

**RESULTS: SALIVA HORMONE TEST**

Accession #: 100035531 • Patient: JOHN SMITH

**Patient:** JOHN SMITH

**Sex:** Male

**Age:** 21 yr

**Date of Birth:** 2001-06-12

**Accession #:** 100035531

**Height:** 6 ft 8 in

**Weight:** 145 lbs

**Waist size:** 40 in

Sample received: 2021-12-05

Report issued: 2021-12-24

**Hormones:** No

**Health Care Professional:** Jane Smith

Sample collection:

2021-12-01 07:30 AM

2021-12-01 12:15 PM

2021-12-01 18:25 PM

2021-12-01 22:35 PM

**FEMALE WELLNESS DAILY CYCLE + MELATONIN (Daytime)**
**17-β ESTRADIOL (E2) pg/ml**
**2.9**

Reference range

Female

21-50 years	Follicular phase	1.3 - 7.8
	Mid cycle	3.8 - 16.0
	Luteal phase	1.2 - 8.4

51-75 years	Post Menopausal	0.6 - 4.4
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Male	1.0 - 4.7
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**PROGESTERONE (Pg) pg/ml**
**0.5**

Reference range

Female

Follicular phase	19.6 - 86.5
Luteal phase	99.1 - 332.6
Post Menopausal	6.0 - 56.4

Male	12.7 - 65.1
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**Pg:E2 RATIO**
**0.2:1**

Optimal (Luteal): 100 - 300:1 when E2 1.2-3.3 pg/ml

**Melatonin (Daytime\Noon) pg/ml**
**1.2**

Reference range 0 - 5

The reference range is derived from a normal distribution of results that encompass 95% of randomly selected individuals in a population.



Dr. Aron Gonshor PhD, DDS, FRCD(C), FAO • Laboratory Director

**DHEA-S (DS) ng/ml**
**0.6**

Reference range

Median

Female

0.2 - 2.5

2.0

Male

0.2 - 3.7

2.0

**CORTISOL (C) ng/ml**

Reference range

Median

Morning

**4.5**

2.0 - 10.7

3.9

Noon

**2.2**

0.7 - 3.5

0.9

Afternoon

**1.4**

0.5 - 3.1

0.6

Night

**2.7**

0.3 - 3.2

0.3

TOTAL

**10.8**

3.5 - 20.5

5.6

**TOTAL C:DS RATIO**
**18:1**

Reference range

Median

4:1 to 5:1

3:1

**TESTOSTERONE (T) pg/ml**
**6**

Reference ranges

Age (years)

Male

Female

Less than 20

Range not applicable

20 - 29

41.4 - 142.5

5.5 - 49.0

30 - 39

31.8 - 100.4

5.2 - 49.0

40 - 49

30.1 - 97.8

4.5 - 49.0

50 - 59

30.0 - 92.0

3.6 - 49.0

60 - 69

23.2 - 86.9

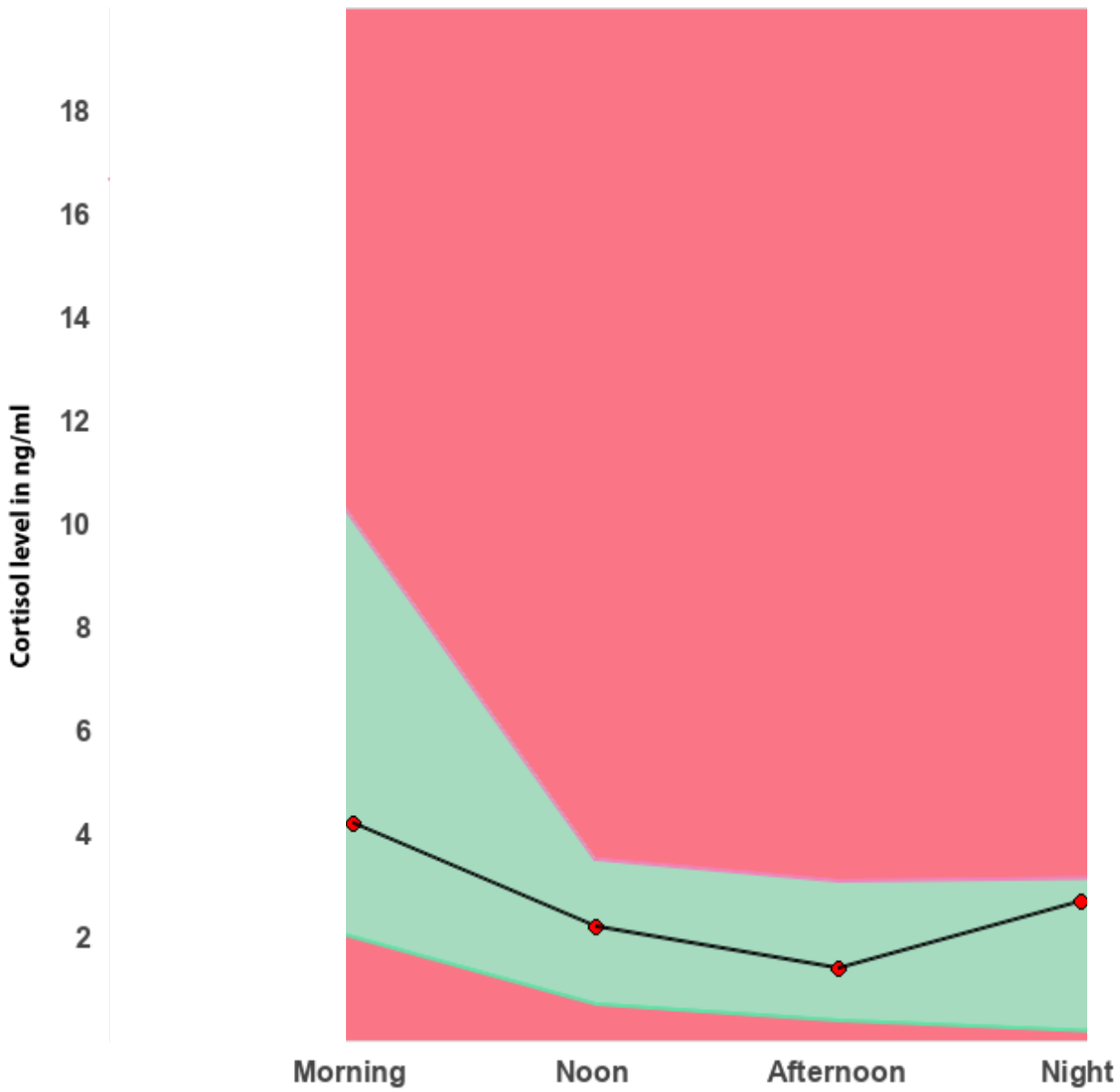
2.9 - 38.8

Greater than 69

Range not applicable

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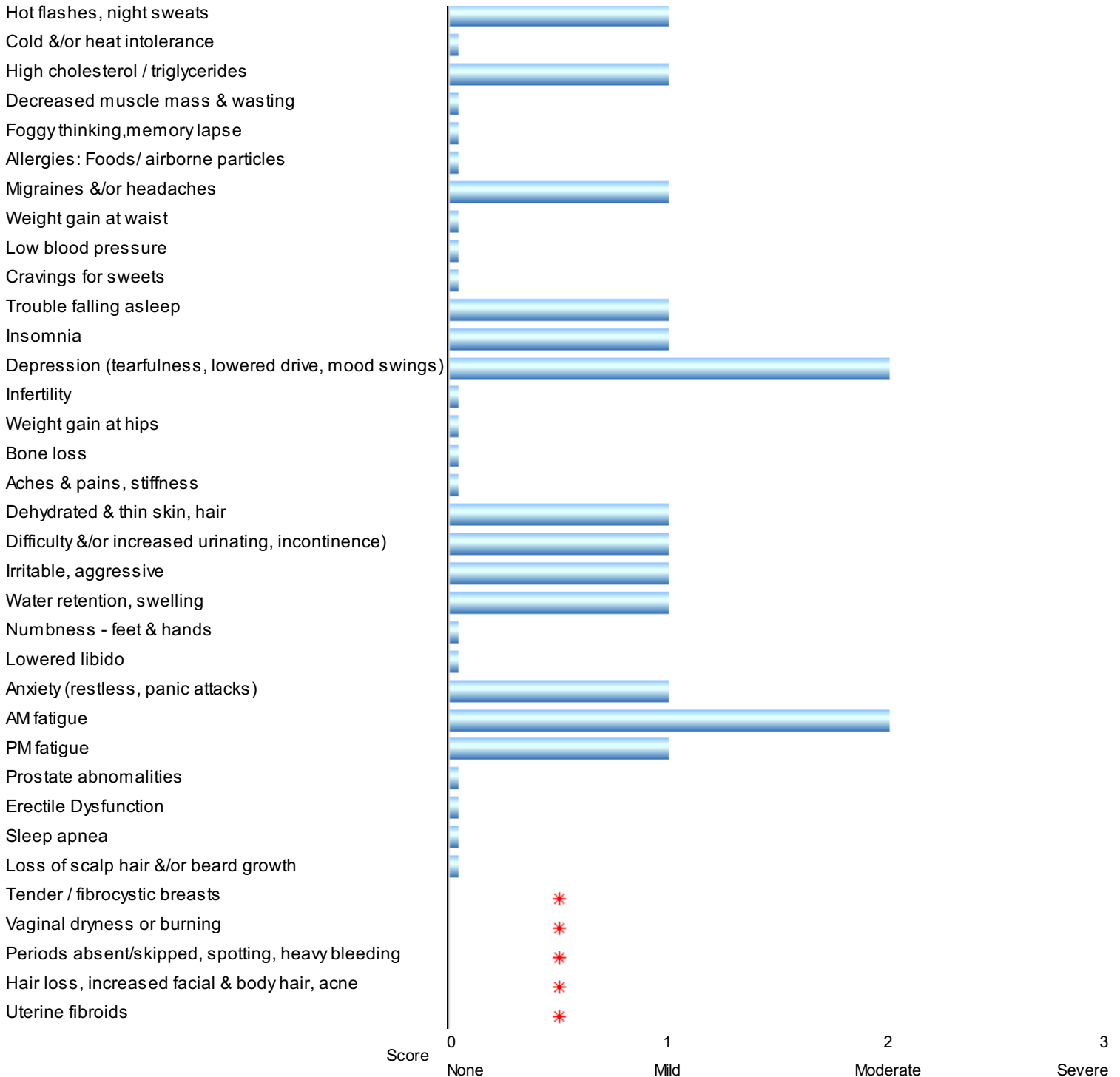
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**JD Clinic AN:**



\* Indicates that symptom left blank

### **Understanding Hormone Excess and Deficiency**

The comments provided here are for educational purposes only. They should not be interpreted as being diagnostic or treatment recommendations. Those decisions are the responsibility of the health care professional. Moreover, the reference range shown in this report is derived from a normal distribution of results that encompass 95% of randomly selected individuals in a population.

#### **IN THE PRESENT TEST**

##### **CORTISOL**

The Morning cortisol level lies inside the reference range. Cortisol levels are normally highest shortly after waking and indicate normal adrenal function at its circadian peak.

The Noon cortisol level lies inside the reference range and indicate that the adrenal glands are responding well to the needs of the day, especially in glycemic control. This highlights the importance of the adrenal glands in the regulation of blood glucose levels.

The Afternoon cortisol level lies inside the reference range and indicate that the adrenal glands are responding well to the needs of the day, especially in glycemic control.

The Nighttime cortisol level lies inside the reference range, and indicates that adrenal glands are functioning normally within the circadian cycle. It is a good indicator of a normal baseline level of adrenal activity.

##### **DHEA-S (Dehydroepiandrosterone Sulphate)**

DHEA-S lies within the reference range. DHEA, together with cortisol, plays an important role in maintaining normal blood glucose levels (glycemic control). Normal levels are important in proper metabolism of carbohydrates, fats and proteins.

## General Discussion

### CORTISOL

**About Cortisol:** Cortisol is produced by the adrenal glands, which are controlled by parts of the brain called the hypothalamus and pituitary. Cortisol plays an important role in breaking down glycogen to glucose in liver and muscle tissue. It mobilizes glucose, so as to maintain normal blood sugar levels, the primary energy source for the brain. Cortisol levels are highest in the early morning (approximately 8 am) and reach the lowest level about midnight to 4 am, or three to five hours after the onset of sleep. Diurnal cycles of cortisol levels are found in human saliva. Cortisol production comes in response to daily stress, as well as emotional upset, infections and surgery. It prevents the release of substances in the body that cause inflammation. It is used to treat conditions resulting from over activity of the B-cell-mediated antibody response. Examples include inflammatory and rheumatoid diseases, as well as allergies. Low-potency hydrocortisone, available as a non-prescription medicine in some countries, is used to treat skin problems such as rashes, and eczema<sup>1,2,3</sup>.

**Low Cortisol**, especially if it remains so throughout the day, may indicate **Adrenal Exhaustion**, which is caused by stress, such as sleep deprivation, emotional stress, poor diet, nutrient deficiencies, and/or synthetic glucocorticoid medications that suppress cortisol production. Chronic stress depletes cortisol and is associated with symptoms of morning and evening fatigue, aches and pains, fibromyalgia, cold body temperature, decreased stamina, slow pulse rate, low blood sugar (sugar craving) and low blood pressure. In addition one often encounters increased allergies (immune dysfunction), and sensitivity to chemicals. Symptoms of thyroid deficiency can also be due to low cortisol levels. Exercise, more adequate sleep, a diet with adequate protein, 'bio-identical' progesterone, adrenal extracts and nutritional supplements are often helpful in correcting low cortisol.

**High Cortisol.** Although normal cortisol levels are essential for life, chronically elevated levels can be very detrimental. Increased cortisol production by the adrenals is a normal response to routine stress, but when stress is chronic and cortisol output remains high over a prolonged period (months/years), break-down of normal tissues (muscle wasting, thinning of skin, bone loss) and immune suppression can result. Common symptoms of chronic high cortisol include sleep disturbances, fatigue, depression and weight gain in the waist and anxiety. Stress and persistently elevated cortisol levels can contribute to premature aging and chronic illness.

## ESTROGENS

(Estrone-E1, 17- $\beta$  Estradiol-E2, Estriol-E3) Estrogens are the primary female sex hormones. They play important roles in stimulating growth of the reproductive tissues, maintaining healthy bones, increasing the levels of neurotransmitters in the brain and helping keep the cardiovascular system healthy. During menopause estrone is the predominant circulating estrogen and during pregnancy it is estriol. Though estriol is the most plentiful of the three estrogens it is also the weakest, whereas estradiol is the strongest, with a potency of approximately 80 times that of estriol. Thus, estradiol is the most important estrogen in non-pregnant females who are between the first menstruation (menarche) and menopause stages of life. However, during pregnancy this role shifts to estriol, and in postmenopausal women estrone becomes the primary form of estrogen in the body. All of the different forms of estrogen are synthesized from androgens, specifically testosterone and androstenedione.

**Low Estradiol** is unusual in premenopausal women, unless they have no ovulation, or are taking birth control pills, since the latter can suppress ovarian estrogen production. It is much more common in post-menopausal women whose ovaries were removed, or those who have not had hormone replacement. Symptoms and signs of low estrogen levels include sleep disturbances, foggy thinking, hot flashes, night sweats, vaginal dryness, thinning skin, incontinence, and heart palpitations.

**High Estradiol** in premenopausal women is usually due to over production of androgens by the adrenal glands and ovaries (DHEA and testosterone), or by estrogen replacement therapy (ERT). In postmenopausal women high estradiol levels are usually due to estrogen supplements. Excess estrogen levels, such as estradiol, even at normal premenopausal levels, when not balanced by adequate progesterone, may create what is referred to as “**Estrogen Dominance**”. Symptoms may include irritability, anxiety, mood swings, weight gain at the hips, water retention, bleeding problems (due to uterine lining overgrowth and fibroids) and thyroid deficiency.

### Estrogen in Females and Males:

Estrogen is considered to be the female hormone, whereas testosterone is considered the male hormone. However, both hormones are present in both sexes. The sexual distinctions are not qualitative differences, but rather result from quantitative divergence in hormone concentrations and differential expressions of steroid hormone receptors. In males, estrogen is present in low concentrations in blood, but can be extraordinarily high in semen; as high as 250 pg/ml in testicular fluids, which is higher than serum estradiol in the female. It is well known that male reproductive tissues have estrogen receptors, but the role of estrogen in male reproduction remains unclear.

Estrogen regulates the reabsorption of luminal fluid in the head of the epididymis. Disruption of this essential function causes sperm to enter the epididymis diluted, rather than concentrated, resulting in infertility. This finding raises further concern over the potential direct effects of environmental estrogens on male reproduction and reported declines in human sperm counts.

**RESULTS: SALIVA HORMONE TEST**Accession #: 100035531 • Patient: JOHN SMITH

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In males, the main biologically active estrogen is estradiol. The primary source of estradiol in men is from the conversion (aromatization) of testosterone by estrogen synthase. As men age, the production of androgens from the adrenals and gonads is decreased. The aromatization of testosterone to estradiol is often maintained, but due to a variety of factors, more testosterone is aromatized in fatty tissues, causing a further imbalance of the ratio of testosterone to estrogen; i.e. too much estradiol and not enough testosterone. The result is a deficiency of beneficial testosterone and an excess amount of estradiol.

As men age, the amount of testosterone produced in the testes diminishes greatly. Yet estradiol levels remain persistently high. The reason for this is increasing aromatase (estrogen synthase) activity along with age-associated fat mass, especially in the belly. Estradiol levels correlate significantly to body fat mass and more specifically to subcutaneous abdominal fat. The epidemic of abdominal obesity observed in aging men is associated with a constellation of degenerative disorders, including heart disease, diabetes, and cancer.

Subcutaneous abdominal fat acts as a secretory gland, often producing and emitting excessive levels of estradiol into an aging man's blood. One's waist circumference is a highly accurate prognostic measurement of future disease risk, with excess estradiol secretion being at least one of the deadly mechanisms associated with the difficult to resolve problem of having too much abdominal fat.

Symptoms of excess estrogen in aging men include the development of breasts, having too much abdominal weight, feeling tired, suffering loss of muscle mass, and having emotional disturbances. Many of these symptoms correspond to testosterone deficiency as well.

**PROGESTERONE**

Progesterone is produced in the ovaries at about 10- 30 mg/day and is important for normal reproductive and menstrual function, especially during the latter half (luteal phase) of the menstrual cycle. It plays a role in the health of the heart, skin, bone, blood vessels and other body tissues. It is also important in breast development, maintaining pregnancy and the control of neurotransmitters in the brain. Although Progesterone is found in both females and males, its role in male physiology is not well understood.

**Low Progesterone** plays a role in abnormal uterine bleeding in females. It may also have an association with lowered neurological function and osteoporosis. Low progesterone is more common in postmenopausal women who are no longer ovulating, have had their ovaries removed, or are using contraceptives or hormone replacement therapy. Low Progesterone levels in males may play a role in male infertility.

**High Progesterone** is found in states of stress and anxiety in men and women. Symptoms can include excessive sleepiness, dizziness, bloating and susceptibility to yeast infections. In women it can also result in abnormalities in blood glucose levels (dysglycemia), hair loss or baldness (alopecia), acne and breast tenderness.

**RESULTS: SALIVA HORMONE TEST**Accession #: 100035531 • Patient: JOHN SMITH

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**PROGESTERONE:ESTRADIOL RATIO (Pg:E2)**

This ratio describes the relationship between progesterone and estradiol levels. It is used clinically to determine the dominance of one hormone over the other.

The ideal Pg:E2 ratio is in the 100:1 to 300:1 range in premenopausal women and in postmenopausal women who have progesterone supplementation. This ratio is not useful when considering postmenopausal women who have low estrogen levels, or women on hormone replacement therapy (HRT) or oral contraceptives.

A low Pg:E2 ratio indicates an estrogen dominance, and women may experience many severe symptoms, such as anxiety, breast tenderness, headaches or migraines, depression, digestive problems, fuzzy thinking, palpitations, irregular bleeding, water retention, weight gain and more. If estrogen levels stay unopposed, women may go on to develop infertility, skipped periods (amenorrhea), heavy bleeding (hypermenorrhea), fibroids, uterine cancer, heart disease and stroke, and decreased cognitive ability, among other conditions.

An elevated Pg:E2 ratio may indicate progesterone dominance and the symptoms will be those seen with high progesterone levels (see above).

**ANDROGENS**

The endocrine glands secrete 5 androgens through a similar pathway: Testosterone, dehydroepiandrosterone (DHEA) and its sulphated form (DHEA-S), androstenedione, and androstenediol. Testosterone, and its biologically active metabolite dihydrotestosterone (DHT), are the only androgens with direct androgenic activity. DHEA-S, DHEA, and androstenedione are all precursors of testosterone.

**a) TESTOSTERONE**

Testosterone is considered the "male hormone". In men it is produced by the testes and in much smaller amounts by the ovaries in women. It is responsible for many of the secondary sex characteristics seen in men such as a deeper voice and hair on the chest, in addition to contributing to a healthy libido, regulating the immune system, maintaining optimal memory, building muscle mass, and maintaining energy levels. In both men and women testosterone levels are highest in the teens and then decline gradually with age, playing a role in the loss of bone density. In women, premenopausal testosterone levels are usually within the high-normal range and postmenopausal levels at low-normal range.

**Low Testosterone** is most often a result of aging, testes or ovary removal, suppression of ovarian and testicular production by stress hormones (cortisol), the use of synthetic HRT and contraceptives, and/or damage to the testes, ovaries, and adrenal glands by medications, radiation therapies, or trauma. Chronically low testosterone, in both sexes, may cause fatigue or decreased energy as well as reduced sex drive or desire (libido). In addition it may cause reduced stamina and the loss of bone and/or muscle mass, loss of body hair, incontinence, aches and pains, memory lapse, cognitive decline and depression. In women, testosterone imbalance has been associated with coronary heart disease and heart attacks (myocardial infarcts), especially in post-menopausal women. In men, testosterone levels decrease with age. While this decrease may not be noticeable in some men, others may experience significant changes starting in middle age, or more commonly at age 60 and above. This drop in testosterone levels is sometimes termed "male menopause", hypogonadism, or andropause.



**RESULTS: SALIVA HORMONE TEST**Accession #: 100035531 • Patient: JOHN SMITH

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Low testosterone levels may result in a decline in physical energy, strength, stamina, and diminished mental aggressiveness. These men may experience more aches and pains in the bones and joints and they may also have a decline in libido and a greater incidence of erectile dysfunction.

**High Testosterone** is the result of excess production by the ovaries, testes and adrenal glands, or androgen supplementation (testosterone, DHEA). In men high levels will manifest in increased scalp hair loss. The higher the levels the more likely these men will exhibit risky and aggressive behavior, whether sexual, injury risk, or criminal. Symptoms of high testosterone levels in premenopausal women include loss of scalp hair, increased body and facial hair, acne, and oily skin. Supplementation with topical testosterone at doses in excess of levels produced by the ovaries (0.3-1 mg) or testes (5-10 mg) can raise testosterone to levels beyond physiological range.

**b) DHEA-S (Dehydroepiandrosterone Sulphate)**

**About DHEA:** DHEA, a testosterone precursor, is the most abundant circulating steroid hormone. DHEA is produced predominately by the adrenal glands, the gonads, and the brain, where it functions predominantly as a metabolic intermediate in the biosynthesis of the androgen and estrogen sex steroids. DHEA-S is the sulphated form, and in blood it approaches levels 300 times that of free DHEA. Whereas DHEA levels are at a peak in the early morning, DHEA-S levels show no diurnal variation. From a practical point of view, measurement of DHEA-S is preferable to DHEA, as its levels are more stable. In the young the levels approach the high end of the range. They decrease with age and get to the lower end of normal in middle age.

**Low DHEA-S** can be caused by adrenal exhaustion and is commonly seen in accelerated aging and diseases such as cancer.

**High DHEA-S** can be associated with insulin resistance/PCOS<sup>4</sup> (polycystic ovaries) or DHEA supplementation.

**TOTAL CORTISOL : DHEA-S RATIO**

Ratios often use the 'mean' value for the analytes being considered. The 'mean' represents the sum of all values, divided by the total number of values. It is also referred to as the 'average', and is a way of deriving the central tendencies of a group of values, because it takes into account every value in the data set. However, one can also use the 'median' value to show the ratio. The median is the 'middle' value, for which half of the observations are larger and half are smaller. The advantage of the median is that it removes extreme measurements from a data set and is not distorted by outliers or skewed data. It therefore often provides a better representation of a 'typical' value.

In the present report, when using the 'median' values for total cortisol and DHEA-S, the median ratio is 3:1 (4:1 to 5:1 if one uses the 'average' values), and is an indicator of the adrenal output of cortisol and the androgens. It is age dependent, since there is a decline in DHEA-S with age, while the levels of morning cortisol remain relatively stable or increase slightly. If the ratio is higher than normal it is due to adrenal dysfunction. When the body experiences chronic stress, pregnenolone, the precursor to all other steroidal hormones, begins to overproduce cortisol. This is at the expense of all the other steroidal hormones (DHEA and its metabolites, including progesterone, testosterone, and the estrogens). As pregnenolone is diverted to cortisol, DHEA-S depletion begins.

## RESULTS: SALIVA HORMONE TEST

Accession #: 100035531 • Patient: JOHN SMITH

This creates an elevated cortisol to DHEA-S ratio. If the ratio is lower than normal for that age, and the DHEA-S level is within the normal range, it is probably due to the maintenance of DHEA-S output with advancing age. However, if the ratio for that age is lower than expected, it is probably due to high DHEA-S levels, low cortisol, or both of these.

### Total Cortisol : DHEA-S Ratio and Metabolic Syndrome

Various studies have shown that both cortisol and DHEAS are related to metabolic syndrome<sup>5</sup> and type 2 diabetes.<sup>6</sup> While high cortisol concentrations are associated with an increased risk of metabolic syndrome, high DHEA-S levels appear to be protective. By far, the strongest associations of these disease states is with the Total Cortisol : DHEA-S ratio. The higher the coefficient, the greater the risk of metabolic syndrome.

### Total Cortisol : DHEA-S Ratio and Depression

A high salivary Cortisol : DHEA ratio, when seen in conjunction with stressful life events, has been shown to be predictive of major depression and its persistence.<sup>7</sup> More recent studies<sup>8</sup> present data in which the salivary cortisol : DHEA ratio clearly differentiates depressed patients from controls, 82.5% of depressed subjects having ratios above the 85th percentile of the control group. Therefore, decreased levels of DHEA and a consequent elevation of the Cortisol : DHEA ratio appears to reflect an additional state of abnormality in adult depression.

## METABOLIC SYNDROME

Metabolic syndrome is a disorder of energy utilization and storage, diagnosed by a co-occurrence of three out of five of the following medical conditions: abdominal (central-waist) obesity, elevated blood pressure, elevated fasting plasma glucose, high serum triglycerides, and low high-density cholesterol (HDL) levels. Metabolic syndrome increases the risk of developing diabetes and cardiovascular disease, particularly heart failure. Some studies have shown the prevalence in the USA to be an estimated 34% of the adult population, and the prevalence increases with age. Recent research indicates prolonged chronic stress can contribute to metabolic syndrome by disrupting the hormonal balance of the hypothalamic-pituitary-adrenal axis (HPA-axis)<sup>5</sup>.

The principal signs and symptoms of metabolic syndrome are central obesity, also known as visceral overweight (male-pattern or apple-shaped adiposity), with fat (adipose) tissue accumulation mainly around the waist and trunk. Other signs of metabolic syndrome include high blood pressure, with decreased fasting serum HDL cholesterol and elevated fasting serum triglyceride level (VLDL triglyceride). It is often accompanied by impaired fasting glucose and insulin resistance, or pre-diabetes, which can manifest by numbness in the feet or hands.

## HYPOMETABOLISM

Hypometabolism is not an illness in itself. It would better be termed a "condition", encompassing a variety of illnesses<sup>6</sup>. The characteristic of hypometabolism is that the biochemical processes of the body are functioning as fast as they should. Since the biochemical reactions of the body give off heat (exothermic), hypometabolism results in hypothermia, a lowered body temperature. While the enzymatic reactions of the body give off heat, the enzymes themselves are also dependent on body heat to have their most efficient action. When body temperature is below 98.2 degrees Fahrenheit, enzymes are not functioning at their best efficiency.

**RESULTS: SALIVA HORMONE TEST**

Accession #: 100035531 • Patient: JOHN SMITH

This enzymatic dysfunction produces a variety of signs and symptoms, which are common to all hypometabolic conditions. These include fatigue (AM and PM), cold and heat intolerance, migraines (headaches), depression and weight gain. Other symptoms include irritability, sleep disturbance such as insomnia, anxiety (panic attacks), as well as poor memory and concentration (foggy thinking). Many individuals experience irregular periods, low sex drive, low ambition and motivation. This may be accompanied by fluid retention, irritable bowel, hair loss, dry skin and hair and generalized muscle aches and joint pain.

**MELATONIN**

Melatonin is a hormone produced during the dark phase of the day by the pineal gland, a small endocrine gland in the brain that regulates the sleep-wake cycle.

Melatonin is also synthesized in the enterochromaffin (EC) cells throughout the intestine and to a lesser extent in lymphocytes, mast cells, epithelial cells and the bone marrow. In the gut, L-tryptophan is a crucial precursor of melatonin synthesis and the EC cells, as well as bacteria within the microbiome, have been reported to be the major sources of L-tryptophan-induced increase of circulating melatonin. Interestingly, at any time of the day or night, the gut contains at least 400 times more melatonin than the pineal gland, but does not contribute to the circulating rhythm of melatonin<sup>7</sup>. This non-pineal melatonin seems to act locally. These local effects are involved in a myriad of actions, including metabolism, immune function, gut function, inflammation, mitochondrial function, free radical scavenging, direct anti-oxidant activity, redox status and influence on anti-oxidant enzymes<sup>8</sup>.

In a 24-hour circadian cycle, melatonin reaches its highest levels during sleep, the middle of the night, often spiking to levels above 50 pg/ml. It then falls to very low levels by the time of waking (~5 pg/ml). The pineal gland begins producing melatonin in the evening, so that some individuals may have rising levels that reach to between 10-15 pg/ml at bedtime<sup>9</sup>.

Melatonin has numerous functions in body hemostasis, of which three major ones are noted here.

- a. It has major physiological importance in the control of sleep time and duration. It is central to the modulation of both circadian and annual biorhythms and has a remarkably tight association with sleep propensity<sup>10</sup>.
- b. It is involved in the regulation of GI motility & local anti-inflammation<sup>11</sup>.
- c. It acts as a strong lipophilic antioxidant, specifically offering mitochondrial protection. Melatonin scavenges free radicals (OH<sup>-</sup>) and upregulates glutathione, acting to promote antioxidant enzymes such as glutathione peroxidase (GPx), glutathione reductase (GR), superoxide dismutase (SOD) and catalase (CAT)<sup>12</sup>.

These melatonin functions interact. As an example, good circadian rhythm helps to decrease oxidative stress, whereas chrono (sleep) disruption causes an increase in reactive oxygen and nitrogen species<sup>13</sup>.

Low levels of melatonin can cause imbalances that may have far reaching effects, including menstrual difficulties, sleep disorders, depression and Seasonal Affective Disorder.

The synthesis and physiological use of melatonin is strongly affected by the length of day, seasonal changes, aging and artificial illumination - especially prolonged exposure to blue light emanating from computers and other similar devices.

**RESULTS: SALIVA HORMONE TEST**

Accession #: 100035531 • Patient: JOHN SMITH

A deficient production of melatonin can also result in lowered basal body temperature, insomnia, and sleep/wake disorders. The disturbance in the circadian rhythm of melatonin may influence other hormones, such as thyroid and testosterone. It may lead to an elevated estrogen/progesterone ratio, decreased cardiovascular and antioxidant protection, as well as immune suppression<sup>14</sup>.

Therefore, accurate measurement of melatonin levels is essential for the development of therapeutic regimes, such as timing of artificial light and melatonin administration.

Excess melatonin is associated with anxiety, stress and depression. These elevated levels are also present in those diagnosed with Seasonal Affective Disorder, a form of depression. It has been observed that this form of bipolar disorder might have elevated sensitivity to light; i.e., a greater decrease in melatonin secretion in response to light exposure at night. This should be contrasted with drug-free, recovered bipolar patients, who show normal light sensitivity<sup>15</sup>. Elevated melatonin is also associated with a lowered estrogen/progesterone ratio, inhibition of ovulation, low thyroid and adrenal function, and hypotension.

**References**

1. Fukaya M et al. Topical steroid addiction in atopic dermatitis. *Drug, Healthcare and Patient Safety* 2014; 6: 131-138.
2. Nieman, LK. Recent Updates on the Diagnosis and Management of Cushing's Syndrome. *Endocrinol Metab* 2018; 33:139-146.
3. Crona J, Beuschlein F, Pacak K and Skogseid B. Advances in adrenal tumors 2018. *Endocrine-Related Cancer* 2018; 25: R405-R420.
4. Gill J. Low Cortisol, High DHEA, and High Levels of Stimulated TNF $\alpha$ , and IL-6 in Women with PTSD. *J Trauma Stress*. 2008; 21: 530–539.
5. Kaur J. A Comprehensive Review on Metabolic Syndrome. *Cardiology Research and Practice*. Volume 2014; 1-21.
6. Storey KB and Storey JM. Tribute to P. L. Lutz: putting life on 'pause' – molecular regulation of hypometabolism. *The Journal of Experimental Biology* 2007; 210: 1700-1714.
7. Chen C-Q et al. Distribution, function and physiological role of melatonin in the lower gut. *World J Gastroenterol* 2011; 17: 3888-3898.
8. Posadzki PP et al. Melatonin and health: an umbrella review of health outcomes and biological mechanisms of action. *BMC Med* 2018; 16: 18. doi: 10.1186/s12916-017-1000-8
9. Arendt J. Melatonin: Countering Chaotic Time Cues. *Frontiers of Endocrinology* 2019; 10: 1-16.
10. Zisapel N. New perspectives on the role of melatonin in human sleep, circadian rhythms and their regulation. *British Journal of Pharmacology* 2018; 175: 3190–3199.
11. Esteban-Zubero E et al. Melatonin's role as a co-adjuvant treatment in colonic diseases: a review. *Life Sci* 2017; 170: 72–81.
12. Reiter RJ et al. Melatonin as an antioxidant: under promises but over delivers. *Journal of Pineal Research* 2016; 61: 253–278.
13. Liu R et al. Melatonin Inhibits Reactive Oxygen Species-Driven Proliferation, Epithelial-Mesenchymal Transition, and Vasculogenic Mimicry in Oral Cancer. *Oxidative Medicine and Cellular Longevity* 2018, <https://doi.org/10.1155/2018/3510970>.
14. Srinivasan V et al. Melatonin, immune function and aging. *Immunity & Ageing* 2005; 2: 17.
15. Whalley LJ et al. Melatonin response to bright light in recovered, drug-free, bipolar patients. *Psychiatry Res* 1991; 38: 13–19.