisol, and aggravate symptoms of deficiency of these hormones, especially if these hormones are already low to low-normal. If symptoms of low androgens, cortisol, or thyroid are problematic consider testing for these binding proteins. Somewhat higher therapeutic doses (assuming supplementation) of androgens, cortisol, and/or thyroid hormones are often required to allow for a physiological delivery of these hormones to target tissues.

E3/E1 + E2 RATIO
The ratio of estriol (E3) to estradiol (E2) + estrone (E1) is lower than the median reference range, indicating low metabolism of estrogens through the estriol pathway. This ratio originally was based on Professor Henry Lemon's hypothesis (Lemon H. Cancer, 25-2, 423-435, 1970) that estriol, relative to estradiol and estrone, is inert as regards it ability to be converted to dangerous metabolites that cause DNA mutations and increase risk for breast cancer. According to Lemon, the more estriol present in urine, relative to estradiol and estrone, the lower the breast cancer risk. Clinically, Lemon found that Japanese women, who have less breast cancer than women in the US, also have higher E3/E2+E1 ratios. Other scientists attributed this to a higher consumption of green leafy vegetables and iodine in the Japanese diet. Original work suggests that the optimal E3/E2+E1 ratio should be > 1; however, with more exacting methods of estrogen testing by mass spectrometry a ratio of > 1 is not likely achieved even in women with low breast cancer risk. During Dr. Lemon's era of research on estriol, which stretched from the 1970s to the 1990s, the estrogen levels in urine were determined by urine extraction followed by radioimmunoassay, which is not as quantitatively accurate as today's measurements by GC and LC mass spectrometry. ZRT's E3/E2+E1 reference range is determined by GC-MS/MS and based on the values seen in US women, which are 0.24 ug/g creatinine in premenopausal and 0.29 ug/g creatinine in postmenopausal women NOT using exogenous estrogens. Values higher than the median, and > 1 (usually a result of estriol therapy) are likely more beneficial. In Europe and Japan estriol therapy has been used successfully as a more conservative form of estrogen replacement therapy (mostly for treating vaginal dryness/atrophy) for over 60 years. For references on estriol see: Lee, JR, Zava DT What Your Doctor May Not Tell You About BREAST CANCER: How Hormone Balance Can Help Save Your Life: Chapter 8; Estriol: A Safer Replacement Estrogen.

HYDROXYLATED (CATECHOL) ESTROGENS (2-OH E2 & E1, 4-OH E2 & E1, 16-OH E1) and 2-OH/16-OH RATIO

The hydroxylated estrogens (2-OH-E2, 2-OH-E1, 4-OH-E2, 4-OH-E1), referred to as catechol estrogens, are all within the upper quadrant of the reference ranges, or higher.

The hydroxylation of estradiol and estrone represent the first phase of metabolism and elimination of these estrogens via urine. Following hydroxylation at the 2-, 4-, or -16 positions, the estrogens undergo further modification (methylation, sulfation, glucuronidation) that increases their solubility and excretion in urine. The sulfate and glucuronide groups are removed by enzyme hydrolysis, which allows for measurement of the different types of hydroxylated estrogens that formed elsewhere in the body but were excreted in urine.

Research and clinical studies show that the 2-hydroxylated estrogens (2-OH E2 and 2-OH E1) are a safer pathway of hydroxylation than the 4-hydroxyestrogens (4-OH E2 and 4-OH E1), which are considered more toxic as they bind to DNA causing mutations that are associated with increased breast cancer risk. For reviews see: Cavalieri EL, Rogan EG Future Oncol 6 (1): 75-79, 2010; and Lee, JR, Zava DT What Your Doctor May Not Tell You About BREAST CANCER: How Hormone Balance Can Help Save Your Life: Chapter 7.

TEST NAME: Urinary Hormone Metabolites Estrogen Elite

The safer 2-hydroxylated estrogen metabolism is increased, relative to the 4-hydroxylation pathways, with cruciferous vegetables and extracts of them. The most commonly used are indole-3-carbinol (I3C) and its metabolite diindolylmethane (DIM). Eating a healthy diet of plants with beneficial phytochemicals (e.g. leafy vegetables with color, soy foods, flax, foods high in antioxidants such as turmeric) also helps prevent toxic estrogen metabolism. Iodine also increases the 2-hydroxylation of estrogens, with a slight increase in 4-hydroxylation (Stoddard FR et.al. Int J Med Sci 5: 189-196, 2008).

The more dangerous 4-hydroxylated estrogen metabolism is enhanced by exposure to environmental toxins, mostly petrochemical-based products but also heavy metals that induce 4-hydroxylation pathway enzymes (1B1), and cause formation of Reactive Oxygen Species (ROS) that co-oxidize the catechol estrogens to much more reactive quinone estrogens. The 4-quinone estrogens, if not inactivated by glutathione, can potentially bind to and damage DNA leading to mutations that increase lifetime risk for cancer.

16-hydroxyestrone is another pathway of estrone metabolism and is a precursor to estriol (see Steroid Hormone Cascade). Early clinical research in humans suggested that a high urinary level of 16-hydroxyestrone relative to 2-hydroxylated estrogens (i.e. a low 2-OH E1 + 2-OH E2/16-OH E1 ratio), was associated with an increased risk of breast cancer in premenopausal women, but not in postmenopausal women. This has remained controversial and newer research suggests that while higher levels of 16-hydroxy estrone may indeed be slightly associated with increased breast cancer risk in premenopausal women, higher levels are associated with a decreased risk in postmenopausal women (Huang J et.al. Analytica Chimica Acta 711: 60-68, 2012). A meta-analysis of nine studies investigating the relationship of the urinary 2/16 ratio have NOT shown it to be useful for predicting breast cancer risk (Obi N et.al. Int J Women's Health 3: 37-51, 2011).

METHYLATION OF HYDROXYESTROGENS

The methylated forms of the 2-hydroxyestrogens are within normal reference ranges or high (beneficial). In contrast, methylation of the more toxic 4-hydroxyestrogens is low or within the lower quadrant of the reference range (considered higher risk). Adequate methylation of the hydroxyestrogens, and an associated high ratio of 4-hydroxylated estrogens to 4-methoxyestrogens (i.e. 4 MeO-E2/4-OH-E2 and 4-MeO-E1/4-OH-E1) is considered beneficial as this indicates the 4-hydroxyestrogens are rendered inert via methylation, preventing them from oxidizing further to more dangerous 4-estrogen quinones that can form adducts with DNA, causing mutations that can lead to increased cancer risk. The ratios of 4-MeO-E1/4-OH-E1 and 4-MeO-E2/4-OH-E2 are within range, but within the lower quadrant of the reference ranges, indicating that these 4-OH-estrogens are not adequately methylated. The 2- and 4- hydroxyl estrogens are methylated by the enzyme Catechol-o-Methyl Transferase (COMT), which renders these catechol estrogens inert and harmless (Cavalieri EL, Rogan EG Future Oncol 6(1): 75-79, 2010). In this form the methylated catechol estrogens are rapidly excreted in urine. However, if methylation pathways are inadequate due to low levels of COMT, or lack of precursors of methylation (i.e. vitamins B6, B12, folate, betaine), the 2- and 4-hydroxyl estrogens can oxidize to 4-estrogen quinones that bind to DNA, forming adducts that can lead to permanent mutations, and eventually to cancer.

Many studies have shown that high urinary levels of these 4-hydroxyestrogens (4-OH-E2 and 4-OH-E1) are associated with increased breast cancer risk if they are not inactivated by methylation, or the more toxic down-stream oxidized 4-quinone estrogens are not inactivated by glutathione sulfation. If glutathione is low the 4-quinone estrogens are less likely to be detoxified (inactivated) and have potential to damage cells/DNA in close proximity to their formation (i.e. the breast cell/DNA). Maintaining adequate glutathione is key to preventing buildup of toxic/mutagenic 4-quinone estrogens, should they form due to poor methylation pathways. If 4-OH-estrogens are high and not well methylated consider avoiding trans-hydrogenated fats and eliminate heavy metals that cause the formation of Reactive Oxygen Species (ROS) that oxidize lipids. Supplementation with essential elements such as selenium and iodine will also help reduce formation of oxidized lipids, which co-oxidize 4-OH-estrogens to 4-quinone estrogens.

BISPHENOL A (BPA)

Bisphenol A (BPA) is within reference range. BPA is an endocrine disrupting chemical (EDC) derived from plastics used for making bottles, wraps for foods, and linings for food cans. BPA is not retained in the body for a prolonged period of time and is rapidly excreted into urine. High urinary levels of BPA indicate recent exposure to plastics that released excessive amounts of BPA into food or beverages consumed in the past 24-48 hr.

BPA acts as an EDC by binding to a activating both membrane and nuclear estrogen receptors in a manner similar to estradiol. Thus by mimicking the actions of endogenous estrogens, high levels of BPA can contribute to symptoms of estrogen dominance. High BPA levels have been associated with increased risks for many different health issues, including diabetes, breast cancer, and prostate cancer. When BPA levels are elevated, identification of its source and reducing exposure is worth considering.

PROGESTERONE METABOLITES (PREGNANEDIOL-PgDiol, ALLOPREGNANOLONE-AlloP)

TEST NAME: Urinary Hormone Metabolites Estrogen Elite

The urinary levels of the progesterone metabolites pregnanediol (PgDiol) and allopregnanolone (AlloP), a neuroactive steroid, are lower than luteal reference ranges. PgDiol serves as a good surrogate marker metabolite of the progesterone as levels increase in parallel with endogenous progesterone production by the ovaries.

AlloP is a neuroactive steroid that freely enters the brain from the bloodstream, where it binds to GABA receptors and induces a calming effect (anxiolytic). This contributes to AlloPs calming and sleep-inducing effects. Insufficient amounts of AlloP can have a paradoxical effect and cause an anxiogenic effect, increasing symptoms such as anxiety and premenstrual dysphoric disorder (PMDD) and premenstrual syndrome (PMS). Only high levels of AlloP, achieved at peak of an optimal luteal phase, during pregnancy, and with progesterone therapy, have the anxiolytic effects on GABAa receptors in the brain.

PREGNANEDIOL/ESTRADIOL RATIO:

The Pgdiol/E2 ratio is low, indicating an excess of estradiol relative to progesterone. The Pgdiol/E2 ratio is based on the optimal luteal levels of urinary Pgdiol (about 1300-2000 µg/g creatinine) relative to the median level of urinary estradiol (1.37 µg/g creatinine). Thus the optimal working ratio of urinary Pgdiol to estradiol in the premenopausal woman during the peak luteal phase should be about 1000 to 1500. A lower ratio, associated with higher estrogens and/or lower progesterone and symptoms of estrogen dominance, is commonly seen in women approaching menopause (perimenopausal) and is often successfully treated by lowering the estrogens with improved diet, exercise, and nutritional supplements that increase estrogen elimination, and/or by increasing progesterone with supplementation. The Pgdiol/E2 ratio is only valid for premenopausal women with menstrual cycles and should not be used for women on synthetic contraceptive hormones.

IMPORTANT NOTE: Topical progesterone raises urinary Pgdiol very little even with pharmacological dosing (50-300 mg), likely because topically delivered progesterone is excreted primarily in bile/feces. In sharp contrast, oral progesterone therapy raises urinary Pgdiol to levels much higher than seen in premenopausal women (luteal phase), without raising blood, salivary, or tissue levels of progesterone very much. For these reasons, the PgDiol is no longer a valid measure of the bioavailable "progesterone" in the body, nor is the urinary PgDiol/E2 ratio a valid way to assess the balance of progesterone and estradiol. Therefore, we suggest for those individuals using oral, topical, or vaginal progesterone, a different test (e.g. saliva or capillary blood) other than urine be used to evaluate the active bioavailable levels of progesterone.

ANDROGEN PRECURSORS (ANDROSTENEDIOL, DHEA)

Androstenedione and DHEA(S) are within expected reference ranges seen in premenopausal women.

In premenopausal women about half of the androstenedione is derived from the ovaries and the other half from the adrenals. At menopause, most of the androstenedione derives from the adrenal glands. DHEA is synthesized in the adrenal glands and is rapidly sulfated to DHEA-sulfate (DHEAS) to extend its half-life in blood. Androstenedione is converted into the androgens, testosterone and Epi-testosterone in near equal amounts in most individuals, or into estrone. More conversion to estrone occurs in individuals with higher amounts of adipose (fat) tissue, which contains high levels of aromatase, an enzyme that converts androgens to estrogens.

ANDROGENS AND METABOLITES

Testosterone (T), and its more potent metabolite, 5-alpha DHT (DHT) are low or lower than the lower quadrant of the reference range for a premenopausal woman. Epi-testosterone (Epi-T), on the other hand, is within the reference range. This is unusual since T and Epi-T are usually produced in equal amounts from androstenedione, a down-stream metabolite of DHEA.

While Epi-T and T are normally created in about equal amounts and the ratio of T/Epi-T is usually about 1 (normal range 0.5-3), T and DHT can be very low and Epi-T within normal range, resulting in a very low T/Epi-T ratio. Low urinary T and DHT occurs more frequently in men and women of Asian and Indian (Asian Continent) descent due to deletion polymorphisms in testosterone glucuronidation. This results in less glucuronidation of testosterone and consequently less of the T-glucuronide conjugate excreted in urine, despite normal levels of T in serum (Jakobsson J J Clin Endocrinol Metab 91: 687-693, 2006; Strahm E. Br J Sports Med 43: 1126-1130, 2009). T levels in saliva and capillary blood (Dried Blood Spots-DBS) would also be within normal range despite the "apparent" low T seen in urine. When T and DHT are low and Epi-T is within normal range, especially when symptoms of low androgens are not particularly problematic, testing of blood or saliva may provide a more accurate result of the true circulating level of these hormones.

Physiological levels of androgens (T and DHT) are important for strengthening structural tissues such as muscles, bone, connective tissue, and skin. They also play an important role in the brain to increase the level of neurotransmitters such as dopamine, which are important for mood elevation and sex drive. T is also a precursor to estradiol via the enzyme aromatase.

Low androgens, particularly the more potent androgens testosterone and DHT, are associated with many different adverse

conditions (bone loss, thinning skin, vaginal dryness, incontinence, cardiovascular disease, insulin resistance/metabolic syndrome, breast cancer) and symptoms (fatigue, low stamina, depression, memory lapses, loss of sex drive, hot flashes, allergies). Because these androgens are all low consider supplementing with DHEA or testosterone.