NutriPATH
Integrative Pathology Services
P: 1300 688 522
E: info@nutripath.com.au
A: PO Box 442 Ashburton VIC 3142

TEST PATIENT

Sample Test Name
Sex : F
Date Collected : 00-00-0000
111 TEST ROAD TEST SUBURB
LAB ID: 00000000 UR#:0000000

TEST PHYSICIAN

DR JOHN DOE
111 CLINIC STREET
CLINIC SUBURB VIC 3000

MICRO SAMPLE ASSAYS

DRIED URINE | Result | Range | Units

Advanced Hormones, Dried Urine

Your Hormone Testing at a Glance

Urinary Estrogens

9ăúNł·Řλ2f ƒ ł ƒ
9ăúN2yŜ ƒ ł ƒ
9ăúNλ2f ƒ ł ƒ
нπh ł 9ăúNł·Řλ2f ƒ ł ƒ
нπh ł 9ăúN2yŜ ƒ ł ƒ
ππh ł 9ăúNł·Řλ2f ƒ ł ƒ
мсʰπh ł 9ăúN2yŜ ƒ ł ƒ
ππa Ŝh 9ăúN2yŜ ƒ ł ƒ
ππa Ŝh 9мкππh ł 9м ƒ ł ƒ
.łăLJKŜy2f ! ƒ ł ƒ

Urinary Progestogens

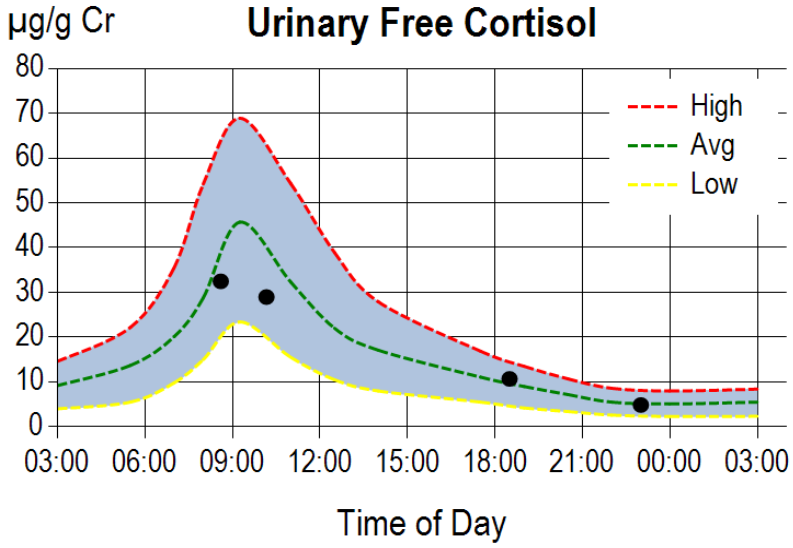
t№ŜƎył·yŜŘλ2f ƒ ł ƒ
! ff2LJ№ŜƎył·y2f2yŜ ƒ ł ƒ
! ff2LJ№ŜƎył·yŜŘλ2f ƒ ł ƒ
oʰπ5ΛKĕŘ№2LJ№2ƎŜăúŜ№2yŜ ƒ ł ƒ
нлʰπ5ΛKĕŘ№2LJ№2ƎŜăúŜ№2yŜ ƒ ł ƒ
5Ŝ2ĖèÔ2№úΛÔ2ăúŜ№2yŜ ƒ ł ƒ

Urinary Androgens

5 ł 9 ! ƒ ł ƒ
! yŘ№2ăúŜ№2yŜ ƒ ł ƒ
9ú№2ŐK2fł·y2f2yŜ ƒ ł ƒ
¢Ŝăú2ăúŜ№2yŜ ƒ ł ƒ
9LJλπ¢Ŝăú2ăúŜ№2yŜ ƒ ł ƒ
pʰπ5 ł ¢ ƒ ł ƒ
pʰĭoʰπ ! yŘ№2ăúł·yŜŘλ2f ƒ ł ƒ

L Items listed in **RED** are reflective of a Low Results *H* Items Listed in **BLUE** are Reflective of a High Result

Your Reported Urinary Free Cortisol Pattern



Tests ordered: 1501

NutriPATH
Integrative Pathology Services
P: 1300 688 522
E: info@nutripath.com.au
A: PO Box 442 Ashburton VIC 3142

TEST PATIENT
Sample Test Name
Sex : F
Date Collected : 00-00-0000
111 TEST ROAD TEST SUBURB
LAB ID: 00000000 UR#:0000000

TEST PHYSICIAN
DR JOHN DOE
111 CLINIC STREET
CLINIC SUBURB VIC 3000

DRIED URINE-INTEGRATIVE MEDICINE

Samples Collected: Urine: 00/00/0000 08:36 Urine: 00/00/0000 10:10 Urine: 00/00/0000 18:30 Urine: 00/00/0000 23:00

BMI: 00
Height: 0 ft in
Weight: 00 kg

Test Name	Result		Range
Urinary Estrogens (µg/g Cr)			
Estradiol (Urine)	0.54	H	0.18-0.49
Estrone (Urine)	1.99	H	0.57-1.67
Estriol (Urine)	0.95	H	0.18-0.64
2-OH Estradiol (Urine)	0.19	H	0.04-0.14
2-OH Estrone (Urine)	0.58	H	0.16-0.48
4-OH Estradiol (Urine)	0.16	H	0.001-0.08
4-OH Estrone (Urine)	0.10		0.04-0.10
16α-OH Estrone (Urine)	0.37	H	0.06-0.21
2-MeO Estradiol (Urine)	0.02		0.01-0.03
2-MeO Estrone (Urine)	0.15		0.05-0.15
2-MeO E1/2-OH E1 (Urine)	0.26		0.20-0.38
4-MeO Estradiol (Urine)	0.02		< 0.04
4-MeO Estrone (Urine)	0.15	H	< 0.002
4-MeO E1/4-OH E1 (Urine)	1.5	H	0.05-0.17
4-MeO E2/4-OH E2 (Urine)	0.12		0.06-0.47
Bisphenol A (Urine)	3.07	H	0.97-2.31
Urinary Progestogens (µg/g Cr)			
Pregnanediol (Urine)	1565	H	47-140
Allopregnanolone (Urine)	11.63	H	0.32-1.20
Allopregnanediol (Urine)	52.16	H	1.57-6.82
3α-Dihydroprogesterone (Urine)	5.89	H	0.19-0.73
20α-Dihydroprogesterone (Urine)	9.40	H	0.51-2.97
Deoxycorticosterone (Urine)	1.80	H	0.28-1.25
Corticosterone (Urine)	7.77		1.95-8.22
Urinary Androgens (µg/g Cr)			
DHEA (Urine)	107.01	H	9.01-93.80
Androstenedione (Urine)	9.39		2.12-9.51
Androsterone (Urine)	1611	H	302-724
Etiocholanolone (Urine)	2427	H	279-775
Testosterone (Urine)	16.46	H	3.81-14.21
Epi-Testosterone (Urine)	12.50	H	3.15-8.85
T/Epi-T (Urine)	1.32		0.5-3.0

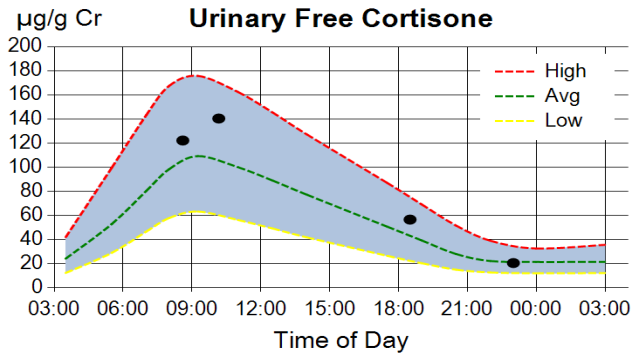
Test Name	Result		Range
5α-DHT (Urine)	6.70	H	0.71-2.46
5α,3α-Androstanediol (Urine)	53.62	H	9.48-24.96
Urinary Glucocorticoids (µg/g Cr)			
Total Cortisol (Urine)	44.09	H	8.73-28.52
Total Cortisone (Urine)	67.44	H	14.12-42.84
Cortisol/Cortisone (Urine)	0.65		0.5-0.7
Tetrahydrocortisol (Urine)	406		201-597
Tetrahydrocortisone (Urine)	1373	H	330-1126
Urinary Free Diurnal Cortisol (µg/g Cr)			
Free Cortisol (Urine)	32.47	H	7.8-29.5 (1st Morning)
Free Cortisol (Urine)	28.97		23.4-68.9 (2nd Morning)
Free Cortisol (Urine)	10.68		6.0-19.2 (Evening)
Free Cortisol (Urine)	4.86		2.6-8.4 (Night)
Urinary Free Diurnal Cortisone (µg/g Cr)			
Free Cortisone (Urine)	122.22	H	31.6-91.6 (1st Morning)
Free Cortisone (Urine)	140.42		63.3-175.8 (2nd Morning)
Free Cortisone (Urine)	56.63		30.6-88.5 (Evening)
Free Cortisone (Urine)	20.60		15.5-44.7 (Night)
Urinary Diurnal Melatonin MT6s (µg/g Cr)			
Melatonin (Urine)	14.30		10.1-26.0 (1st Morning)
Melatonin (Urine)	8.10		6.0-17.0 (2nd Morning)
Melatonin (Urine)	5.95	H	0.5-3.6 (Evening)
Melatonin (Urine)	79.77	H	1.3-8.4 (Night)
Urinary Creatinine (mg/mL)			
Creatinine (pooled) (Urine)	1.18		0.3-2.0
Creatinine (Urine)	2.24	H	0.3-2.0 (1st morning)
Creatinine (Urine)	0.30		0.3-2.0 (2nd morning)
Creatinine (Urine)	1.89		0.3-2.0 (Evening)
Creatinine (Urine)	1.99		0.3-2.0 (Night)

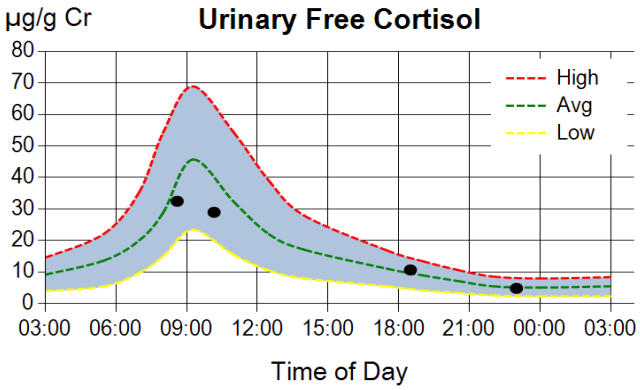
<dL = Less than the detectable limit of the lab.
N/A = Not applicable; 1 or more values used in this calculation is less than the detectable limit.

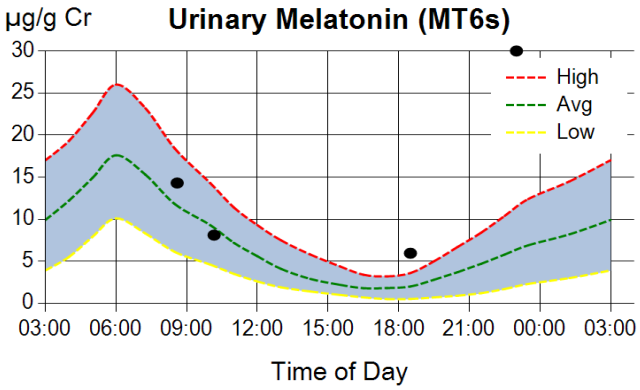
Therapies

BID oral DHEA (OTC) (1 Days Last Used); oral Melatonin (OTC) (1 Days Last Used); oral Pregnenolone (OTC) (1 Days Last Used)

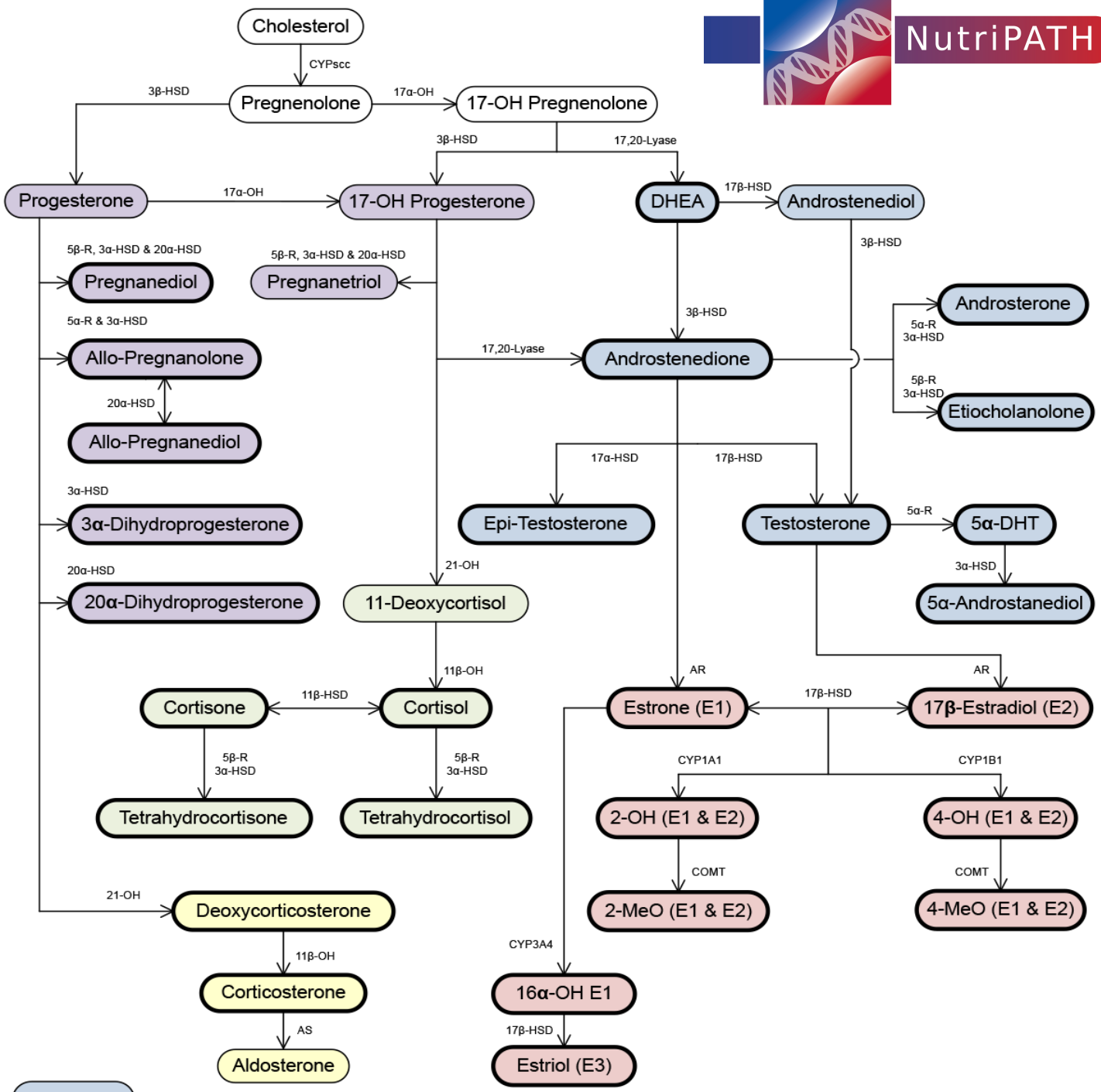
Disclaimer: Graphs below represent hormone levels in testers not using hormone supplementation and are provided for informational purposes only. Please see comments for additional information if results are higher or lower than expected.







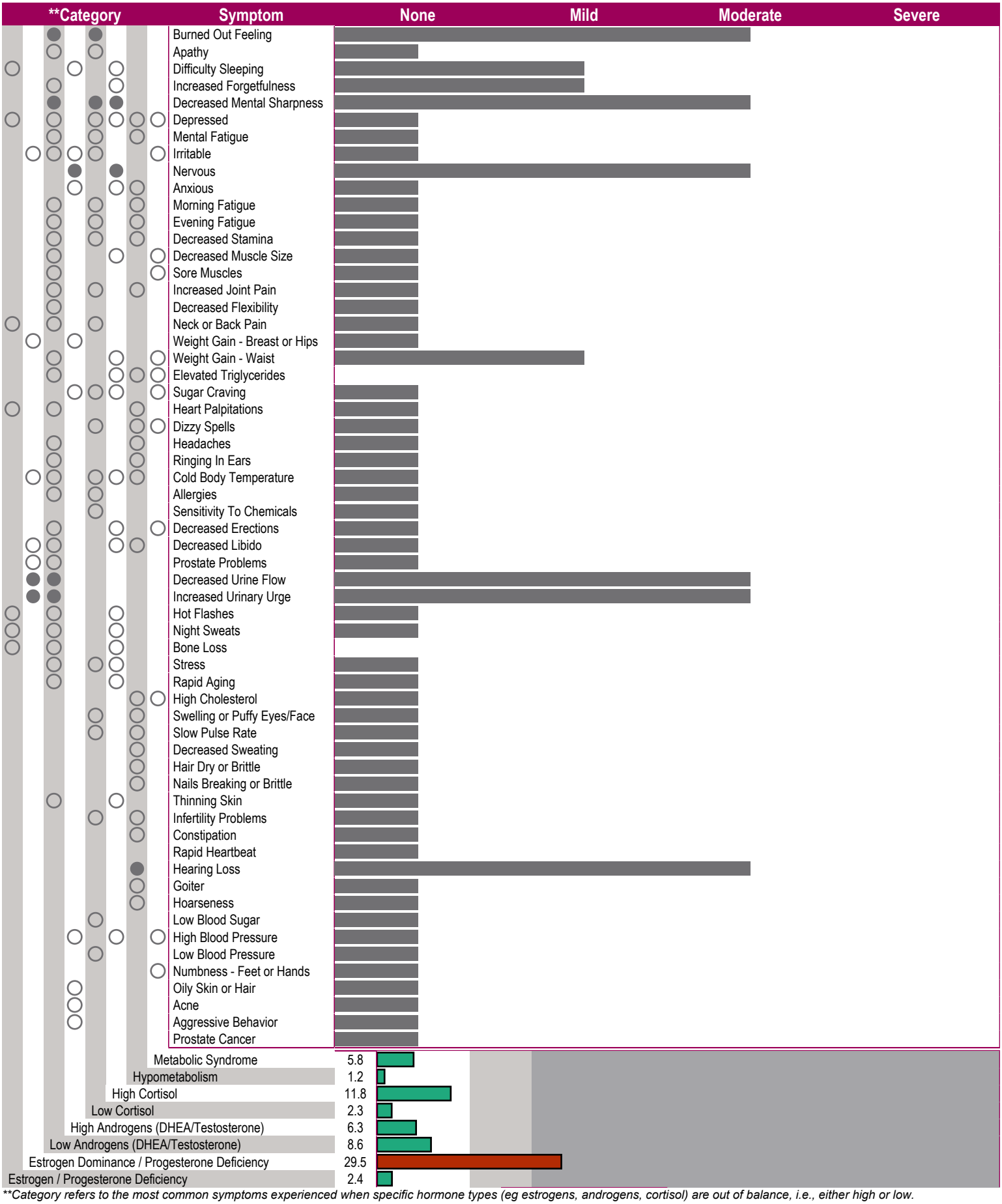
The Steroid Hormone Cascade



Enzyme Abbreviations

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

LAB ID: 000000000 **PATIENT NAME**



***Category refers to the most common symptoms experienced when specific hormone types (eg estrogens, androgens, cortisol) are out of balance, i.e., either high or low.*

Lab Comments

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

The parent estrogens (E2, E1, E3) are slightly higher than the reference ranges seen in healthy men. this likely accounts for self-reported symptoms of estrogen dominance (excess). Patient is using DHEA and Pregnenolone, which in some individuals can convert excessively to estrogens.

Higher levels of estrogens usually result from excessive weight in the mid-section (belly fat). This excessive mid-body fat contains high levels of the enzyme aromatase that converts androgens like testosterone to estrogens. In healthy men with less body fat, and less aromatase activity, the testosterone is converted instead to the more potent androgen, dihydrotestosterone (DHT). Excessive mid-body fat is caused by overconsumption of calories and stress. Stress increases the stress hormone cortisol, which in excess, causes further deposition of mid-body fat. Cortisol also increases the levels of aromatase in adipose (fat) tissue, which further increases androgen conversion to estrogens.

High estrogens in men are associated with symptoms of estrogen excess (weight gain around the hips, thighs, breasts) and prostate problems (BPH-benign prostatic hypertrophy). While normal physiological levels of estrogens are essential to optimal health in men, high estrogens inhibit the beneficial effects of testosterone by decreasing the bioavailability of testosterone and DHT and down-regulating the cellular androgen receptors in target tissues throughout the body. Estrogens decrease bioavailability of testosterone to target tissues by increasing hepatic synthesis and release of Sex Hormone Binding Globulin-SHBG into the bloodstream, which binds tightly to circulating testosterone, reducing its access to tissues. When testosterone therapy is excessive, especially in men who are overweight with high mid-body fat, much of the testosterone is converted to estrogens, which further exacerbates the problem of functional androgen deficiency (i.e. high testosterone, but low androgen symptoms). The body's response to the estrogen (estradiol and estrone) and androgen (testosterone and DHT) milieu is very individual and may depend on tissue levels of estrogen and androgen receptors, which themselves are regulated by their own ligands (estradiol and testosterone).

If symptoms of estrogen excess and/or low androgens are problematic this may be due to a higher relative excess of estrogens to androgens, which can be caused by poor lifestyle habits (sedentary lifestyle, poor eating habits, stressful environment). Improved eating habits, reasonable exercise, adequate sleep, and removing oneself as much as possible from a stressful environment (lowers cortisol) often help correct conditions that cause high estrogens and symptoms of androgen deficiency.

HYDROXYLATED (CATECHOL) ESTROGENS (2-OH E2 & E1, 4-OH E2 & E1)

The hydroxylated estrogens are all either high or higher than the mid reference ranges for a male.

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 position, the estrogens undergo further modification (methylation, sulfation, glucuronidation) that increases their solubility and excretion 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 if not inactivated by methylation can be further oxidized to estrogen quinones that bind to and damage DNA, leading to mutations that are associated with increased risk of estrogen-sensitive tissues (e.g. prostate, breasts). For this reason it is important to keep the levels of the parent estrogens (estradiol and estrone) as well as their down-stream hydroxylated forms within physiological levels to avoid toxic effects from them. For reviews see: Cavalieri EL, Rogan EG Future Oncol 6(1): 75-79, 2010.

The safer 2-hydroxylation of estradiol and estrone is increased with cruciferous vegetables and extracts of them. The most commonly used are indole-3-carbinol (I3C) and its metabolite diindolylmethane (DIM). 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 may cause cancer.

16-hydroxyestrone is another pathway of estrone metabolism and is a precursor to estriol (see Steroid Hormone Cascade). While higher levels of 16-hydroxy estrone may be slightly associated with increased breast cancer risk in premenopausal women, but paradoxically lower risk in postmenopausal women (Huang J et.al. Analytica Chimica Acta 711: 60-68, 2012), very little is known about the role of this estrogen, or its down-stream metabolite, estriol, in risk for prostate cancer.

METHYLATION OF HYDROXYESTROGENS

The methylated forms of the 2- and 4-hydroxyestrogens (2MeO-E1/E2, and 4-MeO-E1/E2) are within normal, or higher, than reference ranges for a male. When an elevated level of 2- or 4-hydroxylated estrogens is coassociated with an elevated level of the corresponding methoxyestrogens this is usually a good indication of adequate methylation of the hydroxylated estrogens, which renders them inert and no longer capable of converting down-stream to the more reactive estrogen quinones. A mid-normal to high ratio of 4-MeO-E1/4-OH-E1 or 4-MeO-E2/4-OH-E2 is desirable as this indicates adequate methylation of the more dangerous 4-hydroxylated estrogens. If this ratio is low for either 4-OH-E1 or 4-OH-E2 then it is possible that either genetic polymorphisms have resulted in defective methylation (low COMT) or nutrients for methylation are low (e.g. B12, B6, folate).

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 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 take a more insidious and dangerous pathway of metabolism, which is oxidation of the 4-hydroxylated estrogens (4-OH-E1 and 4-OH-E2) to their respective quinones. Estrogen quinones, especially the 4-quinone of estradiol and estrone, are highly electrophilic and bind to DNA forming adducts that lead to permanent mutations in the DNA. Many studies have shown that high urinary levels of these 4-quinones of estradiol and/or estrone are associated with increased breast cancer risk, and research also suggests this same mechanism is responsible for increased risk for prostate cancer. The 2- and 4-hydroxy estrogens are converted to their more dangerous oxidized quinone forms under oxidizing conditions in the cell, and this occurs rapidly in the presence of oxidized lipids, especially those from trans-hydrogenated fats. These estrogen quinones, like all oxidized and electron-hungry molecules in the body are inactivated when bound to glutathione, the most ubiquitous antioxidant in the body. However, if glutathione is low, due to insufficient levels of minerals (selenium, iodine) and vitamins (C and E), the 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 or prostate cell/DNA).

BISPHENOL A (BPA)

Bisphenol A (BPA) is slightly elevated. 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

The progesterone metabolites are all higher than the reference ranges for males. This suggests that the exogenous oral pregnenolone is being converted downstream to progesterone metabolites, but does not necessarily mean it is being converted to higher levels of circulating progesterone.

In addition to Pgdiol, four other progesterone metabolites are tested in the urine metabolite profile. These include allopregnanolone, allopregnanediol, 20-alpha-dihydroprogesterone, and 3-alpha-dihydroprogesterone. These progesterone metabolites are also high, further supporting the notion that exogenous (likely oral) progesterone was used but not reported. The only one of these progesterone metabolites hat likely is relevant to males is allopregnanolone, which is an anxiolytic neurosteroid that binds to brain GABA receptors, resulting in a calming (sleep inducing) effect. Progesterone supplementation in men, and the formation of allopregnanolone, has been shown to increase favorable alpha wave sleep patterns and induce a more restful sleep. Higher relative levels of the down-stream pregnane vs pregnene metabolites of progesterone (i.e. allopregnanolone and allopregnanediol vs 20-alpha and 3-alpha-dihydroprogesterone) indicate a higher 5-alpha reductase activity, which is also usually associated with a higher conversion of testosterone to 5-alpha dihydrotestosterone (DHT). However, progesterone itself, inhibits excessive conversion of T to DHT, and thus has subtle anti-androgen activity.

PROGESTERONE METABOLITES: MINERALCORTICOID PRECURSORS

Deoxycorticosterone (DOC) and corticosterone (CC) are near or slightly higher than the reference ranges. Both DOC and CC are down-stream metabolites of progesterone, which is a down-stream metabolite of pregnenolone..

DOC is a weak mineralocorticoid and DOC and CC are precursors to the more potent mineralocorticoid aldosterone (see Steroid Hormone Cascade).

ANDROGEN PRECURSORS (ANDROSTENEDIOL, DHEA)

DHEA(S) is slightly higher than reference range whereas its downstream metabolite, androstenedione is within normal range. Higher levels of these androgen precursors is likely a result of oral DHEA therapy.

Androstenedione is the precursor to testosterone and then to 5 alpha DHT, which interacts with tissue cellular androgen receptors and activates androgen-regulated genes.

ANDROGENS AND METABOLITES

Testosterone (T) and its epimer, epi-testosterone, are slightly higher than the reference ranges for males. This is likely due to supplementation with DHEA and pregnenolone, both of which are precursors to T, Epi-T, and DHT. DHT, the more potent down-stream metabolite of T is also higher than reference range, as is the neuroactive metabolite of DHT, 5alpha, 3alpha androstanediol (Adiol). Adiol binds and activates dopaminergic receptors in the brain responsible for increased feeling of well being and the reward pathway.

T, Epi-T, and DHT are normally higher in healthy young males following puperty, and levels of these androgens progressively drop with age. While androgens naturally decline with age, they can drop more rapidly when the body is exposed to stressors (psychological, physical, surgical, pathogens), excessive estrogens, and some medications.

The most potent of the androgens is dihydrotestosterone (DHT), which is created from testosterone via the enzyme 5a reductase. DHEA or T therapy can sometimes lead to excessive levels of either DHT or estradiol, both down-stream metabolites of T via the enzymes 5-alpha reductase and aromatase, respectively. These enzymes are higher in tissues and organs such as the skin, seminal vessicles, prostate, and other organs such as the brain. Endogenous testosterone is derived mostly from androstenedione and DHEA. In men most of the testosterone is produced in the testes and a much smaller portion is derived from androstenedione in the adrenal glands.

Testosterone, and particularly its more potent down-stream metabolite DHT, are important anabolic hormones that help to maintain both physical and mental health. They help prevent fatigue, help to maintain a normal sex drive, increase the strength of all structural tissues (skin, bone, muscles, heart) and prevent depression and mental fatigue. Testosterone deficiency, particularly when coupled with high estrogens, is more commonly associated with symptoms such as decreased sex drive, memory lapses, grumpiness, thinning skin, weight gain in the hips and thighs (mostly from high estrogens) and loss of muscle and bone mass. Estrogens in excess can block the beneficial effects of T and DHT.

DHT is the most potent of the androgen metabolites and forms from 5-alpha reductase conversion of T. DHT is formed within cells of target tissues such as the skin and prostate, where it binds to androgen receptors and activates androgen-specific genes. Excessive levels of DHT can result from overexpression of 5-alpha reductase in the skin as well as excessive T-therapy. High DHT, especially formed in the skin from topical T therapy, can cause conditions such acne and heavier growth of hair on the face and body, but loss of hair on the scalp. In the brain excessive conversion of T to DHT and estradiol may cause aggitation and aggressive behavior.

5-alpha 3-alpha Androstanediol (Adiol), a down-stream metabolite of DHT, is higher than reference range. High Adiol is usually associated with high levels of its precursor, DHT (note: DHT is also high). Adiol is considered a neuroactive steroid that forms peripherally and can passively enter the brain from the bloodstream through the blood brain barrier.

Adiol binds to GABAa receptors in the brain and has a similar anxiolytic (calming) effect, albeit weaker than allopregnanolone. It also interacts with the dopaminergic pathways in the brain and is associated with the dopamine reward pathway. Thus, higher levels of Adiol, as seen herein, are more likely to be associated with conditions common to high dopamine.

TOTAL GLUCOCORTICOIDS

Total cortisol (F) and cortisone (E), and their down-stream metabolites, tetrahydrocortisol (THF) and tetrahydrocortisone (THE), are higher than the expected reference ranges, suggesting some type of adrenal stressor. The total levels of these glucocorticoids are determined from the average of four urine collections throughout the day and are very similar to the 24 hour urine values. High cortisol is consistent with self-reported symptoms characteristic of this condition.

While a high cortisol is a normal and healthy response to an acute stressor, a persistent stressor and chronic high cortisol can lead to multiple dysfunctions and disease. Elevated cortisol is usually caused by different types of stressors (emotional, physical-(e.g. excessive exercise, injury, surgery), chemical-(e.g. environmental pollutants, medications), inflammations-(e.g.

cancer, metabolic syndrome), pathogens-(e.g. bacterial, fungal, viral infections).

Typical acute symptoms/signs of high cortisol can include anxiety, nervous-irritability, self-perceived stress, sleep disturbances. More chronic elevated cortisol is commonly associated with the same symptoms seen with acutely high cortisol but also include memory problems, depression, loss of muscle mass, and weight gain in the waist. Insulin resistance and metabolic syndrome are also a consequence and cause of elevated cortisol, as are the diseases of aging such as diabetes, cardiovascular disease, cancer, and bone loss. When cortisol remains high these symptoms/conditions/syndromes/diseases progressively become more problematic over time.

For additional information about strategies for supporting adrenal health and reducing stress(ors), the following books are worth reading: "Adrenal Fatigue", by James L. Wilson, N.D., D.C., Ph.D.; "The Cortisol Connection", by Shawn Talbott, Ph.D.; "The End of Stress As We Know It" by Bruce McEwen; "Awakening Athena" by Kenna Stephenson, MD.

URINARY FREE CORTISOL (F) AND URINARY FREE CORTISONE (E)

Urinary Free Cortisol (F) and cortisone (E) are following a normal circadian rhythm with the exception of the first morning void, which is slightly higher than reference ranges for F and E. High first morning F suggests high levels during the night as the first void represents the full night production of cortisol. Cortisol returns to a more normal level in the second morning void as well as in the evening and at night before bed. Cortisone, the inactive metabolite of cortisol is following a similar circadian rhythm.

The enzyme 11-beta hydroxysteroid dehydrogenase type II (11-beta HSD-II) (for review see: Seckl JR and Chapman KE Eur J Biochem 249, 361-364, 1997), which converts F to E helps maintain a healthy F/E ratio and prevents excessive tissue buildup of cortisol. This enzyme is expressed at high levels in tissues such as the kidneys, liver, lungs, colon, salivary glands, and adipose tissue. The synthesis and enzymatic activity of 11-beta HSDII activity can be inhibited and activated by various hormones, pharmaceutical medications, and natural herbal supplements. When 11-beta HSD II is inhibited, for example, with licorice extracts, it results in buildup of tissue levels of cortisol. For individuals with low cortisol this would be beneficial, but for those already suffering with hypercortisolism this would have detrimental effects on health. At high level cortisol co-activates the mineralocorticoid receptor in addition to the glucocorticoid receptor, the latter of which it only activates at physiological levels of cortisol. Excessive cortisol, caused by 11-beta HSD II inhibitors can lead to mineralocorticoid excess syndrome, causing high blood pressure and low potassium levels.

High tissue levels of cortisol can cause tissue resistance to other hormones such as insulin (i.e. insulin resistance, which leads to fat deposition), thyroid, and sex-steroids (estrogens, progestogens, androgens). A persistently high night cortisol can eventually lower melatonin production, which is important for maintaining normal biorhythms and immune function. Chronic high cortisol, particularly at night, leads to conditions such as weight gain in the waist, muscle and bone loss, depression, and immune suppression. As described above, dysfunction of other hormones is closely associated with chronic excess cortisol.

Because chronic stressors and associated high night cortisol can have adverse effects on health and wellbeing, it is important to develop strategies to identify and eliminate or reduce the stressors or consider bioidentical hormone replacement therapies, foods, and/or nutritional supplements that help control excessive accumulation of cortisol. For additional information about adrenal dysfunction and strategies for adrenal support and lowering stress/cortisol levels the following books and journal articles are worth reading: "Adrenal Fatigue," by James L. Wilson, N.D., D.C., Ph.D.; "The Cortisol Connection," by Shawn Talbott, Ph.D.; "The End of Stress As We Know It," by Bruce McEwen. “The Role of Stress and the HPA Axis in Chronic Disease Management” by Thomas Guilliams, PhD.

MELATONIN METABOLITE 6-SULFATOXYMELATONIN (MT6s)

The melatonin metabolite MT6s is following a normal circadian rhythm in the first and second morning voids, but is higher than reference ranges in the afternoon, and evening collections. MT6s should be at its highest level in the in the first morning void, which is reflective of the dark period, progressively fall throughout the daylight hours and then begin to rise again with darkness and more subdued lighting. During the darkness of night melatonin synthesis should peak around 2 am. The first morning void, which represents the sum of melatonin produced during the night, should have the highest MT6s level. High evening and night melatonin levels may be normal for this individual if exposed to less light, or may represent melatonin supplementation in the late afternoon (none indicated).

In a healthy individual the circadian rhythm of melatonin is inversely related to cortisol, i.e. melatonin rises with darkness and peaks about 2-3 am, while cortisol falls to its lowest level at this time of day. With morning and onset of light exposure, melatonin drops rapidly and cortisol rises, peaking to its highest level about 30 min to 1 hr after waking. By mid-afternoon and continuous light exposure melatonin drops to its lowest level during the day. With lower lighting as darkness approaches melatonin then gradually begins to rise again. Cortisol continues to fall as melatonin rises during the dark hours of the night, when both hormones reach their nadir (cortisol) and peak (melatonin) about 2-3 am.

Melatonin synthesis by the pineal gland is controlled by light exposure, while cortisol synthesis is controlled by the hypothalamic-pituitary-adrenal axis in response to stressors. Melatonin and cortisol have opposing circadian rhythms; however, neither hormone directly controls the synthesis of the other.

The circadian patterns of melatonin are easily tracked with collections of urine timed throughout the day and measurement of 6-methoxymelatonin (MT6s), a stable metabolite of melatonin and surrogate marker of melatonin synthesis. MT6s levels in urine lag several hours behind active circulating levels of melatonin found in blood and saliva, which makes early morning first void MT6s measurements convenient for determining melatonin's average synthesis during the dark hours of sleep at night. Melatonin, produced by the pineal gland in the brain and released into the circulation, rapidly enters tissues throughout the body where it carries out its restorative properties.

Melatonin is known to have many different beneficial effects in the body. It helps slow the aging process, is a potent anti-oxidant, inhibits formation and growth of tumors such as breast and prostate cancers, and helps regulate the synthesis of the sex-hormones estradiol and progesterone (melatonin increases progesterone and decreases estrogens). Melatonin also down-regulates cellular estrogen receptors, further inhibiting response of estrogen target tissues (e.g. breast, uterine, and prostate) to circulating estrogens. Pineal calcification, which is accelerated with aging and diseases, including breast cancer, is associated with very low melatonin production at night. Low melatonin has been associated with many different conditions and diseases such as immune dysfunction, neurodegenerative disorders (Alzheimer's disease, senile dementia), pain disorders, cardiovascular disease, cancers of the breast and prostate, and type 2 diabetes (Hardeland R. Aging and Disease 3 (2): 194-225, 2012).

Low melatonin is also thought to contribute to obesity in people with insomnia or those who do night shift work. Low night time melatonin levels are seen commonly in breast and prostate cancer patients. The WHO's International Agency for Research on Cancer has concluded that "shift work that involves circadian disruption is probably carcinogenic to humans", because of the suppression of melatonin production by exposure to light during the night.

Because of its established role in the regulation of the circadian rhythm, treatment with exogenous melatonin has been found useful in people with circadian rhythm sleep disorders, such as delayed sleep phase disorder, jet lag, shift worker disorder, and the non-24-hour sleep-wake disorder most commonly found in totally blind individuals; however, its utility for the treatment of insomnia is not established and remains controversial.

If melatonin is taken as a supplement (available OTC) to correct low levels or treat a condition, the timing and dosage are important to its effectiveness, especially as a sleep aid. Response to supplemental melatonin can be very individual. For optimal benefit it is best to work with a health care provider familiar with melatonin dosage and timing. Excessive dosing can result in spillover of melatonin into daylight hours, excessive sleepiness during the day, and disruption of the normal melatonin-cortisol circadian rhythms. This will be seen as very high levels of MT6s in the first and second urine voids, and often carry-over into the evening when levels should be low. Consider dosage reduction if MT6s levels are excessive throughout the daylight hours and this is associated with persistent sleepiness during the day. While MT6s is an excellent surrogate marker for melatonin levels in the circulation, oral melatonin supplementation results in much higher MT6s levels in urine that are NOT reflective of active circulating levels of melatonin, since most of the exogenous oral melatonin is rapidly metabolized by the liver and kidney and excreted into urine.