Childhood Adversity and Adrenal Compromise in Adulthood: Advanced HPA Axis Dysfunction and Hypocortisolism

Erin Lommen, ND
CEO, Labrix
Who IS Normal?

Salivary cortisol diurnal rhythm

Hour of Sample Collection

Adrenal Phase: 0

0800 1200 1700 2100
Symptoms **fatigue** on questionnaires correlates with the Labrix phasing of adrenal fatigue.
Blunted morning cortisol and flattened daytime cortisol curves are associated with suboptimal physiologic and psychological development and a diminished sense of well-being

Marsha, 48 yo F | Cortisol Series
Charlotte, 52yo F | Cortisol series

- 2008
- 4/2011
- 9/2011
- 5/2012
- 12/2012

Adrenal Phase:

Adrenal Phase: 1
Being ‘Stressed Out’
Allostatic Overload

The wear and tear that results from either too much stress or from inefficient management of allostasis, eg, not turning off the response when it is no longer needed (cortisol, sympathetic activity, and proinflammatory cytokines, with a decline in parasympathetic activity).

- Life experiences
- Genetic load
- Individual lifestyle habits (diet, exercise, substance abuse, developmental experiences which set life-long patterns of behavior and physiological reactivity)
Behaviors that signal ‘Allostatic Overload’

Marked by:
• Overeating
• Sleep deprivation
• Other health-damaging behaviors
• Anxious and/or depressed,
• Losing sleep at night,
• Eating comfort foods
• Taking in more calories than our bodies need,
• Smoking, drinking or ‘using’ excessively.
• Neglecting to see friends,
• Neglecting to take time off or
• Quitting regular physical activity
• Staying at a computer far too long
  • to try to get out from under the burden of too much to do.
  • Or to distract and divert from feelings of overload
• Taking medications—anxiolytics, sleep-promoting agents—to help cope
HPA Axis
... *bridges mind and body*...

- Circadian regulation makes it one of the most important and powerful regulators of the body
- Influences and controls nearly every other system in the body
Every Nucleated Cell has Glucocorticoid Receptors

• Only cells in body which are anuclear:
  • RBC
  • and those resulting from flawed cell division
• Hence the widespread effects of cortisol
HPA axis/adrenals

- Regulates
  - Endocrine System
  - Nervous System
  - Sympathetic Nervous System
- Modulates
  - Immune System

HPA axis Initiates and Coordinates Responses to:

- Infection
- Dehydration
- Thermal exposure
- Hemorrhage
- Anticipation
- Fear
Diagnosis Associated With HPA Axis Dysfunction:

- Angina
- Asthma
- Auto-Immune diseases
- Alzheimer's
- Cancer
- Cardiovascular disease syndrome
- Chronic fatigue syndrome
- Common cold
- Depression
- Diabetes (adult onset, type II)
- Fibromyalgia
- Headaches
- Hypertension
- Hormonal imbalances
- Immunosuppression
- Irritable bowel disease
- Inflammatory bowel disease
- Menstrual irregularities
- Premenstrual tension
- Rheumatoid arthritis
- Ulcerative colitis
- Ulcers
**Advanced Learning Objectives**

- Discuss Industry standards and clarify nomenclature for Functional Medicine and Scientific Research (unification)
- Gain an understanding of Allostasis and Allostatic Load (AL).
- Learn advanced information for identifying HPA axis dysfunction and understanding hypocortisolism (hypoadrenia) and childhood adversity
- CORE™ Review; HPA axis concepts and Functional Medicine tenets of adrenal dysfunction.
- Obtain Research Update on salivary testing and adrenal function and assessment.
- Gain advanced treatment protocols which have been shown to correct complex cases.
- Myth Busters for Functional Medicine Clinical Practice on Adrenals
- Identify clinical conundrums and gain clinical pearls for navigating complex cases.
Glossary of Terms associated with Functional Adrenal Gland Assessment and Treatment

- **CAR** - Cortisol Awakening Response - 30 minutes after awakening (the most sensitive response to ACTH for the next 24-hours)
- **HPA Axis** - The Hypothalamus, Pituitary Adrenal Axis
- **HPA Axis Dysfunction** - blunting or over reaction to ACTH stimulation
- **Adrenal Fatigue** - (slang) functional medicine concept which originally connoted blunted ACTH sensitivity resulting lack of responsiveness
- **Flatliner** - (slang) Flat diurnal graph due to multiple factors which have reduced the HPA axis sensitivity to ACTH stimulation (blunted response)
- **Hypocortisolism** - Due to HPA Axis Dysfunction, there is a blunted or lack of responsiveness and little or no cortisol synthesis and secretion ensue with stimulation from ACTH
- **Allostasis** - maintains homeostasis - achieving stability through change
- **Allostatic Load** - Chronically increased Allostasis leads to maladaptive responses throughout the body which result over-loading” and exceeding the body’s capacity to maintain physiologic resilience resulting in disease
Hypocortisolism

- Hypocortisolism is an important yet incompletely understood maladaptive consequence of chronic stress exposure and HPA axis dysfunction. A clinically integrative approach is necessary to identify hypocortisolism as the primary clinical aberration rather than to promote “adrenal fatigue” as the all-encompassing mold into which all forms of low-cortisol states must fit....
Theories on pathophysiology in the evolution of Hypocortisolism

• Developmental
• CRF (corticotrophin –releasing Factor Receptor Down-regulation
• Inadequate Glucocorticoid signaling
• Intrinsic Adrenal Gland Dysfunction
• Adaptive Response
Developmental pathophysiology for the evolution of hypocortisolism

- Hellhammer and Wade
- Propose a model whereby hypocortisolism may develop via hypoactivity of the HPA axis after prolonged period of chronic stress. (after an initial period of hyperactivity and hypersecretion, hypocortisolism may develop as a type of maladaptive “overcompensation” of the self-preservation mechanisms designed to protect metabolic machinery (specifically the brain) from the ill effects of persistent cortisol elevation
Chronic psychological stress and consequent physiological dysregulation are catalysts of accelerated aging and agitators of disease trajectories

- Individual differences in the brain’s interpretations of the body’s reactions to stressors are nevertheless the ultimate determinants of either vulnerability towards or resilience against stress related diseases.

- “stress to the majority of us – most of the time – is not due to external stimuli but to the pressure of our own suppressed emotions...these suppressed emotions become the primary stressor so that even in a calm external environment we are still subject to chronic internal stress”

Primitive Brain

am I safe or am I in danger?
Times Have Changed...
WE are Changing
Healthy Responsiveness to Stressors

- **Allostasis**: active process by which the body responds to daily events and maintains homeostasis-achieving stability through change

- Chronically increased Allostasis will lead to maladaptive responses throughout the body which result in a “stretching or over-loading” beyond the body’s capacity to maintain physiologic resilience

- resulting in disease (allostatic load-AL)

Equanimity or Overload?
So how does Hypocortisolism (ICD-10 E27.9) happen? And why do we (Functional Medicine Practitioners) see so much of it?

Childhood Adversity
Hypocortisolism

• Maternal separation within the first few days of birth induced permanent increased sensitivity of the adrenal cortex to ACTH.

• In adults without diagnosable psychopathology, childhood maltreatment is associated with diminished HPA axis response to a psychosocial stressor.

• Women reporting childhood physical abuse displayed a significantly blunted cortisol response to the stress test compared with subjects without PA

Early Environment Affects Neuroendocrine Regulation in Adulthood

Data show: The size of the cortisol response diminished as the number of lifetime adverse events increased

• ...healthy adults show reduced cortisol stress reactivity when reporting early life adverse experiences
• ...study found blunted HPA Axis reactivity in 12-16 yr old girls exposed to childhood maltreatments
• exposure to childhood trauma seemed to be related to a blunted HPA-axis reactivity in women who were free of current or lifetime psychopathology.
• women with a history of childhood abuse may hypersecrete CRF, resulting in down-regulation of adenohypophyseal CRF receptors and result in symptoms of depression and anxiety
• *These findings provide further support for hypothalamic-pituitary-adrenal axis dysregulation among maltreated youth.*
Early Environment Affects Neuroendocrine Regulation in Adulthood: references


HPA Axis Responsiveness and Diurnal Cortisol Curve:
Four types of allostatic load. The top panel illustrates the normal allostatic response, in which a response is initiated by a stressor, sustained for an appropriate interval, and then turned off. The remaining panels illustrate four conditions that lead to allostatic load:

top left- **repeated “hits”** from multiple stressors; top right- **lack of adaptation**; bottom left- prolonged response due to delayed shut down; and bottom right - inadequate response that leads to compensatory hyperactivity of other mediators (eg, inadequate secretion of glucocorticoid, resulting in increased levels of cytokines that are normally counter-regulated by glucocorticoids).
Protective factors insulating against Allostatic load:

• Parental bonding
• Education
• Social support
• Healthy workplaces
• Sense of meaning

are available or manifest at different time points throughout lifespan development, and yet they each have the capacity to promote life-long resiliency against AL.

Is diminished (HPA) responsiveness to stress a bad thing?

Evidence exists implicating hypocortisolism in disease (physiologic and psychologic) development:

- Causing increased pro inflammatory cytokines
- Immune system activation
- Loss of counter regulation by normal glucocorticoid activity

It is **wrongly assumed** that larger responses to stress are worse for health outcomes than smaller responses to stress

- ...a systems dysregulation has the worst potential health consequences...

- And small stress responsiveness has both autonomic and endocrine indicators which are characteristic of persons at high risk for disease

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Pro Inflammatory Cytokines

- Tumor necrosis alpha interleukin-6 (IL-6)
  - Suppresses lymphocyte function
  - Disrupts T-cell signaling
  - Inhibits natural killer cell activity
Chronic Disease States

Are ultimately caused by harmful signals that overwhelm the tissues ability to self-heal or the absence of signals disallow tissue recovery.
(Early) Clinical Manifestations of Hypocortisolism

- Fatigue
- High stress sensitivity
- Chronic fatigue
- Chronic pain
- Functional bowel disturbances (IBS)
- Major depression

Consequences of Chronic Inflammatory Pathway Up-regulation Due to Hypocortisolism

- Chronic Fatigue Syndrome
- Fibromyalgia
- IBD
- Autoimmune diseases
- Cancer
- Chronic Pain
- Atopy
- Insulin Resistance
- Asthma
- PTSD
- Mood disorders
- Major Depression
- Alzheimer’s disease
- Cognitive impairment of Aging
- Gulf War Illness

Coping with Allostatic Overload
Food and Screens

• Americans spend 11 hours and 52 minutes with media a day


www.marketer.com
Chronic Stress Causes Structural Remodeling to Alter Behavioral and Physiologic Responses

Brain regions such as the hippocampus, amygdala, and prefrontal cortex respond to acute and chronic stress

Chronic stress leads to blunting of Memory, Mood and Cognitive Ability

- Structural and functional imaging reveals **smaller hippocampal** volume in stress-related conditions
- Mild cognitive impairment in aging
- Prolonged major depressive illness
- Increased low self esteem.

...*regulating emotion, memory (particularly long term memory and spatial navigation)

Fight, Flight Or Freeze

- Increased heart rate and force of contraction and blood pressure
- Increased respiration rate increases the rate and depth of breathing and dilates the bronchioles to allow faster movement of air in and out of the lungs
- Paling or flushing (alternating) constricts the blood vessels of nonessential organs such as the skin
- Inhibition of digestion slows down or event stops processes that are not essential for meeting the stress situation, such as muscular movements of the gastrointestinal tract and digestive secretions
- Decreased immunity
- Constriction of blood vessels to periphery
- Dilation of blood vessels to skeletal muscles, cardiac muscle, liver, and adipose tissue
- Inhibition of lacrimal and salivary glands
- Dilation of pupil (mydriasis)
- Relaxation of bladder
- Inhibition of erectile function
- Hearing loss
- Tunnel vision
- Increased availability of glucose through increased gluconeogenesis (raises blood sugar as the liver glycogen is converted to glucose)

Sensory Input...Stimuli...Stressor
Stressor Can Be Beneficial Or Negative

Engaging in a memory task activated the immune system

Passively watching a violent video weakens immunity

Stress

• Stress can dramatically increase the ability of exogenous chemicals to pass through the blood-brain barrier. During the Gulf War, Israeli soldiers took a drug to protect themselves from chemical and biological weapons. Normally, it is not expected to cross the BBB, but scientists observed that with the stress of war—had somehow increased the permeability of the BBB...

• Nearly one-quarter of the soldiers complained of headaches, nausea, and dizziness – symptoms which occur only if the drug reaches the brain.

ICD-10 considerations for hypocortisolism

- E27.49 Glucocorticoid deficiency. Insensitivity to ACTH.
- R53.83 Other fatigue
- R53.82 Chronic fatigue longer than 6 months
Review of Key concepts Regarding Stages of Adrenal Development

- Fetal adrenal gland
- Adrenarche
- Adult adrenal gland
- Adrenopause
- These stages of adrenal development refer almost entirely to only one zone of the adrenal glands: 
  
  **Zona Reticularis**

- The other zones maintain the same functions throughout life, while the function and secretion of the zona reticularis changes.
Zones of the Adrenal Gland

Figure 2: Adrenal Gland Cross Sections

Transverse Section

Microscopic Section

Capsule
Cortex
Medulla

Capsule
Zona Glomerulosa
Zona Fasciculata
Zona Reticularis
Medulla
Fetal adrenal gland function

The role of the fetal adrenal gland is to maintain pregnancy. In order for the fetal adrenal gland to maintain pregnancy large amounts of estrogen are needed. Almost all of the estrogen is converted by the placenta from DHEA made in the fetal adrenal glands.

Over 200 X the amount of DHEA we make as adults.

Cortisol Awakening Response

![Graph showing cortisol levels following awakening.

- X-axis: Time post awakening (minutes)
- Y-axis: Cortisol (nmol/L)
- The graph displays a characteristic increase and subsequent decrease in cortisol levels over time.

Labrix Clinical Services, 2008
SCN-Suprachiasmatic Nucleus

- Sunlight is responsible for regular diurnal rhythm...secretion of CRH, AVP ACTH and ultimately glucocorticoids
- Sunlight also regulates the sensitivity of the adrenal cortex to ACTH (via the SCN)
# Phases of adrenal gland fatigue

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<th>Phase 0</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
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<tr>
<td>Healthy adrenal response&lt;br&gt;(Cortisol levels within range with desired rhythm)</td>
<td>Acute fight or flight&lt;br&gt;(Increased HPA tone)</td>
<td>HPA axis dysfunction&lt;br&gt;(Zig Zag patterns)</td>
<td>Established adrenal fatigue /Hypoadrenia&lt;br&gt;(Hypofunctioning HPA axis)</td>
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<tr>
<td>Early adrenal fatigue&lt;br&gt;(Elevated/high range AM with HPA blunting thereafter)</td>
<td>Evolving adrenal fatigue&lt;br&gt;(Suboptimal or low AM cortisol with HPA blunting thereafter)</td>
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Bio-identical Cortisol AKA Hydrocortisone

3 options:
- Rx
- Compounded cortisol
- Glandular – standardized
Glandular Hydrocortisone

• Not standardized cortisol in most preparations
• Other constituents in these preparation may change metabolism etc.
• Popular brand no longer available
Metabolism Of Cortisol

- Short half-life: 8 to 12 hours
  - Cortisone
  - Cortisol

- Cortisol is metabolized in most tissues, but primarily in the liver to biologically inactive compounds. The half-life of cortisol may be prolonged in patients with hypothyroidism.

- Inactive metabolites are excreted by the kidneys. Negligible amounts are excreted in bile.
Potency Comparisons

• 0.5mg of dexamethasone = 15mg cortisol
• In a dexamethasone suppression test usually 1mg of dex is given orally (i.e, 30mg cortisol).
• 5 mg prednisone = 20mg cortisol
• A normal starting dose of prednisone is between 5-60mg/day.
• Multiple Sclerosis treatment starts at 200mg/day and tapers to 80mg/day.

<table>
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<th>Cortisol (hydrocortisone)</th>
<th>Prednisone</th>
<th>Dexamethasone</th>
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<tr>
<td>20 mg</td>
<td>5 mg</td>
<td>0.75 mg</td>
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Physiologic Vs. Pharmacologic
Safe Uses Of Cortisol

Low dose physiological cortisol supplementation does not produce signs or symptoms of glucocorticoid excess and has not been shown to cause clinically significant adrenal suppression. **20 mg** of oral hydrocortisone has far less glucocorticoid effect on bone for example, than 5mg of prednisone. Studies have shown that 10mg and 40mg of hydrocortisone, the amount increases depending upon body weight does not cause bone loss, suppression of immune system, weight gain, elevated blood sugar, elevated blood pressure thinning skin, easy bruising or suppression of endogenous cortisol production.

Use of Physiologic Cortisol References


• Tablets are available for oral administration in three strengths; each tablet contains either 5 mg, 10 mg, or 20 mg of cortisol.
  • Inactive ingredients: calcium stearate, corn starch, lactose, mineral oil, sorbic acid, sucrose.
Compounded Cortisol

• Cortisol can be compounded into any dose you choose.

• Especially when giving the patient doses different than 5 mg, 10 mg or 20 mg.

• Can have regular release and sustained release blend (70:30 ratio – 70% reg. cortisol: 30% slow release agent).
Novel Strategies for Hydrocortisone Replacement

• Best Practice & Research Clinical Endocrinology & Metabolism Volume 23, Issue 2, Pages 221-232, April 2009

• M. Debono, MRCP (Academic Clinical Fellow Endocrinology)

• J. Newell Price, MA, PhD, FRCP (Senior Lecturer in Endocrinology and Honorary Consultant Physician)

• Richard J. Ross, MD, FRCP (Head of Section Endocrinology and Reproduction, and Professor of Endocrinology)

• Academic Unit of Diabetes, Endocrinology & Metabolism, School of Medicine, Royal Hallamshire Hospital, Glossop Road, Sheffield S10 2JF, UK

• Current therapy with immediate-release hydrocortisone is the most commonly used regimen for replacement in patients with primary and secondary adrenal insufficiency. However, conventional hydrocortisone cannot provide the physiological rhythm of cortisol release. Physicians have used fixed twice- or thrice-daily doses, but these regimens inevitably result in temporary over- or under-replacement. Patients with adrenal insufficiency, although on treatment, have a poor quality of life and an increased mortality. Optimization of current treatment has been attempted with thrice-daily, weight-related dosing, but this still fails to simulate the normal diurnal rhythm of cortisol. Recent research has investigated circadian hydrocortisone therapy imitating the physiological cortisol rhythm. Proof-of-concept studies using hydrocortisone infusions predict improvements in biochemical control and quality of life. Now delayed and sustained release oral formulations of hydrocortisone are being developed, and these offer a more practical and effective solution for patients with adrenal insufficiency and congenital adrenal hyperplasia.
Flat Liners and Other Symptoms

- People who report more nocturnal awakenings had flatter slopes.
- Low morning cortisol means higher levels of fatigue and physical symptoms later that day. (Adam et al. 2006)
- Marital disruption is associated with flatter slopes.

Hypothalamo-pituitary-adrenal axis dysfunction in chronic fatigue syndrome, and the effects of low-dose hydrocortisone therapy.

• Evidence supports previous findings of impaired adrenal cortical responsivity in CFS.
• Low-dose hydrocortisone supplementation is able to increase the overall cortisol throughout, suggesting that there is not (over 28 d) a compensatory switching off of endogenous cortisol production.
• Those who responded to treatment, had a significant decrease in fatigue as compared to normal population levels, – there was a corresponding normalization of the blunted cortisol response to hCRH challenge.

Cortisol and chronic fatigue syndrome

• There is a strong association between chronic fatigue and low cortisol levels.
• Cortisol has been shown to be effective at relieving many of the symptoms of chronic fatigue including pain relief and significant improvement in fatigue.
• Studies indicate patients do best with 5-10mg of cortisol every morning (not exceeding 10mg). (Cleare, 2003)

Flat Line Cortisol And Metastatic Breast Cancer Survival

Patients with relatively flat cortisol slopes experienced shorter subsequent survival. 77% of those with flat rhythms died, after surviving an average of 3.2 years. In contrast, 60% of the patients with relatively steep rhythms died, but they survived more than 1 year longer on average, with an average survival of 4.5 years.

Cortisol and rheumatoid arthritis

• Rheumatoid arthritis (RA) is associated with low cortisol levels
• People with RA often talk about their symptoms of pain being worse in the morning and improving as the day goes on
• The flattening of their circadian rhythm is thought to play a role in the disease
• Low dose cortisol therapy helps symptomatically with RA and may improve its progression of the disease

Zig Zag Pattern

- In this situation the cells that secrete CRH become less sensitive to cortisol later in the day rather than early in the morning.
- It is seen more often in individuals with depression. Depressed individuals exhibit increased cortisol secretion in the afternoon.
- Elevated evening cortisol levels are often seen in people with financial difficulties and unemployed individuals.
- It can lead to a change in the sleep wake cycle. People will have difficulty settling down and falling asleep at night and then have trouble waking up in the morning. wired and tired syndrome
Monitoring Levels

• Monitor patients on cortisol via four salivary cortisol levels collected throughout the day 1-3 months after starting.
• Patients can be instructed to dose as usual the day of testing to monitor cortisol therapy.
• Discontinue supplementation for 4-5 days prior to testing to assess endogenous levels.
Saliva Testing Bibliography for Cortisol


Treatment

• Cortisol
• DHEA
• Amino Acids
• Melatonin
• Vitamins and Minerals
• Adaptogens
## Adrenal Treatment Guidelines

| Phase 0 | • Multivitamin / Multi mineral  
• Omega 3 EFAs  
• Consider vitamin D, iodine and probiotics |
|---|---|
| Phase 1 | • Phosphorylated serine 100mg TID or at times when elevated  
• Vitamins B5 (500mg), C (1000mg) TID; B6 (100mg) BID; E (800 i.u.) QD  
• Melatonin (3mg) qhs if cortisol levels elevated at night  
• Lifestyle modification: deep breathing, stress management, exercise, optimal diet, etc. |
| Phase 2 | • Vitamins B5 (500mg), C (1000mg) TID; B6 (100mg) BID; E (800 i.u.) QD  
• Adrenal glandular and/or herbal adaptogens in morning and at noon  
• Lifestyle modification: deep breathing, stress management, exercise, optimal diet, etc. |
| Phase 3 | • Vitamins B5 (500mg), C (1000mg) TID; B6 (100mg) BID; E (800 i.u.) QD  
• Adrenal glandular and/or herbal adaptogens in morning and at noon.  
• Cortef or hydrocortisone supplementation 5-10mg in AM and 5-10mg at noon  
• Lifestyle modification: deep breathing, stress management, exercise, optimal diet, etc. |
Hydrocortisone

- Mimic the diurnal rhythm for timing of prescription
  - Most often upon arising (within 30 minutes) and 4 hours later (before noon or lunch time)

- Dosing should never exceed what the body would be making naturally when in optimal health—general consensus is 20 mg (total maximum)

- But commonly my Rx is 5-10 mg morning and 5 mg noon
DHEA

• The amount of DHEA needed to bring a male with Addison’s disease into normal physiological range is 50-70 mg
• If you are following physiological (not replacement) doses you would most likely not exceed:
  • Males – 15-50 mg/day
  • Females – 5-25mg/day
• Starting place: 10 mg for males and 5 mg for females.

DHEA

• It can be delivered:
  • Orally
  • Sublingually
  • Topically
  • All work well

• Pearl: When DHEA is put into a compounded transdermal Prescription with other hormones such as progesterone and biest, DHEA may “out compete” the receptors and progesterone especially will not be absorbed.
DHEA Supplementing decisions

• Contraindicated In Children

• Remember children’s adrenal glands have a zone in the cortex that is at rest (zona reticularis),

• Hence children will have not produced DHEA and one would never supplement a child-since DHEA can promote early puberty and would cause the epiphyseal plates to fuse ...which can lead to reduced height.
Melatonin

- Melatonin is naturally synthesized in the **pineal gland** from the amino acid tryptophan (derived from serotonin) by the enzyme 5-hydroxyindole-O-methyltransferase.
- Melatonin is also manufactured by the retina, lens and gastrointestinal tract.
- Melatonin has a variety of functions in the body, including regulating sleep (inducing tiredness prior to sleep), boosting the immune system, and as a powerful anti-oxidant.
Melatonin – 1-6 mg nightly*

• Regulates circadian rhythm and induces sleep.
• Cushing's syndrome was shown to have significantly lower levels compared to healthy control groups.
• Studies also have shown that nightly administration of 2mg of melatonin have supported adrenal recovery after 6 months of administration

**Vitamin C – 1000 mg tid**

- Of all the vitamins and minerals involved in adrenal metabolism, vitamin C is probably the most important. In fact, the more cortisol made, the more vitamin C used. Vitamin C is so essential to the adrenal hormone cascade and the manufacture of adrenal steroid hormones.

- Studies show that vitamin C can attenuate and influence cortisol, inducing an anti-inflammatory response to prolonged exercise and stress. Vitamin C has been shown to reduce the elevation of cortisol in response to heavy exercise. In human studies, 3000mg of vitamin C daily mitigated a rise in blood pressure, cortisol, and subjective response to acute psychological stress.

B5-Pantothenic Acid – 500 mg tid

- (Co-A)the basis for the production of hemoglobin, bile, sex and adrenal steroids, cholesterol, and other brain chemicals and neurotransmitters

- **Pantothenic acid deficiency results in adrenal insufficiency**, which is characterized by fatigue, headache, sleep disturbances, nausea, and abdominal discomfort

Pantothenic Acid And Pantethine, Michael Lam, MD, MPH (Tarasov et al. 1985; Smith et al. 1996; Murray et al. 1997).
Vitamin B6 – 50 mg tid

B6 (pyridoxine) is also a coenzyme in several of the biochemical pathways in the adrenal cascade and plays a role in the functioning of the hypothalamic/pituitary/adrenal (HPA) axis that modulates adrenal activity and the stress response.
Vitamin E – 400 iu
Mixed Tocopherols supplement specifically one high in beta-tocopherols

• Absorbs and neutralizes these damaging free radical molecules inside the adrenal glands (vitamin C enhances vitamin E’s activity inside the cell by regenerating the capacity of vitamin E to sequester the free radicals).

• Works hand in hand with vitamin C to keep the adrenal cascade functioning.

• High amounts of vitamin E are necessary in order for the adrenals to maintain high levels of steroid production and recover adequately.

Adaptogens
Have a normalizing effect on the body and are capable of either toning down or strengthening the activity of hyper and hypo functioning systems.

- Antioxidant activity
- Improved blood-sugar metabolism
- Less craving for alcohol or sugar
- Improved immune resistance
- Increased energy and stamina
- Improved muscle tone
- Better motivation and productivity
- Liver protection and antitoxin activity

- Increased strength
- Faster recovery
- Better focus and concentration
- Less anxiety
- Better sleep
- A feeling of well-being
- Better moods
Rhodiola – 50 to 200mg per day

- Diminishes fatigue
- Improves attention span
- Improves memory
- Makes workers “more productive”.
- Increases the capacity for mental/cognitive work
- Enhances permeability of the blood-brain barrier to dopamine and serotonin.

Siberian Ginseng – 
(Eleutherococcus senticosus) 
500-3000mg/day

• The mechanism of the anti-stress or adaptogenic activities of Radix Eleutherococci appears to be threefold.
  • Extracts of the roots have an adaptogenic effect that produces a nonspecific increase in the body’s defense against exogenous stress factors and noxious chemicals.
  • The roots also stimulate the immune system.
  • and promote an overall improvement in physical and mental performance."
Siberian Ginseng
(Eleutherococcus senticosus)

- A large study reviewed the results of a number of clinical trials involving 2,100 healthy men and women ages 19 to 72. Subjects were given doses of ginseng ranging from 2 to 16 ml of fluid extract, 33 percent ethanol, from one to three times daily for up to 60 days. Subjects had increased mental alertness and work output, enhanced athletic performance and improved work quality. They also exhibited an improved ability to withstand adverse conditions such as heat, noise, increases in workload and physical exertion.

Medicinal plants in therapy. Norman R. Farnsworth, Olayiwola Akerele, Audrey S. Bingel, Djaja D. Soejarto, and Zhengang Guo
Asian Ginseng (Panax Ginseng) 100-200 mg/day

- Effective at improving a person’s ability to withstand stress:
  - Improved work performance and quality
  - Enhances mental function
  - Increases the release of adrenocorticotropic hormone (ACTH), which stimulates an increase in adrenal hormone secretion
- Counteracts the shrinkage of the adrenal gland caused by corticosteroid drugs

Ashwaganda – Up to 35 mg /day

• Immuno-modulating
• Modifies anxiety and other psychological complaints.
• When cortisol is too high, it lowers it, and if it is too low, it raises it.


www.smart-publications.com
Wilson, James. Adrenal Fatigue.
Licorice Root (Glycyrrhiza glabra) no more than 1000 mg of glycyrrhizin

- Promotes or enhances immune system function
- Stimulates the adrenal cortex
- Inhibits the breakdown of adrenal hormone by the liver, thereby increasing corticosteroid levels in circulation
- Inhibits cortisol's ability to promote thymus atrophy

5 HTP for Adrenals

- 50-100 mg
Phosphorylated Serine

• 100 mg up to 3 times per day corresponding with elevated cortisol.

• ONLY Use for 1-3 months


Adrenal summary

- Optimal Adrenal function is the foundation for endocrine hormone balancing
- Because on intake, symptoms of adrenal dysfunction “sound” alike in patients (“I’m tired”) – testing is mandatory for individualization and success of treatment (Salivary testing of four (or five) timed cortisols and DHEA levels will direct and define treatment)
- The adrenals are resilient and will usually re-calibrate and return individuals to optimal functioning (if possible)* with correct diagnosis and treatment within 6 months – 2 years
Clinical Pearls And Pitfalls

• No direct feedback between zona fasciculata and zona reticularis—treat each zone as if separate gland...
• Treat the ‘pathway’ as well as the level
• Treat HPA dysfunction first...then may need to treat Hypoadrenia if present
• Melatonin, phosphorylated serine and even DHEA, can be used to quiet HPA dysfunction
• ACTH is preferentially stimulating increased androgen secretion (rather than cortisol) in some women with metabolic syndrome and PCOS
Adrenal

1. Adrenal “fatigue”
2. Pregnenolone “Steal”
3. DHEA/Cortisol ratio
4. DHEA supplementation does NOT increase cortisol levels!
Adrenal Fatigue: *The adrenals are not fatigued!!*

The HPA axis has adapted as a result of chronic stressors, traumatic stressors and or perception of heightened stress.
Pregnenolone Steal

unfounded
DHEA/Cortisol Ratio-no basis for it physiologically because of anatomical separation of adrenal compartments and other regulators for synthesis and release of androgens/DHEA.

• Hyperinsulinemia in PCOS and metabolic syndrome...
Treating low cortisol with DHEA

No feedback loop between zona reticularis and zona fasiculata...treat as separate zones to modify and recalibrate HPA axis
DHEA supplementation does NOT increase cortisol levels!

DHEA will not increase cortisol levels, it will not strengthen the area of the adrenal glands that makes cortisol (zona fasciculata) and it will not exert a negative feedback on the HP axis.
Show me a day when the world was not new

Barbara Hence
RESEARCH UPDATE

salivary testing

The proof... is in the proof
Testing HPA Axis Function

- Salivary Testing
- 1983:
Salivary cortisol, brain volumes, and cognition in community-dwelling elderly without dementia

• Stress hormone levels in saliva could pinpoint seniors with cognitive decline
• Older adults with high cortisol levels in their saliva had smaller brain volume and poorer memory and thinking skills than those with low levels of the hormone.
• A new study claims testing the saliva of healthy seniors could help identify those who are at risk for cognitive decline.
• Study co-author Dr. Lenore J. Launer, of the National Institute on Aging - a part of the National Institutes of Health - and colleagues believe their findings could lead to a saliva test that helps determine which individuals may be at risk of Alzheimer's disease and other dementias, as well as strategies that may reduce cortisol's potential negative impact on cognitive function.

Launer LJ et al., Salivary cortisol, brain volumes, and cognition in community-dwelling elderly without dementia, Neurology. 2015 Sep 15;85(11):976-83
Distribution characteristics of salivary cortisol measurements in a healthy young male population

BACKGROUND:

• Salivary cortisol has been used in various fields of science as a non-invasive biomarker of stress levels. This study offers the normative reference values of cortisol measurement for healthy young males.

FINDINGS:

• Salivary cortisol levels were measured in 267 healthy young males (age: 21.7 ± 1.5 years) in the early morning on two consecutive days and were analyzed by radioimmunoassay. Frequency distribution analysis was conducted with mean values of the measurements taken on the 2 days. The mean salivary cortisol level was 20.39 ± 7.74 nmol/l (median: 19.31 nmol/l). The skewness and kurtosis of the distribution of the raw data were 0.72 and 0.68, respectively. They were both improved by a square root transformation but not by a logarithmic transformation.

CONCLUSIONS:

• The skewness of the distribution for salivary cortisol measured in the early morning is considerably smaller than that previously reported from afternoon measurements. A "floor effect" may be an explanation for the difference in the distribution characteristics of salivary cortisol.

Salivary and serum cortisol levels during recovery from intense exercise and prolonged, moderate exercise.

The aim of this study was to compare serum (SERc) and salivary cortisol (SALc) responses during recovery from two different exhaustive exercises to determine peak cortisol sampling time and the agreement between SERc and SALc levels. Twelve healthy men underwent a maximal treadmill graded exercise to exhaustion (MEx) and a prolonged, submaximal cycle exercise in the heat for 90 min (PEx) while SERc and SALc samples were taken in parallel at baseline, end of exercise, and 15 min intervals over one hour of recovery. MEx and PEx significantly increased SERc and SALc levels (p < 0.01) while absolute SERc levels were approximately 7-10 folds higher than SALc. SERc and SALc showed highly positive correlation (R = 0.667-0.910, p < 0.05) at most sampling times and only a few individual values were out of 95% limit of agreement when analyzed by Bland-Altman plots. However, peak SERc levels (MEx: 784.0±147, PEx: 705.5±212.0 nmol · L(-1)) occurred at 15 min of recovery, whereas peak SALc levels (MEx: 102.7±46.4, PEx: 95.7±40.9 nmol · L(-1)) were achieved at the end of exercise in MEx and PEx. The recovery trend of SERc and SALc also differed following MEx and PEx. Activity of 11β-hydroxysteroid dehydrogenase type 2 enzymes may be suppressed following MEx compared to PEx. In conclusion, sampling for peak SERc and SALc levels should take into account their evolution and clearance characteristics as well as type of exercise performed, whereas SALc appeared to be a more sensitive marker than SERc for the measurement of cortisol responses during exercise recovery.

Age and the metabolic syndrome affect salivary cortisol rhythm: data from a community sample

Measurement of cortisol levels in saliva is a marker of free hormone. How salivary cortisol rhythm is affected by age, gender, the metabolic syndrome and estrogen-progestin therapy was evaluated in a community sample of adults.

SUBJECTS AND METHODS:

- One hundred twenty volunteers recruited from the Hospital staff and family members of the Endocrinology Unit were instructed to collect 7 salivary samples: the first on awakening (F(0)) and 6 more (F(1.5), F(5), F(6), F(10), F(11.5) and F(14)) over the next 14 hours. Each volunteer also underwent a complete physical evaluation and a comprehensive medical history was taken. Salivary cortisol was measured using a radioimmunometric assay. Daily cortisol secretion was evaluated computing the Area Under the Curve (AUC(F0)(→)(F14)); the F(14)/F(0) ratio was calculated as a marker of cortisol rhythm.

RESULTS:

- Median F(14) levels were higher in the subjects in the third tertile of age than in those falling in the second or in the first age tertile (respectively, 2.09 vs 1.33 vs 1.25 ng/mL, p=0.023 and p=0.006), in the hypertensive volunteers (2.44 vs 1.44 ng/mL, p=0.030) and in those with the metabolic syndrome (2.95 vs 1.4 ng/mL, p=0.002), with an elevated median F(14)/F(0) ratio (0.48 vs 0.19, p=0.006). According to the Kruskal-Wallis analysis of variance, the most important factor affecting F(14) value was age (p=0.001). AUC(F0)(→)(F14) was not influenced by gender, age, metabolic syndrome or estrogen-progestin therapy.

CONCLUSIONS:

- While it did not affect the daily cortisol rate, late-night salivary cortisol levels were found to be increased in the subjects in the higher age tertile and in those with the metabolic syndrome.

Measurement of salivary cortisol level for the diagnosis of critical illness-related corticosteroid insufficiency in children

• To compare serum total, serum free and salivary cortisol in critically ill children- We enrolled 59 patients (4 weeks to 18 years of age) between January 2012 and May 2013. Thirty-four patients were included in the salivary to serum free cortisol correlational analysis.

• Serum free and salivary cortisol values correlate in critically ill children. Salivary cortisol can be used as a surrogate for serum free cortisol in critically ill pediatric patients. Salivary cortisol is a cost-effective and less invasive measure of bioavailable cortisol and offers an alternate and accurate method for assessing critical illness-related corticosteroid insufficiency in children.

The relation of the cortisol awakening response and prospective memory functioning in young children.

Abstract

Recent research suggests that the cortisol awakening response (CAR) is linked to cognitive functions depending on hippocampal and frontal cortex circuits and may possibly be modulated by prospective memory (PM). However, the link between the CAR and PM abilities has not been investigated so far. Addressing this open issue, we report data from 97 children aged 37-87 months. Salivary cortisol levels were assessed 0 and 30 min post-awakening over three study days. Thereby a valid CAR measurement was ensured by using objective measures of awakening and sampling times. A game-like task served as behavioral measure of PM performance. Bayesian analysis revealed a positive association between children's PM performance and the CAR, with better PM performance being related to a greater CAR. This association persisted after controlling for age. Overall, the current finding supports the prediction that PM functioning may be linked to the CAR, possibly as both the CAR and PM rely on a common neurophysiological basis.

Acute and chronic stress increase salivary cortisol: a study in the real-life setting of a national examination undertaken by medical graduates

Spanish medical graduates who apply for a medical specialty training position (MIR) must take an examination that will shape their future personal and professional lives. Preparation for the test represents an important stressor that persists for several months. The aim of this study was to elucidate the stress pattern of this group and evaluate possible changes in the circadian rhythm of cortisol release in medical graduates preparing for this test. A repeated-measures longitudinal study was performed, measuring the salivary cortisol concentrations in 36 medical graduates (13 males and 23 females; mean age of 24.2 years) on five sampling days. Five cortisol samples were collected from 07:00 to 21:00 h in order to monitor changes in the circadian rhythm. On all sampling days (except on the day of the official examination), anxiety and psychological stress were evaluated with the Spanish versions of the State-Trait Anxiety Inventory (STAI) and the Perceived Stress Scale (PSS). During the study period, participants showed higher levels of anxiety than the Spanish reference population as well as a progressive increase in self-perceived stress. A significant increase in salivary cortisol concentration was observed in both chronic (study and examination preparation) and acute (examinations) situations. Our results suggest that the cortisol awakening response (CAR) may be a good indicator of anticipatory stress but is unaffected by long-term examination preparation. Comparison of results between the official examination day and the mock examination days yielded evidence that learning may modulate the behavior of the hypothalamic-pituitary-adrenal axis.

Reassessing the reliability of the salivary cortisol for the diagnosis of Cushing syndrome.

• The cortisol concentration in saliva is 10-fold lower than total serum cortisol and accurately reflects the serum concentration, both levels being lowest around midnight. The salivary cortisol assay measures free cortisol and is unaffected by confounding factors. This study analyzed published data on the sensitivity and specificity of salivary cortisol levels in the diagnosis of Cushing syndrome.

• METHODS:
  - Data from studies on the use of different salivary cortisol assay techniques in the diagnosis of Cushing syndrome, published between 1998 and 2012 and retrieved using Ovid MEDLINE®, were analyzed for variance and correlation.

• RESULTS:
  - For the 11 studies analyzed, mean sensitivity and specificity of the salivary cortisol assay were both >90%. Repeated measurements were easily made with this assay, enabling improved diagnostic accuracy in comparison with total serum cortisol measurements.

• CONCLUSIONS:
  - This analysis confirms the reliability of the saliva cortisol assay as pragmatic tool for the accurate diagnosis of Cushing syndrome. With many countries reporting a rising prevalence of metabolic syndrome, diabetes and obesity—in which there is often a high circulating cortisol level—salivary cortisol measurement will help distinguish these states from Cushing syndrome.

An increase in salivary interleukin-6 level following acute psychosocial stress and its biological correlates in healthy young adults.

Although interleukin-6 (IL-6) has been investigated frequently in stress research, knowledge regarding the biological processes of IL-6 in association with psychosocial stress remains incomplete. This study focused on salivary IL-6 and reports its temporal variation and biological correlates following acute psychosocial stress. Fifty healthy young adults (39 male and 11 female students) were subjected to the psychosocial stress test 'Trier Social Stress Test' (TSST), wherein the participants were asked to deliver a speech and perform a mental arithmetic task in front of 2 audiences. Collection of saliva samples, measurement of heart rate, and assessment of negative moods by visual analogue scales were conducted before, during, and after TSST. Salivary IL-6 levels increased by approximately 50% in response to the TSST and remained elevated for 20 min after the stress tasks were completed. Cluster analyses revealed that individuals with sustained elevation of IL-6 levels following the TSST exhibited a lower cortisol response compared to individuals with lower IL-6 levels. In the correlation analyses, a greater IL-6 response was associated with a higher heart rate during the mental arithmetic task (r=.351, p<.05) and with a lower cortisol response (r=-.302, p<.05). This study demonstrates that salivary IL-6 levels are elevated for a relatively long period following acute psychosocial stress, and suggests that sympathetic activity and cortisol secretion are involved in elevation of salivary IL-6 levels.

Performance of salivary cortisol in the diagnosis of Cushing's syndrome, adrenal incidentaloma, and adrenal insufficiency

- Salivary cortisol has recently been suggested for studies on the hypothalamic-pituitary-adrenal (HPA) axis. The lack of circadian rhythm is a marker of Cushing's syndrome (CS), and some authors have reported that low salivary cortisol levels may be a marker of adrenal insufficiency. The aim of our study was to define the role of salivary cortisol in specific diagnostic settings of HPA axis disease.

SUBJECTS AND METHODS:
- We analyzed morning salivary cortisol (MSC) and late-night salivary CORTISOL (LNSC) levels in 406 SUBJECTS: 52 patients with Cushing’s disease (CD), 13 with ectopic CS, 17 with adrenal CS, 27 with CD in remission (a mean follow-up of 66±39 months), 45 with adrenal incidentaloma, 73 assessed as having CS and then ruled out for endogenous hypercortisolism, 75 with adrenal insufficiency, and 104 healthy subjects.

RESULTS:
- A LNSC value above 5.24 ng/ml differentiated CS patients from controls with high sensitivity (96.3%) and specificity (97.1%); we found higher LNSC levels in ectopic CS patients than in CD patients. We found no difference in MSC and LNSC levels between patients with CD in remission and healthy subjects. Both MSC and LNSC levels were higher in patients with adrenal incidentaloma than in healthy controls. A MSC value below 2.65 ng/ml distinguished patients with adrenal insufficiency from controls with high sensitivity (97.1%) and specificity (93.3%).

CONCLUSIONS:
- Salivary cortisol is a useful tool to assess endogenous cortisol excess or adrenal insufficiency and to evaluate stable CD in remission.

Ageing, depression, anxiety, social support and the diurnal rhythm and awakening response of salivary cortisol.

• Older adults exhibited a significantly reduced awakening response, overall cortisol levels, area under the curve (AUC) and diurnal slopes than younger adults, resulting in a flatter diurnal rhythm. Younger adults with higher depression scores had significantly higher overall cortisol and higher levels upon awakening and 30 min post-awakening. In the younger adults, anxiety and depression correlated positively with AUC and the cortisol awakening response (CAR). Older adults with lower social support had a reduced AUC where younger adults with lower social support displayed a larger AUC. compared the cortisol awakening response and diurnal rhythm in 24 young healthy students and 48 community-dwelling older adults.

• These findings suggest that the diurnal rhythm and awakening response of salivary cortisol are significantly reduced in older adults and the associations between anxiety, depression and social support and diurnal cortisol vary with age.

Conclusions This large cohort study shows significant, although modest, associations between MDD and specific hypothalamic-pituitary-adrenal axis indicators. Because a higher cortisol awakening response was observed among both subjects with current MDD and subjects with remitted MDD, this may be indicative of an increased biological vulnerability for depression.

Higher cortisol levels have most frequently been reported among medicated inpatients with more severe melancholic or psychotic depression,25,26 that the dynamic of the CAR as well as total cortisol secretion is increased in subjects with MDD compared with control subjects.31,33

our study found significant differences in HPA axis activity indicators among depressed subjects when compared with healthy control subjects.

Diagnosis of secondary adrenal insufficiency in patients with hypothalamic-pituitary disease: comparison between serum and salivary cortisol during the high-dose short synacthen test.

Conclusion: We suggest the determination of basal SeC or SaC as first-line test. In comparison to the ITT, the HDT has only limited value in screening for alterations of the HPA axis. If the HDT is performed, sampling may be limited to 30 min post-synacthen, using either SeC or SaC. Due to the ease of collection and the independence of binding proteins, Salivary Cortisol may be preferable.

Advantage of salivary cortisol measurements in the diagnosis of glucocorticoid related disorders.

Morning salivary cortisol is as good as serum as screening test for patients with Addison's disease and nighttime salivary cortisol is more accurate than serum in the screening of Cushing's syndrome.

Exploration of basal diurnal salivary cortisol profiles in middle-aged adults: associations with sleep quality and metabolic parameters.

The use of saliva samples is a practical and feasible method to explore basal diurnal cortisol profiles in free-living research. This study explores a number of psychological and physiological characteristics in relation to the observed pattern of salivary cortisol activity over a 12-h period with particular emphasis on sleep. Basal diurnal cortisol profiles were examined in a sample of 147 volunteers (mean age 46.21+/7.18 years). Profiles were constructed for each volunteer and explored in terms of the area under the curve (AUC) of the cortisol-awakening response with samples obtained immediately upon waking (0, 15, 30 and 45 min post waking) and at 3, 6, 9 and 12h post waking to assess diurnal decline. Diurnal mean of cortisol was based on the mean of cortisol at time points 3, 6, 9 and 12h post waking. Psychological measures of perceived stress and sleep were collected with concurrent biological assessment of fasting plasma glucose, insulin, blood lipids and inflammatory markers. Blunted cortisol profiles, characterised by a reduced AUC, were observed in the majority (78%) of a middle-aged sample and were associated with significantly poorer sleep quality and significantly greater waist-hip ratio (WHR). Blunted cortisol profiles were further associated with a tendency to exhibit a less favourable metabolic profile. These findings suggest that reduced cortisol secretion post waking may serve as an additional marker of psychological and biological vulnerability to adverse health outcomes in middle-aged adults.

The cortisol awakening response in relation to objective and subjective measures of waking in the morning

Studies of the salivary cortisol awakening response (CAR) may be confounded by delays between waking in the morning and obtaining the 'waking' salivary sample. We used wrist actigraphy to provide objective information about waking time, and studied the influence of delays in taking the waking sample on the CAR. Eighty-three men and women (mean age 61.30 years) who were referred to hospital with suspected coronary artery disease were studied. Saliva samples were obtained on waking and 15 and 30 min later. The mean interval between waking defined by actigraphy and reported waking time was 6.12±(S.D.) 14.8 min, with 55.4% having no delay. The waking saliva sample was obtained an average 5.78±15.0 min after self-reported waking, and 12.24+-20.3 min after objective waking. The waking cortisol value was significantly higher in participants who had a delay between waking and sampling >15 min (mean 14.46+/6.34 nmol/l) than in those with zero (mean 10.45+/6.41 nmol/l) or 1-15 min delays (mean 11.51+/5.99 nmol/l, p=0.043). Cortisol did not increase between 15 and 30 min after waking in those who delayed >15 min. There were no differences in CAR between participants with zero and 1-15 min delays from objectively defined waking to reported sample times. A small proportion (14.7%) of participants who did not delay saliva sampling showed no increase in cortisol over the 30 min after waking. These CAR nonresponders did not differ from the remainder on sleep patterns, waking time, clinical or medication characteristics, but were more likely to be of higher socioeconomic status (p=0.009).

We conclude that long delays between waking and obtaining 'waking' cortisol samples will lead to misleading CAR results, but that delays up to 15 min may not be problematic. A small minority of individuals do not show a positive CAR despite not delaying saliva sampling after waking.

Evidence for altered hypothalamus-pituitary-adrenal axis functioning in systemic hypertension: blunted cortisol response to awakening and lower negative feedback sensitivity

We found evidence for altered HPA axis activity in men with systemic hypertension evident with the CAR. Hypertensives showed relative attenuation in the CAR and in the HPA axis feedback sensitivity following dexamethasone suppression. Such alterations in HPA axis regulation might contribute to the atherosclerotic risk in hypertensive individuals.

Impact of exogenous glucocorticoid use on salivary cortisol measurements among adults with asthma and rhinitis.

The diurnal rhythm of cortisol secretion in chronic disease can reflect the interactions between exogenous and endogenous factors. Exogenous glucocorticoid use may impact salivary cortisol measurements, but this has not been well-studied in ambulatory settings. In this report salivary cortisol levels were used to evaluate aspects of the diurnal rhythm of cortisol secretion within an ambulatory population of patients with asthma and allergic rhinitis. 183 persons with asthma with or without concomitant rhinitis and 34 persons with rhinitis alone were asked to collect at home, two saliva samples, 30 min after awakening and 12h later. The salivary cortisol levels were quantified by enzyme immunoassay. The recent use of glucocorticoids in the study group was determined by interview and direct examination of medications. We report that the median salivary cortisol levels 30 min post-awakening significantly differed by exogenous steroid status: no glucocorticoid use (n = 91), 10.1 nmol/l; nasal glucocorticoid use alone (n = 25), 11.4 nmol/l; inhaled glucocorticoids (with or without concomitant nasal glucocorticoids; n = 76), 9.0 nmol/l; systemic glucocorticoids (n = 17), 4.0 nmol/l; (P = 0.02). 12-h post-awakening salivary cortisol values among the groups were similar (P = 0.85). The median 30-min post-awakening cortisol differed significantly by type and amount of inhaled steroid used: non-fluticasone users (n = 21), 11.5 nmol/l; lower dose fluticasone (<800 microg per day, n = 35); 9.2 nmol/l; and higher dose fluticasone (> or =800 microg, n=20), 5 nmol/l; (P=0.01). We conclude that in an ambulatory setting, exogenous glucocorticoid use can decrease the 30 min post-awakening but not the 12-h post-awakening salivary cortisol levels, an effect that should be taken into account in assessing the effects of other potential determinants on cortisol secretion.

Optimism, positive affectivity, and salivary cortisol.

- Examine the impact of optimism and positive affect on **salivary cortisol** with the effects of their negative counterparts controlled for.

- These findings suggest that positive psychological resources including optimism and generalized positive affect had higher impact on cortisol secretion than their negative counterparts, and point to the need for increased attention to the potential contribution of positive mental states to well-being.

Sleep disturbances are correlated with decreased morning awakening salivary cortisol

Morning and evening salivary cortisol levels were correlated with sleep parameters in 14 patients with primary insomnia and 15 healthy controls. Salivary cortisol was sampled immediately after awakening (T1), 15 min later (T2), and immediately before going to bed (T3) for 1 week at home. In parallel with this, subjects estimated parameters of sleep in a daily sleep log. Patients and controls were all non-smokers who did not differ regarding morning awakening time or bedtime. Cortisol after awakening was significantly decreased in primary insomnia. **Salivary cortisol at the time of awakening correlated negatively with the subjective estimation of sleep quality, i.e. a low salivary cortisol level directly after awakening correlated with a higher frequency of nightly awakenings (r = -0.50), a diminished sleep quality (r = -0.34) and a decreased feeling of recovery after awakening (r = -0.35; all p < 0.05). Furthermore, awakening cortisol was negatively correlated with the Pittsburgh Sleep Quality Index (r = -0.43) and with a questionnaire on sleep-related cognitions with the subscales rumination in bed (r = -0.56 ) and focusing on sleep-related thoughts (r = -0.46; all p < 0.05).**

Ultrasound measures of bone and the diurnal free cortisol cycle: a positive association with the awakening cortisol response in healthy premenopausal women.

In this study we examined the relationship between characteristics of the diurnal pattern of salivary free cortisol concentration and ultrasound (US) measures of bone in premenopausal women. Subjects were 36 healthy, eumenorrhoeic, nonsmoking women mean age (SE) 30.9 (1.3) years. Saliva samples were collected on awakening and 10, 20, 30, 120, 240, and 600 minutes thereafter. Calcaneal broadband ultrasonic attenuation (BUA) and speed of sound (SOS) were determined. Mean (SE) salivary cortisol concentration was 4.7 (0.5) nmol/l on awakening, peaked at 8.6 (0.9) nmol/l 30 min later, and declined to a trough of 2.3 (0.2) nmol/l 600 min after awakening. BUA and SOS were significantly associated with cortisol 0 and 30 min after awakening (r = 0.40 and 0.40 for BUA and 0.33 and 0.37 for SOS, respectively, with body mass included as covariate). Cortisol levels 240 and 600 min after awakening were not significantly associated with bone variables. Women above the median for peak (30 min after awakening) cortisol had significantly higher BUA and SOS than those below the median [BUA 51.8 (1.0) vs 47.4 (1.5) dB/MHz, P = 0.017; SOS 1554.0 (2.5) vs 1546.4 (1.5) m/sec, P = 0.008]. A high peak in cortisol following awakening was associated with higher US measures of bone in healthy premenopausal women. This finding suggests the possibility that diurnal variation in cortisol may have a role in bone metabolism.

Salivary cortisol measurement in normal-weight, obese and anorexic women: comparison with plasma cortisol

Salivary cortisol measurement is a valuable and convenient alternative to plasma cortisol measurement. It enables demonstration of the overdrive of the HPA axis in anorexia nervosa and subtle perturbations of the cortisol diurnal rhythm in women with visceral obesity. With the establishment of more specific and widely acceptable cut-off values for dynamic testing, measurement of salivary cortisol could largely replace plasma cortisol measurement.

Exploration of the awakening cortisol response in relation to diurnal cortisol secretory activity.

Adrenocortical activity can be assessed by measurement of free cortisol in saliva. Cortisol status has important health implications in both physical and psychological terms. Assessment of cortisol status is complicated by the marked diurnal cortisol cycle. This cycle is characterised by an increase in secretory activity following awakening to achieve the morning acrophase. Thereafter it falls with a declining trend over the remainder of the day. For between subject studies the timing of sampling in relation to this cycle is an important consideration. We report a comprehensive study of the diurnal free cortisol cycle designed to analyse its components and to investigate their reliability and inter-relatedness. We instructed 42 healthy volunteers to collect saliva samples at home on two consecutive days. On each day the first sample was collected immediately upon awakening, followed by a further three samples at 15-minute intervals which collectively comprised the "awakening samples". A further four sample's were collected through the day at 3-hour intervals, all synchronized to awakening time. The cortisol response to awakening was calculated in two ways. Overall cortisol production in the first 45 minutes after awakening was calculated as area under the cortisol curve with reference to zero (AUC). The dynamic of the cortisol response to awakening was calculated as area under the cortisol response curve (AURC) with reference to the first awakening sample. In addition the underlying cortisol secretory activity was assessed based upon the diurnal three-hourly samples. All three parameters of adrenocortical activity showed reasonable stability across the two sampling days indicating all were reliable indexes of trait characteristic. AUC was representative of underlying diurnal activity but AURC was not. Measurement at any time point, 3, 6, 9 or 12 hours post-awarening was representative of the underlying 12-hour diurnal activity.

Actual stress, psychopathology and salivary cortisol levels in the irritable bowel syndrome (IBS).

Although irritable bowel syndrome (IBS) can be considered a biopsychological disorder in which an association between life stress and physiological changes leading to bowel irregularity is present, there is a lack of data concerning possible modifications of the adrenal function during the disease. The aim of the present study was to measure biological and psychological variables related to the activity of the hypothalamo-pituitary-adrenal axis in IBS patients compared to healthy subjects. **Cortisol was measured in the saliva** (obtained by a stress-free, non invasive collection procedure) of 55 IBS outpatients and 28 matched controls. Moreover, each subject completed the following self-administered questionnaires: the Rome Burnout Inventory (RBI) in its physical (RBI-PE) and emotional-mental exhaustion (RBI-EME) components, Beck Depression Inventory, State and Trait Anxiety Inventory (STAI), Perceived Social Support Scale (PSSS) and a Scale for the Assessment of Perceived Actual Work-Non Work Stress. Compared with controls, IBS subjects showed significantly higher levels of cortisol in the morning and lower in the evening, while they maintained the physiological circadian fluctuation (i.e. cortisol morning level higher than in the evening). Moreover, IBS patients presented a significant difference from controls in RBI-PE scores, which confirms the presence of fatigue, a symptom frequently reported by the patients. Compared with controls, no differences were found in IBS patients with respect to other psychological parameters. These findings suggest a dysregulation of the adrenal activity in IBS patients. The results may be relevant considering that changes in cortisol levels have been shown to be sensitive indicators of psychosocial stress and coping patterns in both laboratory and life situations.

Clinical applications of salivary cortisol measurements

The clinical applications of salivary cortisol measurements were evaluated by radioimmunoassay of time-matched saliva and plasma samples. Salivary cortisol levels of normal subjects exhibited a significant (p less than 0.001) diurnal variation with a mean (+/- SD) concentration of 8.7 +/- 4.8 nmol/L at 0800-1000 h and 2.4 +/- 1.1 nmol/l at 1500-1700 h. After an overnight dexamethasone suppression test, morning salivary cortisol levels decrease to 2.7 +/- 0.7 nmol/L (p less than 0.001 vs normal). An excellent correlation (r = 0.805) of cortisol measurements with time-matched saliva and plasma samples was obtained (y = 0.03x + 0.88, p less than 0.001, n = 91). Hypercortisolism was confirmed by raised salivary cortisols in only half of patients with elevated total plasma levels, thereby indicating that salivary cortisol measurements are a better index of adrenal status.

The effect of oral contraceptives on plasma-free and salivary cortisol and cortisone.

The effect of a low estrogen oral contraceptive (OC) on glucocorticoid levels in plasma and saliva as well as glucocorticoid binding was studied in 23 healthy women using 30 micrograms ethinyl estradiol (EE2) + 150 micrograms desogestrel (Marvelon) (II). Fifteen healthy females with normal menses served as controls (I). Blood and salivary samples were taken between 9.00 and 9.30 a.m. on the 18th day of menstrual or pill cycle. Assay accuracy had been optimised by applying extraction and chromatographic purification before radioimmunoassay (RIA) of cortisol and cortisone in both plasma and salivary samples. Free steroid assays were performed by applying the same procedure to equilibrium dialysates obtained after dialysing plasma against an equal volume of buffer, instead of measuring tracer distribution. Corticosteroid Binding Globulin (CBG) was measured by a commercial RIA. As expected, CBG as well as plasma total cortisol were elevated in the pill group. Interestingly both plasma free and salivary cortisol were higher than in controls (free cortisol I: 18.0 +/- 7.95 nmol/l; II: 32.3 +/- 9.03 nmol/l; salivary cortisol I: 9.2 +/- 3.88 nmol/l; II: 18.8 +/- 6.92 nmol/l. Salivary cortisol closely paralleled plasma free cortisol both within and between the groups, though at a much lower level (about 50%). Free cortisone was slightly lower in the pill group (I: 10.8 +/- 2.55 nmol/l; II 8.5 +/- 1.86 nmol/l) whereas salivary cortisone was 2.3 (I) and 4.4 (II) times higher than plasma free cortisone and tended to follow the plasma free and salivary cortisol pattern, both within and between the study groups.

CORE TRAINING

CORE curriculum covers in-depth:

• I. Adrenal stages of development:
• II. CAR; cortisol awakening response-what is it, why is it significant, how do we measure it?
• III. Labrix developed (Industry congruent) phases of HPA/adrenal dysfunction
• IV. Physiologic dosing of hydrocortisone
• V. Pharmacologic dosing of Hydrocortisone and Synthetics and warnings