Sleep Balance Profile

Diurnal Melatonin / Cortisol / Cortisone in Dried Urine

Adequate sleep has long been known to be vital to good health. Melatonin, a hormone produced by the pineal gland during the dark phase of the light/dark cycle, regulates the sleep/wake cycle and the "biological clock". However, it is now known also to have free radical scavenging and antioxidant properties and a significant role in stimulating the immune system to protect against the growth of abnormal tissues such as breast and prostate cancers. Melatonin is also neuroprotective. Adequate melatonin production during the night, as well as suppression of production during the day by exposure to daylight, form a balance that is vital to optimal health. Circulating melatonin is rapidly and efficiently hydroxylated and conjugated with sulfate in the liver to form its primary metabolite, 6-sulfatoxymelatonin (MT6s), and excreted into urine; it is this metabolite that is measured in the Sleep Balance Profile.

Cortisol, a hormone produced by the adrenal glands in response to stress, is also known for its diurnal variation linked to the sleep/wake cycle. It has the opposite pattern to melatonin production in a healthy individual. While melatonin rises at night to peak during the early hours of the morning, cortisol is at its lowest levels throughout the night. After waking, melatonin production dips with the onset of daylight and cortisol rises and peaks about 30 minutes to 1 hour after rising. Cortisol production falls gradually during the day, while melatonin begins to rise during the evening as daylight diminishes, and the cycle repeats itself. When the cortisol pattern is disrupted, for example as a result of excessive stressors, this can lead to high night cortisol, disrupted sleeping patterns, and exposure to more night time light, which in turn leads to lowered levels of melatonin. Thus, excessive stressors can lead to higher cortisol and indirectly lower melatonin synthesis, preventing melatonin from carrying out its other beneficial and protective functions.

Available Tests

Sleep Balance Profile

Tests: Free Cortisol x 4, Free Cortisone x 4, Melatonin (MT6s) x 4 (dried urine)

Allows physicians to pinpoint imbalances of melatonin and cortisol circadian rhythms associated with acute or chronic sleep disturbances. Consider for patients with inability to get to sleep, frequent waking, or chronic sleeplessness affecting vitality, cognition, weight, and diabetes/cardiovascular disease risks.

Norepinephrine & Epinephrine Add-On:

Tests: Epinephrine x 4, Norepinephrine x 4 (dried urine)

This optional add-on gives a fuller picture when there are adrenal issues.

1998-2018 20 years

Hormone Testing
Non-invasive home test kit

Cortisol & Melatonin Imbalance & Sleep Disturbance

Lack of sleep can be detrimental to health on a number of levels. Sleeplessness at night results in lack of alertness during the day, impairing judgment and increasing risk of accidents. Chronic sleeplessness affects skin appearance and health, reduces libido and overall vitality, reduces cognitive function, contributes to weight gain, and increases risk of diabetes and cardiovascular diseases.

The diurnal cortisol and cortisone patterns reflect hypothalamic-pituitary-adrenal (HPA) axis function, with levels of cortisol and cortisone normally highest immediately after waking and dropping throughout the day to a night-time nadir. Abnormal patterns include elevated cortisol levels throughout the day and night in chronic stress, a suppression of cortisol levels in the condition known as adrenal fatigue, and a recognizable diurnal variation, but with overall lower cortisol and cortisone levels at each time point in chronic fatigue syndrome[1].

Cortisol is reversibly metabolized to its inactive form, cortisone, in tissues by the action of the 11β-hydroxysteroid dehydrogenase types 1 and 2. The relative amounts of cortisol and cortisone are therefore determined by the activities of these enzymes, which can be affected by compounds such as licorice and carbenoxolone. Measurement of both hormones gives a better picture of total cortisol production by the adrenals.

Chronic insomnia is closely related to stress. A disrupted diurnal cortisol pattern with high night-time levels can be an indicator of a stress response that extends into the night-time hours, causing hyperarousal that disrupts sleep. Conversely, deep sleep suppresses the HPA axis and keeps cortisol production low[2]. Insomnia related to stress can be improved by lifestyle modifications and therapies to reduce stress.

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[3].

Epinephrine & Norepinephrine

Epinephrine (also known as adrenaline) and norepinephrine play an important role both as neurotransmitters and hormones. Circulating epinephrine is derived solely from the adrenal glands. Approximately 20% of circulating norepinephrine is produced by the adrenals, and the rest is released by sympathetic nerves innervating the adrenal tissue. When originating from the adrenal glands, the epinephrine/norepinephrine response is hormonal in nature as opposed to neural. Sufficient levels of epinephrine and norepinephrine throughout the day ensure that the body maintains appropriate blood pressure, cardiac output, smooth muscle contractility, and glucose levels for normal daily functions.

Under conditions of little to no stress, early morning norepinephrine and epinephrine levels are low, increase towards mid-morning, peak in the afternoon, and decrease by bedtime with low levels during the night. Under conditions of acute stress, the sympathetic nervous system signals to release epinephrine and norepinephrine as it activates the “fight or flight” response. This involves high epinephrine and norepinephrine contributing to higher blood pressure, increased breathing rate, mobilization of glucose from storage, increased heart rate and increased muscle strength. Cortisol controls the conversion of norepinephrine to epinephrine in the adrenal medulla by increasing the enzyme phenylethanolamine-N-methyltransferase (PNMT)[4]. Therefore when cortisol is low, there may be a decrease in the epinephrine-mediated physiological response to stress.

Detailed characterization of the diurnal rhythms of circulating epinephrine and norepinephrine along with the circadian rhythm of cortisol may aid in identifying specific imbalances in an individual's response to stress, and how their body adjusts sympathetic nervous system parameters accordingly. Diurnal patterns of epinephrine and norepinephrine are also affected by conditions or circumstances that affect sleep. For example, individuals with a genetic predisposition to high blood pressure have higher diurnal urinary excretion rates of norepinephrine and epinephrine and an accentuated nocturnal increase in cortisol[5]. A nocturnal drop in blood sugar is also a cause of sleep disturbance, and is accompanied by an increase in epinephrine levels. This has two consequences: first, it triggers waking, perhaps to allow the individual to go look for food. Second, nocturnal epinephrine release directly helps the body avoid a hypoglycemic state as it promotes glycogen breakdown in the liver (glycogenolysis) to increase plasma glucose levels.

Therapies to support the enzymes monoamine oxidase (MAO) and catechol-O-methyltransferase (COMT), which are involved in the metabolism of epinephrine and norepinephrine, are helpful to lower elevated levels. These include magnesium, SAMe, Vitamin B2, and copper. When epinephrine and norepinephrine levels are low, commonly seen with low cortisol, adrenal support to improve cortisol levels will help to raise epinephrine and norepinephrine. Other therapies like iron, vitamin B6, tyrosine, and vitamin C may also be helpful in increasing levels.

Impact of Chronic Sleep Disruption on Diseases of Aging (Cancer, Diabetes, Alzheimer's Disease)

Chronic sleep problems resulting in longer-term HPA axis dysregulation and deficiencies in melatonin production can impact multiple aspects of overall health. Melatonin is a potent free radical scavenger and stimulates the release of antioxidative enzymes, thereby protecting DNA and other molecules from injury[6,7]. Melatonin's ability to prevent oxidative stress is demonstrated in placebo-controlled studies[8]; it also protects against diseases related to premature aging, as well as cancer and cardiovascular disease.

Cancer

Melatonin has a potent anticancer effect, particularly in hormone-dependent cancers. It inhibits tumor growth through a variety of mechanisms[9], including antioxidation, antiestrogenic actions[10], promotion of apoptosis, and immune system activation. Melatonin acts as a selective estrogen receptor modulator in breast tumor cells and also down-regulates aromatase, reducing local estrogen synthesis from androgenic precursors[11]. Low night time melatonin levels are seen in breast[12] and prostate cancer[13] patients; the pineal gland which secretes melatonin is more likely to be calcified in advanced breast 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", probably because of the suppression of melatonin production by exposure to light during the night[14].

Insulin Resistance / Type 2 Diabetes

Sleep disturbances, including obstructive sleep apnea, sleep deprivation, and shift work, contribute to the development of insulin resistance and the metabolic syndrome[15]. While chronic HPA axis hyperactivity, typified by higher than normal night-time cortisol, contributes to insomnia, it is also thought to be a consequence of obstructive sleep apnea[16], because nocturnal awakenings result in pulsatile cortisol release. HPA axis activation due to sleep apnea can exacerbate glucose intolerance in metabolic syndrome and lead to diabetes, with consequent increased cardiovascular disease risk.

A low nocturnal melatonin is also associated with insulin resistance and high insulin levels[17], and women with low nocturnal melatonin have been found to be more likely to develop type 2 diabetes[18]. Rat studies have indicated a mechanism for the link between melatonin and obesity; melatonin increases leptin, a hormone that regulates appetite, in the presence of insulin in rat adipocytes[19], and melatonin was also found to be involved in lipid metabolism, enhancing fat mobilization and reducing fat storage in response to exercise training[20]. This could have implications for susceptibility to obesity in people with low melatonin as a result of shift work or insomnia.

Brain Health – Alzheimer's Disease

Age-associated neurodegenerative disorders such as Alzheimer's, Parkinson's, and Huntington's Diseases have been linked with oxidative damage; melatonin levels are known to decline with advancing age, and this is thought to contribute to the rise in oxidative stress that may contribute to these disorders[21]. A decline in nocturnal melatonin production is common in patients with Alzheimer's disease, and sleep-wake disturbances increase as the disease progresses. The use of melatonin and its analogs for the treatment or prevention of Alzheimer's disease is under investigation.

Methods to Assess Melatonin & Cortisol Balance

An abundance of scientific literature supports the use of serum/plasma, saliva, and 24-hour urine to assess the levels of melatonin and cortisol in humans. Each has advantages and disadvantages. Serum/plasma testing has the disadvantage that it requires venipuncture at times when melatonin is peaking (e.g., 2:00 am), and total cortisol is often inaccurate due to use

of hormones (e.g., estrogens) that increase cortisol binding globulin, which lower actual bioavailable cortisol. Saliva has the advantage that samples can be collected by the individual at multiple times during the day, and the melatonin and cortisol levels represent the bioavailable fraction of these hormones. However, the disadvantage of saliva testing to assess the sufficiency of melatonin production during the night is that it requires collecting a sample at 2 a.m. when melatonin normally peaks, which is inconvenient, and the annoyance of having to get up after attempting to sleep for 2-4 hrs may affect melatonin levels. Serum and 24-hour urine have the disadvantages that they only represent the average melatonin and cortisol production throughout the day, and don't provide an appreciation for the opposing diurnal patterns of these two hormones.

ZRT Laboratory has developed a melatonin and cortisol dried urine test that circumvents the disadvantages of serum, saliva, and 24-hour urine tests commonly used for testing these hormones. Urine is collected on filter strips at 4 time points throughout the day that are representative of the peaks and troughs of melatonin and cortisol production. The advantage of the dried urine test is that the first urine void represents the 8 hours or so of overnight peak melatonin production, a time when melatonin should be high and cortisol low. Melatonin is measured as the sulfated conjugate of its primary metabolite, known as MT6s, which is extremely stable in urine that collects in the bladder overnight, and on the filter strips sampled from the first morning void. The second urine sample, which is collected about 2 hours later, reflects the cortisol awakening response, when the melatonin should be falling rapidly from the first overnight level, and cortisol should be peaking. Urine is collected in the evening when melatonin and cortisol should both be low, and then again just before bed when the melatonin should be rising and cortisol at its nadir.

The test report includes graphs showing the diurnal MT6s, cortisol, and cortisone results at the actual test times, which is a unique feature of ZRT test reporting.

A SIMPLE, CONVENIENT, AT-HOME TESTING OPTION

- Circumvents the disadvantages of serum, saliva, and 24-hour urine tests commonly used for testing these hormones
- Collecting four dried urine strips at four time points during the day is easy and convenient
- First morning MT6s represents night time melatonin production – no need to sample in the middle of the night
- Cortisol, cortisone, and MT6s are exceptionally stable in dried urine for weeks at room temperature, allowing flexibility in collection, shipment, testing, and storage
- Results expressed in μg/g creatinine take into account the hydration status of the patient, so that test results are accurate even when urine is very concentrated or dilute

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