Functional Adrenal & Thyroid Replacement

Nayan Patel PharmD
One of the most common but under-diagnosed health problems any doctor will see in their practice

All ages, occupations, races, social and economic groups

A contributing factor to many chronic illness

Triggered by many chronic conditions
Adrenal Gland Dysfunction

A spectrum of stress-related disorders

Addison’s

Low cortisol

Majority of people

Cushing’s

High cortisol

Central Drugs

NAYAN PATEL

PHARMD
Causes of Adrenal Problems

- Emotional stressors
- Physical stressors
- Physiologic stressors
- Chemical stressors
- Immune stressors

Stress Response
- Cortisol
- Epinephrine
  “Flight or Fight”

Nervous system
Hormones
“Sympathetic”
STRESSORS

Physical
- Toxic exposure
- Light cycle disruption
- Food intolerance
- Temperature extremes
- Trauma

Physiological
- Glucose dysregulation
- Chronic infection
- Pain
- Lack of sleep
- Dietary Imbalances
- Excessive exercise
- Chronic inflammation
- Serotonin
- GABA

Mental
- Emotional drain
- Anxiety
- Depression
- Alpha adrenal stimulus

Normal Stress Response

Following a stressor, the normal stress response involves:
- Increased ACTH
- Increased cortisol and DHEA(S)
- Cortisol to DHEA(S) ratio is maintained in balance
- Increased cortisol inhibits further ACTH output thereby moderating stress response
- The increase steroid output promptly returns to normal when stressor is removed
### Stressors

**Physical**
- Toxic exposure
- Light cycle disruption
- Food intolerance
- Temperature extremes
- Trauma

**Physiological**
- Glucose dysregulation
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**Mental**
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**Stressors**

```mermaid
diagram flowchart
  start [Stressors]
  Physical [Toxic exposure, Light cycle disruption, Food intolerance, Temperature extremes, Trauma]
  Physiological [Glucose dysregulation, Chronic infection, Pain, Lack of sleep, Dietary Imbalances, Excessive exercise, Chronic inflammation, Serotonin, GABA]
  Mental [Emotional drain, Anxiety, Depression, Alpha adrenal stimulus]
  HP [Sympathetic stress, Epinephrine, NE]
  NFL [ACTH]
  Adrenal cortex [Total Cortisol, Free Cortisol]
  Total DHEA(S)
  Free DHEA(S)
  Reduced HP sensitivity to negative feedback loop
  Normal no increase
```

**Energy Production**
- Insulin sensitivity ↓
- Glucose utilization ↓
- Blood sugar levels ↑
- Gluconeogenesis ↑

**Other Influences**
- Osteoporosis (bone loss) ↑
- Fat accumulation (waist) ↑
- Protein breakdown ↑
- Salt & water retention ↑

**Immune activity**
- Secretory IgA ↓
- Antigen penetration ↑
- Circulation IgG ↑
- NK cell activity ↓
- Interleukin 2 ↓
- T-Lymphocytes ↓

**Other**
- Increased infection
- Chronic EBV, CMV
- Yeast overgrowth
- Allergies
- Insomnia
- Reduced Vitality
- Hunger
- PMS...etc

**KEY**
- Association
- Stimulus
- Outcome
- Inhibition
- HP: Hypothalamus
- NFL: Negative feedback loop
- NE: Norepinephrine

Divergence has occurred when elevated cortisol is not paralleled by a DHEA(S) increase.
**Roles of Cortisol**

- **Energy production** – stimulates gluconeogenesis (low cortisol → hypoglycemia)
- **Fluid and electrolyte balance** (low cortisol → hypotension)
- **Fat storage** (high cortisol → weight gain, low cortisol → hard to lose weight)
- **Immune system regulation** (abnormal cortisol → impaired immune function).
Symptoms

- Fatigue
- Difficulty wakening in the morning
- Afternoon fatigue
- Improved evening energy
- Poor quality of sleep
- Decreased libido
- Depression
- Lack of spontaneity
Symptoms

- Poor Memory
- PMS
- Increased allergies
- Decreased resistance to infections
- Decreased stress tolerance
- Feeling overwhelmed
- Increase startle response
- Salt cravings
- Feeling light headed
- Sugar cravings
Adequate Adrenal Function

* Restorative sleep 7 – 8 hours
* Meaningful work, normal hours
* Adequate protein, good fats, veggies; limiting processed foods, sugar, etc.
* Exercise (not too little or too much)
* Low toxin load
* Regular relaxation methods
Adrenal Glands “Stressed”

- Poor sleep
- Night work, Overwork, over-scheduled.
- Processed food, sugars, transfats, GMO foods (?), etc.
- No exercise & no sweating
- Toxin overload (metals; phtalates; yeast; pesticides, etc.)
- No down time i.e. relaxation practices.
Metabolic Consequences

* High insulin and blood sugars
* Muscle wasting
* Blocks TSH release
* Increase T4 → rT3 conversion
* Blocks progesterone production & receptors
* Accelerated mineral/vitamin depletion
  * Vitamin C
  * B-vitamins
  * Zinc & magnesium (4 x utilization)
Treatment

- Lifestyle factors
- Nutrients
- Herbs
- Hormones
Lifestyle support for Adrenals

- Stress management
- Avoid sugar, alcohol & caffeine
- Frequent small meals to stabilize blood sugars
- Gentle exercise
- Adequate sleep
Nutrients for Adrenals

- Vitamin C
  - 2-4 grams/day or per bowel tolerance
- Vitamin B’s (especially B5 – pantothenic acid)
  - 1 gram daily as a co-factor for cortisol production
- Magnesium
  - Glycinate, malate or citrate 400 – 1000mg/day
- Chromium 2.5mg BID for 3 to 6 months (to reduce carb craving)
- Glandular extracts
  - Porcine or bovine desiccated adrenals
Herbs

* **Adaptogens** – help maintain homeostasis

**Effects of Adaptogens on the Central Nervous System and the Molecular Mechanisms Associated with Their Stress—Protective Activity**

* **Glycyrrhizin (licorice root extract)**
  * 200-600mg daily reduces the breakdown of cortisol.
  * Contraindicated in high blood pressure

* **Phosphatidylserine (PS)**
  * 100-600mg with dinner to reduce cortisol levels
* Ashwagandha 200 – 800mg daily
* Panax ginseng 200 – 400mg daily
* Holy Basil (ocimum tenuiflorum) 100 – 400mg daily
* Cordyceps
* Maca
* Rhodiola
* Rehmannia

Herbs often work best in combination
Hormonal support for adrenals

- **Corticosteroids**
  - Fludrocortisone, hydrocortisone, prednisone... In low doses just enough for supplementation without suppression.
- **Oral Progesterone** 50 to 200mg.
- **Oral Pregnenolone** 10 to 50mg
- **DHEA** 5-15mg (women), 25-100mg (men) to counteract excess cortisol driving DHEA levels low.
Adrenals & Progesterone

- “Progesterone Steal” – progesterone is converted into cortisol
- Results in PMS symptoms, estrogen dominance
- Women with adrenal fatigue often need higher doses of progesterone
- Progesterone supplementation also benefits adrenal function
Adrenals & Testosterone

- High cortisol suppresses testosterone production
- Cortisol interferes with testosterone at the receptor level.
Adrenals & Thyroid

- Cortisol affects T4 to T3 conversion
- Cortisol problems may affect pituitary function and TSH levels
- Symptoms of adrenal fatigue and hypothyroidism overlap
- Always treat adrenals first!
Cortisol & TSH Summary

* Elevated cortisol  low TSH
* Low cortisol  high TSH
Beware of Too Early Thyroid Replacement

- Thyroid hormone = Accelerator pedal
- Cortisol = Gasoline Tank
- Wait 4-6 weeks before replacing or increasing doses.
Less Than Optimal Thyroid Function

- A number of situations can contribute
  - Inadequate production of T4
  - Poor conversion from T4 to T3
  - Problems with the cell’s ability to take up T3
  - Problems with receptor function
  - Problems with intracellular transport
5 Diodeinase

INHIBITION

Stress
Fasting
Illness
↑ cortisol
↓ mg, se, Zn, Iodine
Factors That Inhibit T4 to T3 Conversion

- Nutrients deficiency
- Stress -- excessive cortisol
- Inadequate production of adrenal hormones
- Halogen toxicity
- Anti-thyroid peroxidase antibodies
- Excess reverse T3
- Estrogen
- Obesity
- Liver and kidney disease
- Starvation
- Medication
Factors That Inhibit T4 to T3 Conversion

<table>
<thead>
<tr>
<th>Nutrients</th>
<th>Medications</th>
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<tbody>
<tr>
<td>Selenium</td>
<td>Glucocorticoids</td>
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<tr>
<td>Zinc</td>
<td>Beta Blockers</td>
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<tr>
<td>Chromium</td>
<td>Birth Control Pills</td>
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<tr>
<td>Iodine</td>
<td>Estrogen Replacement</td>
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<tr>
<td>Iron</td>
<td>SSRIs</td>
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<tr>
<td>Copper</td>
<td>Opiates</td>
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<tr>
<td>Vitamin A</td>
<td>Phenytoin</td>
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<tr>
<td>Vitamin B2, 12, 6</td>
<td>Chemotherapy</td>
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<tr>
<td>Vitamin E</td>
<td>Theophylline</td>
</tr>
<tr>
<td>Fluoride</td>
<td>Lithium</td>
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</tbody>
</table>
Factors That **Increase** Conversion of T4 to T3

- Selenium, zinc, chromium, potassium, iodine, iron, Vitamins A, B2, E
- Growth hormone
- Testosterone, melatonin
- Insulin, glucagons
- Tyrosine
- High protein diet
- Ashwaganda
Thyroid testing

* Don’t rely on TSH only
* Also measure
  * fT4
  * fT3
  * rT3
  * Thyroid antibodies.
Thyroid Level Gradients

**Lab Range**
- TT4: Low, Mid, High
- FT4: Low, Mid, High
- TT3: Low, Mid, High
- FT3: Low, Mid, High
- rT3: Low, Mid, High

**Patients Value**
- TT4: Low, Mid, High
- FT4: Low, Mid, High
- TT3: Low, Mid, High
- FT3: Low, Mid, High
- rT3: Low, Mid, High
<table>
<thead>
<tr>
<th>TEST</th>
<th>RESULTS</th>
<th>UNITS</th>
<th>EXPECTED RANGE</th>
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<tbody>
<tr>
<td>T3 UPTAKE</td>
<td>32.8</td>
<td>%</td>
<td>20.0-38.5</td>
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<tr>
<td>T3 TOTAL</td>
<td>141</td>
<td>NG/DL</td>
<td>90-200</td>
</tr>
<tr>
<td>T4 (THYROXINE)</td>
<td>11.2</td>
<td>UG/DL</td>
<td>4.4-12.5</td>
</tr>
<tr>
<td>FREE T4</td>
<td>1.48</td>
<td>NG/DL</td>
<td>0.73-1.95</td>
</tr>
<tr>
<td>FREE T3</td>
<td>2.5</td>
<td>PG/ML</td>
<td>2.3-4.2</td>
</tr>
<tr>
<td>REVERSE T3</td>
<td>317</td>
<td>PG/ML</td>
<td>90-350</td>
</tr>
</tbody>
</table>
Thyroid Level Gradients Example

TT4
6.425
10.475
4.4
12.5
11.2

FT4
1.035
1.645
.73
1.95
1.48

TT3
117.5
172.5
90
200
141

FT3
2.775
3.725
2.3
4.2
2.5

rT3
155
285
90
350
317
Excess Binding

* Imagine these gradients curves as the upper portion of a clock.
* If the binding were normal, TT<sub>4</sub> & FT<sub>4</sub> as well as TT<sub>3</sub> & FT<sub>3</sub> should be about the same position on the clock.
* As you can see, they are not. This indicates excessive binding which may be secondary to excess estrogen or T<sub>4</sub>. 
Decreased Conversion of T4 to T3

* If there is proper conversion of FT4 to FT3, both FT4 & FT3 should be at the same position on the clock.
* As you can see, they are not.
* This represents a conversion problem. Now you must try to find the etiology by looking at the many causes of poor conversion.
Decreased Conversion of T4 to T3

TT4
11.2

TT3
141

FT4
1.48

FT3
2.5

rT3
317
Free T₃ and rT₃

* If the conversion of T₄ to FT₃ and rT₃ is normal, FT₃ and rT₃ should have about the same position on the clock.
* Even though rT₃ is within the normal range for this laboratory, it is in excess of FT₃.
* Since FT₃ and rT₃ occupy the same receptor and FT₃ will activate the receptor and rT₃ will not, if the patient has excess rT₃ they will have symptoms of tissue hypometabolism despite all the laboratory tissue falling within the normal range.
Etiology and Correction of Excess rT3

* Excess rT3 will further inhibit conversion from T4 to T3
* Since rT3 is derived from T4, you must lower T4
* If the patient is on a T4 preparation, give slow release T3 and discontinued T4 preparation (slowly over time to control TSH)
* If the patient is not on a T4 preparation, still give slow release T3
* This will decrease TSH and the production of T4 from the thyroid gland and its inappropriate conversion to rT3
Thyroid Replacement Therapy Options
Thyroid Preparations?

- Thyroid Desiccated USP
  - Derived from pork or beef
  - Nature thyroid®
  - Armour® Thyroid
  - Thyroid USP (various manufacturers)
- Cytomel® (T3 only in 5mcg & 25mcg immediate release)
- Synthroid® (T4 only in various strengths)
- Levothyroxine Sodium USP (T4) Pentahydrate and Liothyronine Sodium USP (T3) are pure, bio-identical hormones
1 Grain (60 mg) of Thyroid USP contains only 38 mcg of T4 and 9 mcg of T3
More than 99.9% of contents of thyroid USP are not the thyroid hormones T3 and T4
Ratio of T4:T3 is 4.2:1
May also contain T2, T1, selenium, calcitonin
  * T2 & T1 may provide biological activity but overall contribution is considered minimal
  * The amounts are not identified, quantified, or standardized
Ratio is fixed – doesn’t allow for individual differences in metabolism or changes with time
0.17-0.23% Iodine

1 grain of Desiccated Thyroid contains: 0.20% x 60mg = 120µg
Compounded Thyroid

* Allows individualized ratio and strengths of T4 and T3 for every patient
* Lower T4 to T3 ratio for patient not converting well
* Ratio of ingredients can be adjusted based on levels and response – individualized to the patient
* Correcting the problem(s) causing poor conversion should change the ratio of T4:T3 required
* Precisely compounded to optimize metabolism, symptom resolution, labs and body temperatures
* Compounded thyroid preparations allow for addition of adjunctive therapies
  * Hydrocortisone for proper thyroid utilization in adrenal dysfunction
  * combine with co-factors (Se, Zn, Mg, Iodine) to facilitate the conversion from T4 to T3 effectively.
* Allow for varying doses at different times of the day based on individual responses
Compounded: The Best of Both Worlds

* Slow release T3
  * Decreases side effects
  * Decreases suppression of thyroid gland & TSH
  * Can add nutrition and or hydrocortisone
* Combined T4/T3 in slow release capsule for increased ease in compliance and less cost
* Ratios individualized to the patient
* Compounded thyroid preparations allow for addition of adjunctive therapies
Considerations

* Poor thyroid function can lead to absorption problems and poor nutrient absorption can lead to poor thyroid function
* Hypothyroid skin may affect absorption of lipophyllic substances (hormones)
* Gut problems may affect absorption of slow release preparations contain HPMC as well as nutrients
* No one size fits all
* Nothing works as well as the thyroid gland!
  * “Kick-start or “wake-up” with iodine, Vitamin B-6 L-tyrosine, zinc, magnesium, glutamine
Consideration IF you use T4

* Patient feels better at 30 day follow up (TSH and T4 “look good”), but symptoms return over next few months
* Adrenal insufficiency
* Converting to improper ratio of rT3 to T3 and build up of rT3 occurs
* Oral thyroid can increase TBG, and increase can take place over several months
Considerations for Combined T4 and T3

- T4:T3 ratio is initially arbitrary
- Ratio an strengths adjusted based on
  - Symptoms
  - Body temperature
  - Levels and balance of free T4, free T3 and reverse T3 along with TSH
  - Retest in 60-90 days
- Monitor basal temperatures, lab work, physical exam signs and symptoms
Ratios are modified as indicated by the combination of follow up symptom resolution, temperature log results and balance of free T4, free T3, rT3 and TSH in the blood.

Some patients need T3 gradually released over 24 hours especially as the doses become higher to avoid side effects or to maximize a more even distribution of energy throughout the day and to avoid later afternoon or evening fatigue.
Suggested Approaches for Autoimmune Thyroid Conditions

- Use enough thyroid hormones to keep TSH ≤ 1.0
- Selenium 200-800 mcg daily
- Gluten-free diet for at least 60 days
- Rectify any iodine deficiency
- Remove aspartame, trans fats and processed whole foods from diet
- Magnesium
- Treat any underlying infections
- Correct any hormone imbalances, especially DHEA insufficiency and adrenal dysfunction
- Restore proper gut function
- Avoid Thyroid glandulars.
Conclusion
Underlying cause of adrenal fatigue

* Allergies
* Food sensitivities
* Leaky gut
* Dysbiosis
* Toxic exposures
* Chronic viral or other infections

* Chronic pain
* Chronic inflammatory disease
* Autoimmune disease
* Chronic insomnia
* Candida
* Toxic metals
Treating low cortisol

- Lifestyle support for adrenal health
- Vit C, B5, magnesium to support cortisol production
- Adaptogenic herbs, including licorice
- Glandular extracts
- Hormone precursors, hydrocortisone
Adrenal function and thyroid are completely intertwined and for best results consider using a combo therapy that includes all of

- Lifestyle modifications
- Proper nutrition, vitamins & herbs
- Correct combination of all bio-identical hormones

As we all know now Balance is what we need to achieve.