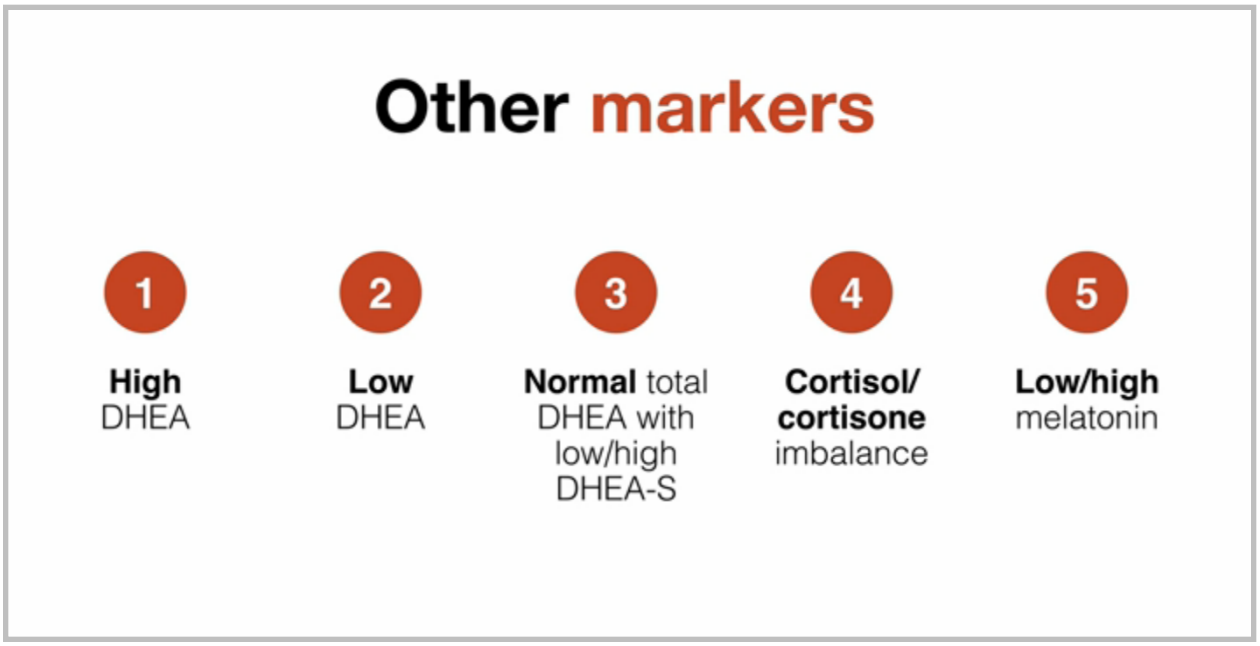
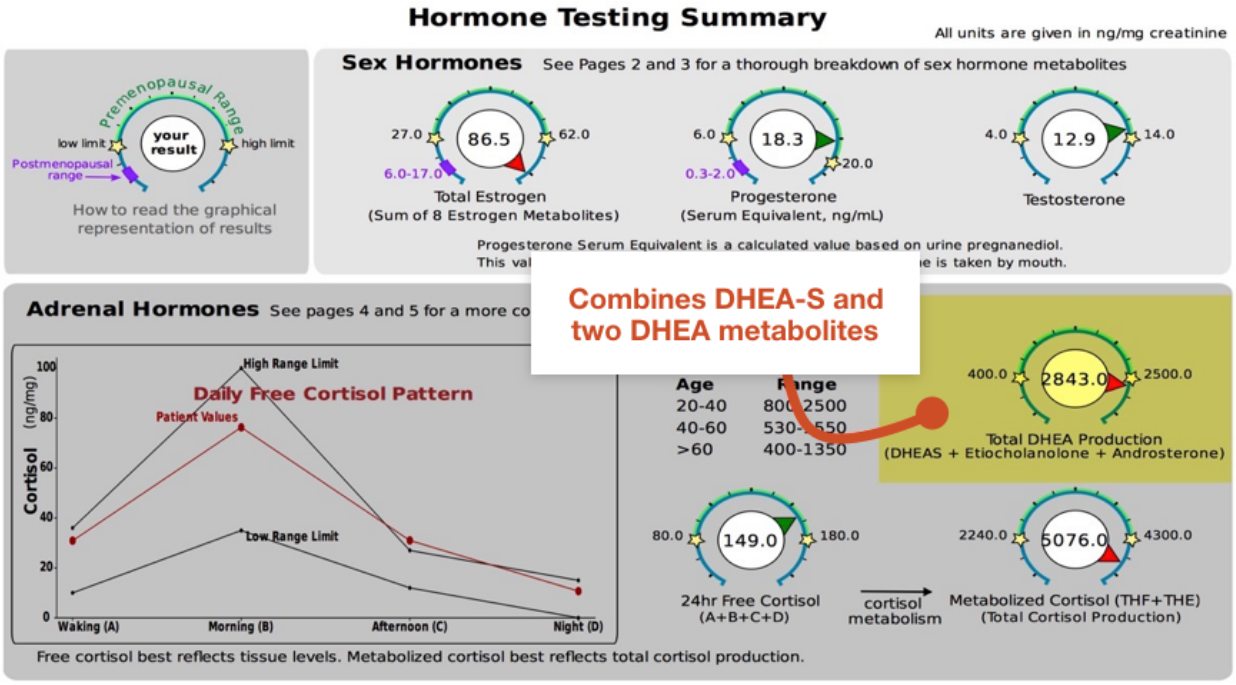
KRESSER INSTITUTE FOR FUNCTIONAL AND EVOLUTIONARY MEDICINE

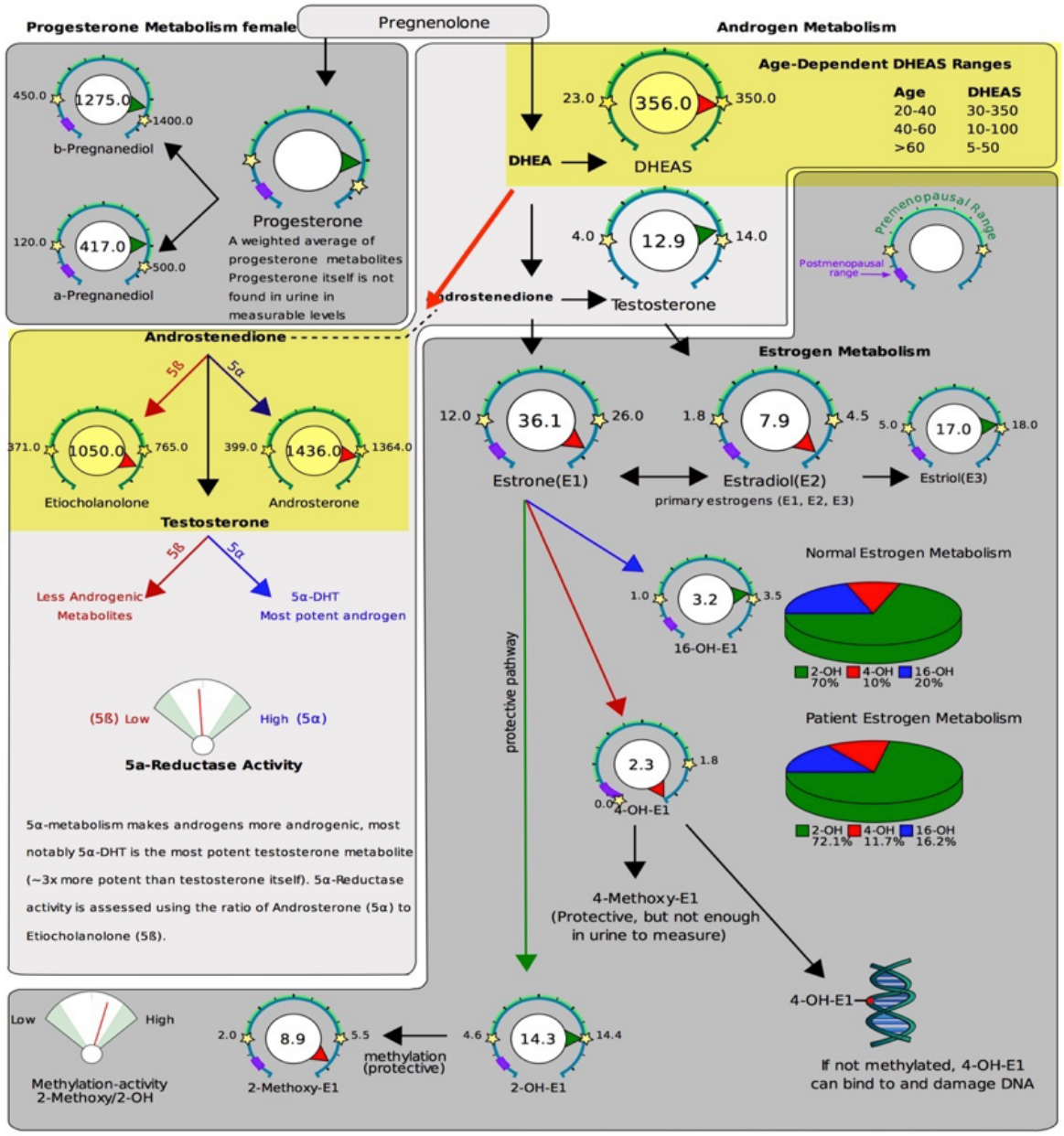
HPA-D: DUTCH Test II - Part 1

Hey, everybody. In this presentation, we're going to continue talking about how to use the DUTCH test to address HPA axis function.



In particular, we're going to look at some of the other markers we haven't discussed yet: high DHEA, low DHEA, normal total DHEA with low or high DHEA sulfate, cortisol and cortisone imbalance, and low or high melatonin.

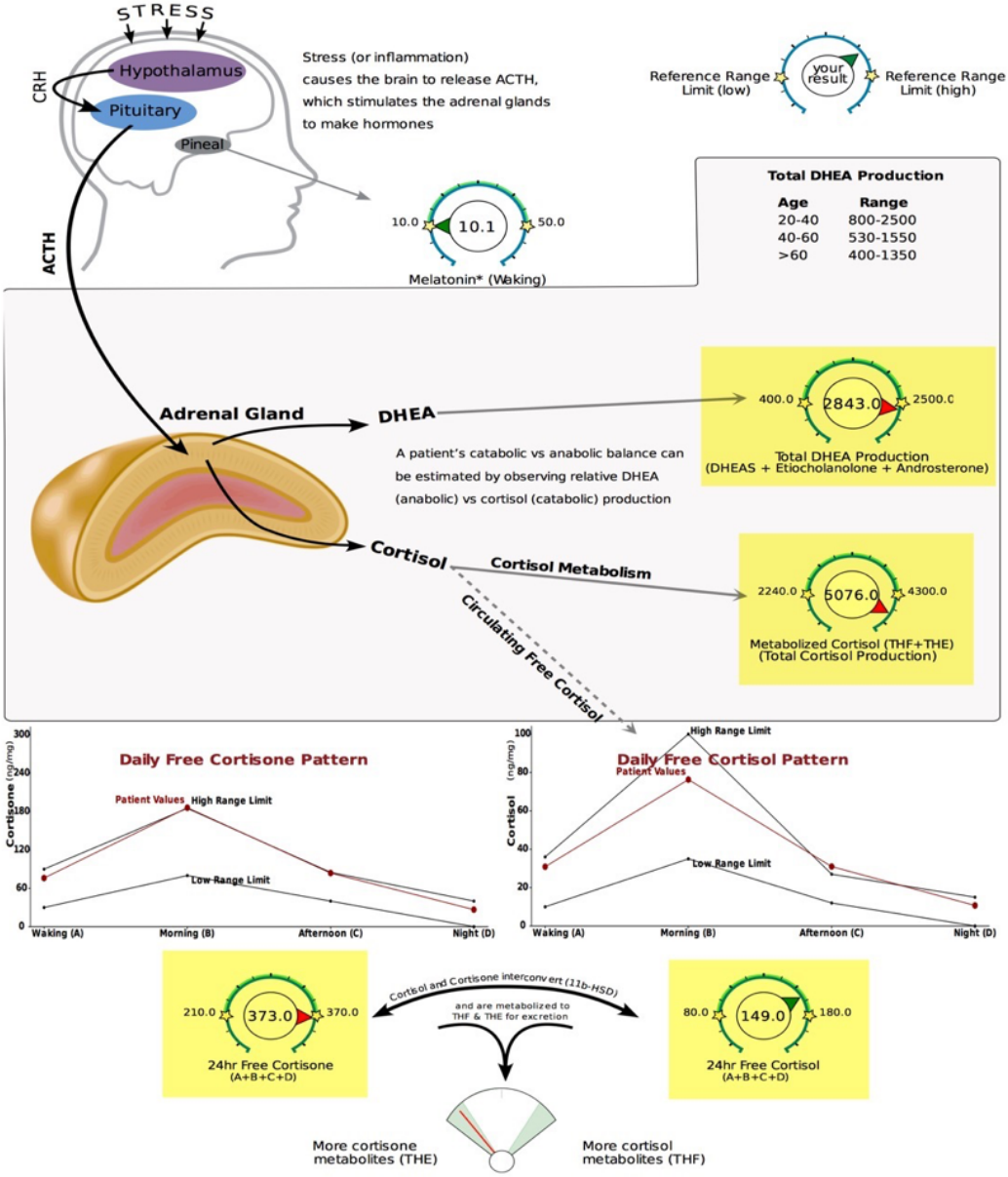


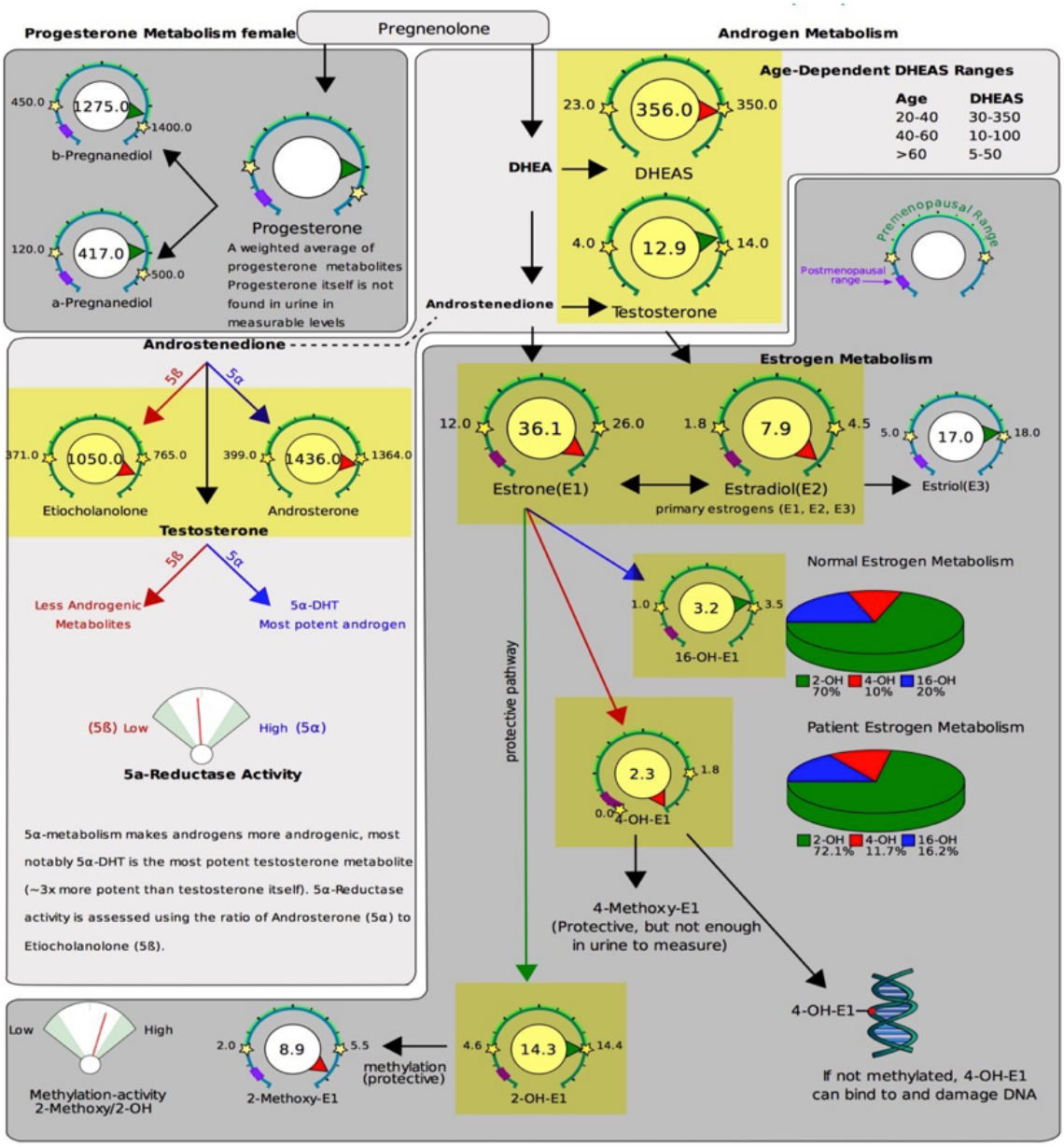


On the DUTCH test, there are a couple ways to look at DHEA, depending on which test you are using. Note that DHEA itself does not appear in the urine, but DHEA sulfate does, so that is what is measured by the DUTCH test. If you're running the comprehensive hormone profile, on the first page it lists total DHEA value, which you see here highlighted on the slide. This is a combination of DHEA sulfate and two DHEA metabolites, etiocholanolone and androsterone. Measuring this combination gives you a better idea of overall DHEA production than just looking at DHEA sulfate alone. One reason for this is that sulfation can be upregulated or downregulated in certain disease

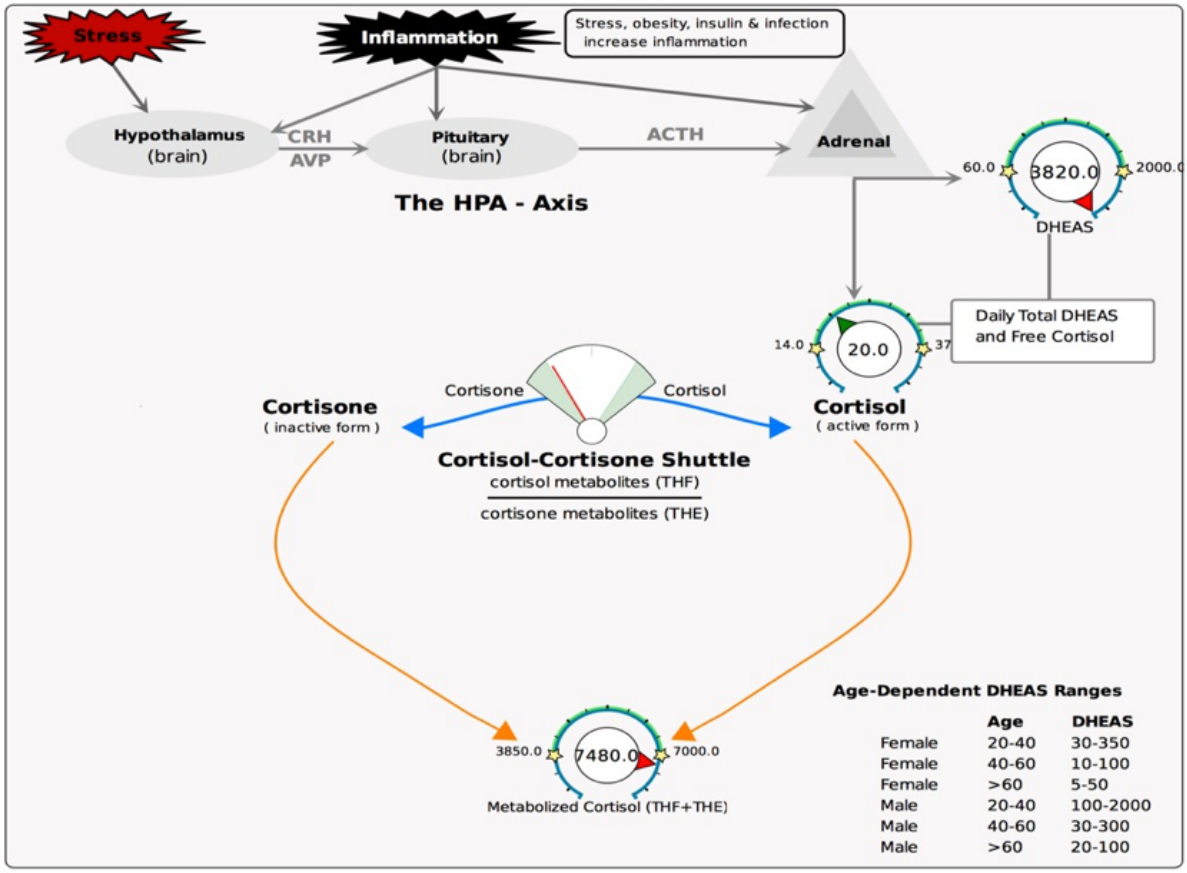
states. This can give a falsely low or high impression of DHEA if you only measure DHEA sulfate, and I'll show you a test result illustrating this shortly. If you're running the adrenal panel instead of the comprehensive, it only reports DHEA sulfate, and that is still a good marker and will be accurate in most cases, but you do need to keep in mind that, as I said before, sulfation can be upregulated or downregulated in certain disease states, and DHEA sulfate alone may not provide an accurate representation of total DHEA levels in those cases.

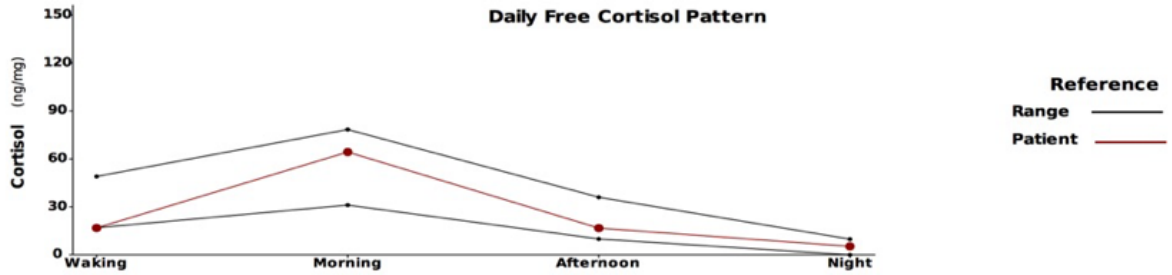
Let's look first at high DHEA. Remember that the DHEA range is age and gender specific, and the DUTCH test results report takes that into account. The primary causes of high DHEA are PCOS, acute stress, obesity, benzodiazepine use—drugs such as Xanax—and antidepressant use.


STRESS
Hypothalamus
CRH
Pituitary
Pineal
ACTH
Stress (or inflammation) causes the brain to release ACTH, which stimulates the adrenal glands to make hormones
Reference Range Limit (low)
your result
Reference Range Limit (high)
10.0
10.1
50.0
Melatonin* (Waking)
Total DHEA Production
Age Range
20-40 800-2500
40-60 530-1550
>60 400-1350
Adrenal Gland
DHEA
400.0
2843.0
2500.0
Total DHEA Production
(DHEAS + Etiocholanolone + Androsterone)
A patient's catabolic vs anabolic balance can be estimated by observing relative DHEA (anabolic) vs cortisol (catabolic) production
Cortisol
Cortisol Metabolism
Circulating Free Cortisol
2240.0
5076.0
4300.0
Metabolized Cortisol (THF+THE)
(Total Cortisol Production)
Daily Free Cortisone Pattern
Cortisone (ng/mg)
Patient Values
High Range Limit
Low Range Limit
Waking (A)
Morning (B)
Afternoon (C)
Night (D)
Daily Free Cortisol Pattern
Cortisol (ng/mg)
Patient Values
High Range Limit
Low Range Limit
Waking (A)
Morning (B)
Afternoon (C)
Night (D)
210.0
373.0
370.0
24hr Free Cortisone
(A+B+C+D)
Cortisol and Cortisone interconvert (11b-HSD)
and are metabolized to THF & THE for excretion
80.0
149.0
180.0
24hr Free Cortisol
(A+B+C+D)
More cortisone metabolites (THE)
More cortisol metabolites (THF)

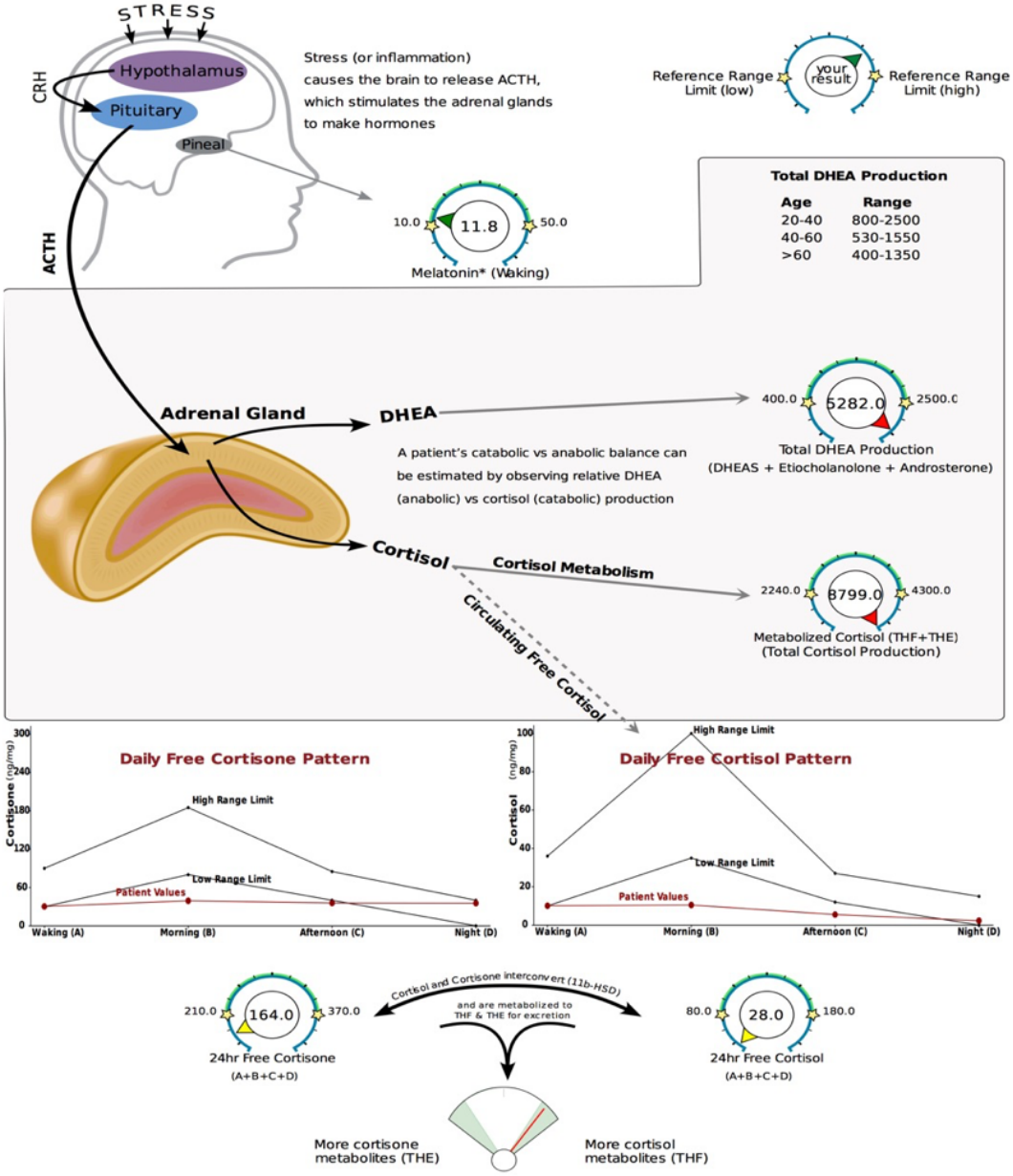


This patient here is a 38-year-old female. Her chief complaint was PCOS. As you can see, her total DHEA is high. Also her testosterone was high-normal. It will often be frankly high out of the lab range in PCOS. In this case, it was high-normal. Estrogens and estrogen metabolites are also high, as is consistent with PCOS presentation. Her free cortisone is high. Free cortisol was high-normal, and metabolized cortisol was high. So this is a fairly typical presentation, but you will often see estrogen metabolites even higher than you see here. You'll see testosterone often out of the lab range, as I mentioned, and DHEA can often be higher as well.



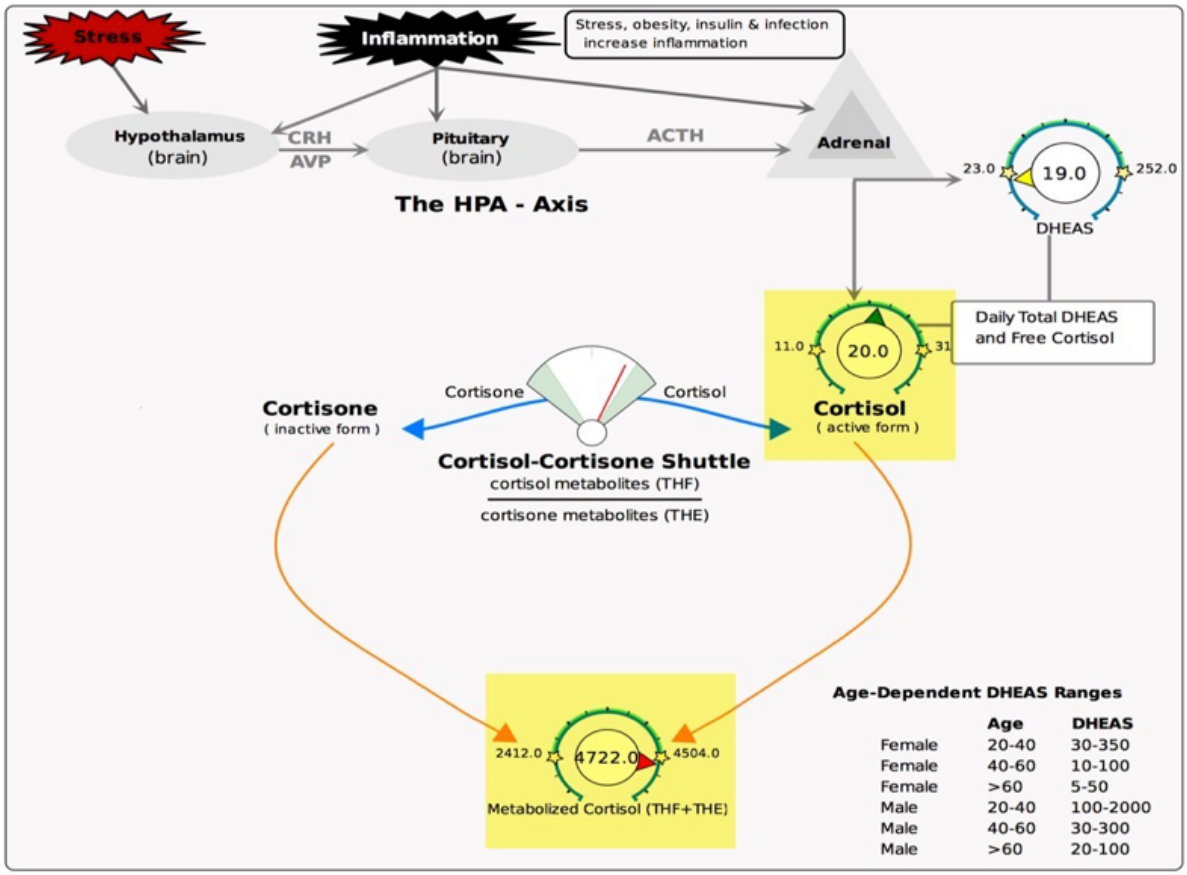


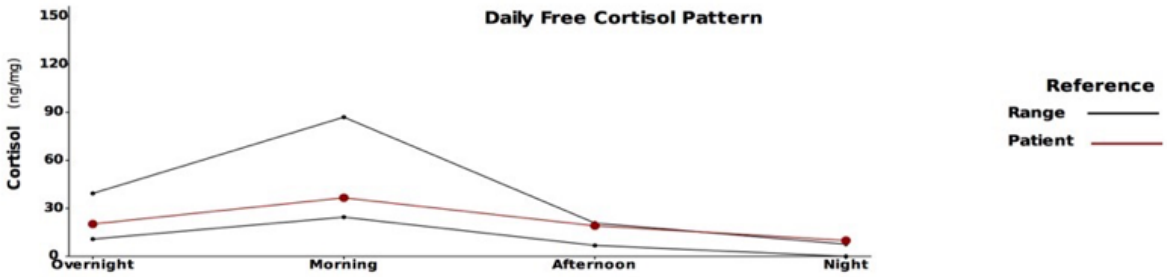
This patient is a 34-year-old male who complained of a constant off-balance feeling with chest tightness and a restricted feeling when inhaling, throat tightness, and fatigue. It sounds a lot like stress-related symptomatology, right? DHEA is very high, nearly two times the upper end of the range. Free cortisol is low-normal, but check out metabolized cortisol. It is high. The upper end of the range is 7,000, and he is at almost 7,500.

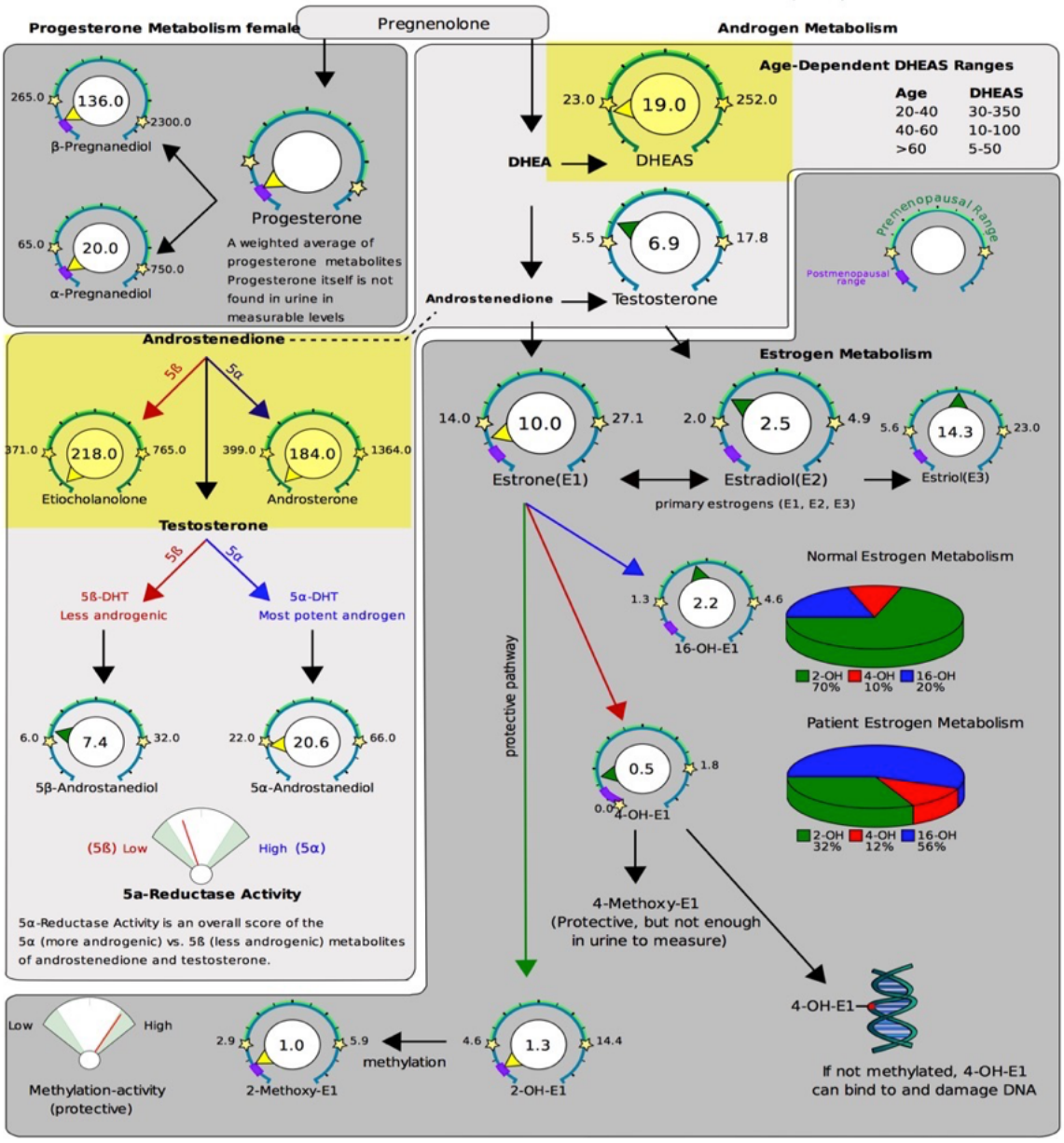


Here is an earlier result I showed you from the patient who was 420 pounds. DHEA is two times the upper end of the range and the same with metabolized cortisol. Of course, you recall that his free cortisone and free cortisol were low, which would give the false impression of adrenal fatigue if only saliva cortisol was being measured.

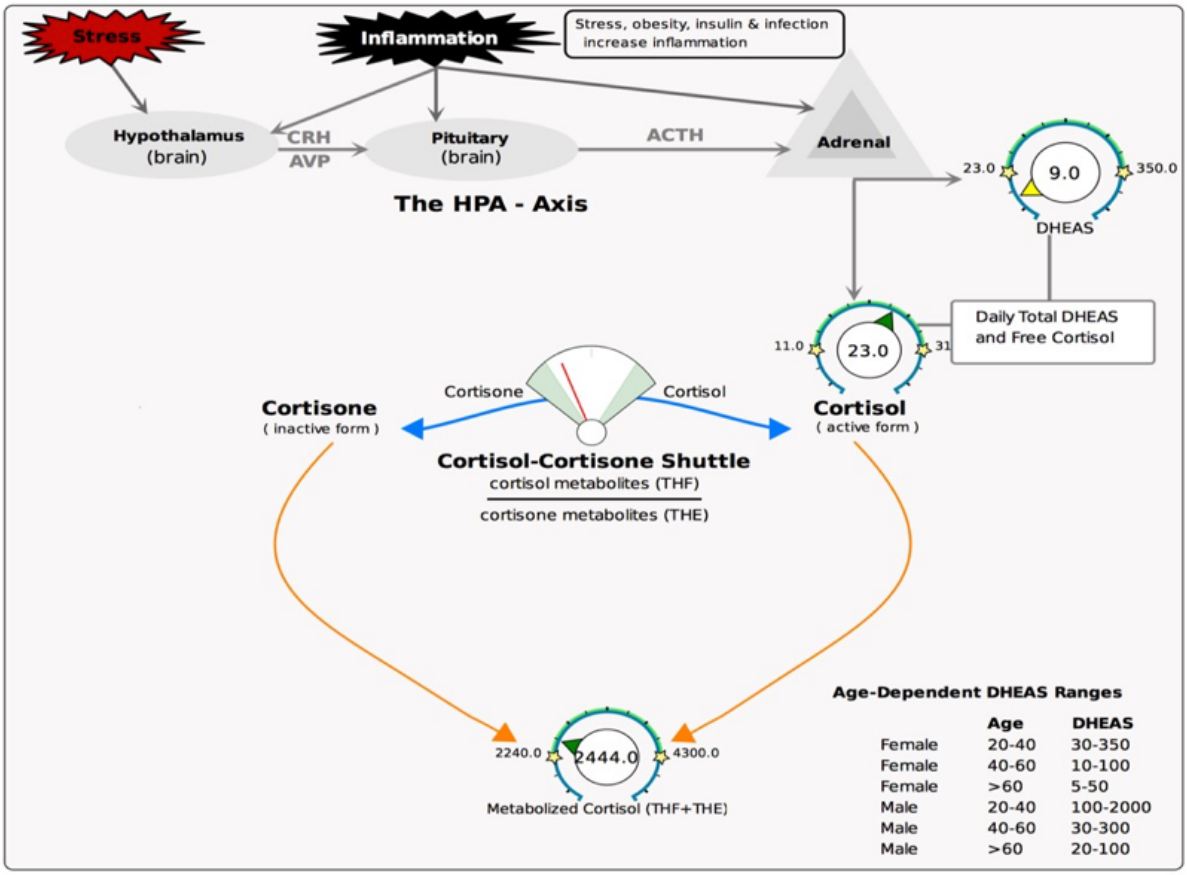
Let's talk a little bit about low DHEA now. DHEA can be low with stress, aging, rapid weight loss, opioids, glucocorticoids, birth control pills, hormone replacement therapy, antipsychotics, and some diabetes medications.

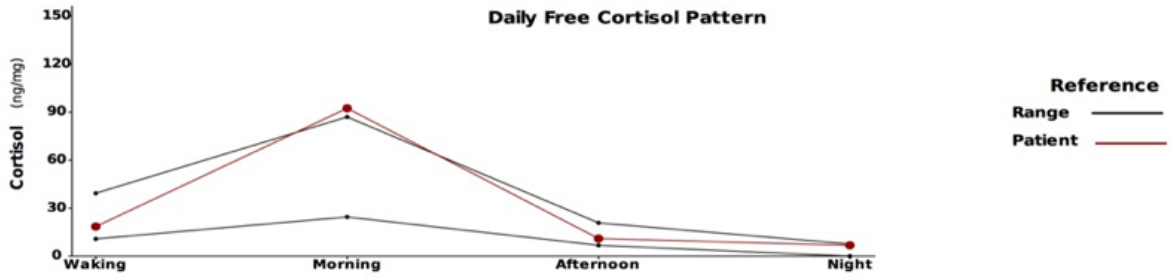

Stress
Inflammation
Stress, obesity, insulin & infection increase inflammation
Hypothalamus (brain)
CRH
AVP
Pituitary (brain)
ACTH
Adrenal
The HPA - Axis
23.0
19.0
252.0
DHEAS
Daily Total DHEAS and Free Cortisol
11.0
20.0
31
Cortisone
(inactive form)
Cortisone
Cortisol
Cortisol
(active form)
Cortisol-Cortisone Shuttle
cortisol metabolites (THF)
cortisone metabolites (THE)
2412.0
4722.0
4504.0
Metabolized Cortisol (THF+THE)
Age-Dependent DHEAS Ranges
Age DHEAS
Female 20-40 30-350
Female 40-60 10-100
Female >60 5-50
Male 20-40 100-2000
Male 40-60 30-300
Male >60 20-100

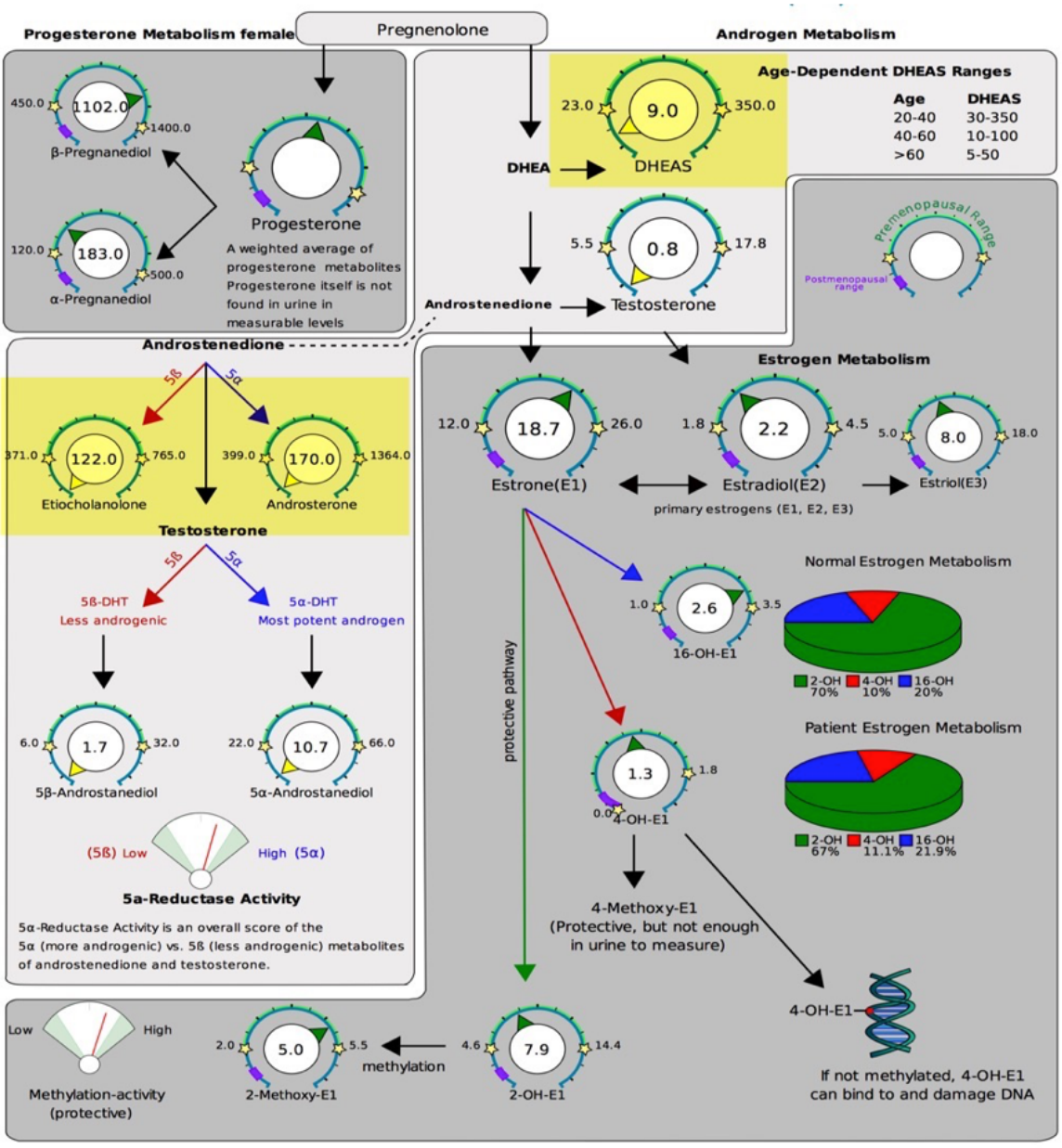

Daily Free Cortisol Pattern
Cortisol (ng/mg)
150
120
90
60
30
0
Overnight
Morning
Afternoon
Night
Reference
Range
Patient



This is a 38-year-old female engineer who works for Google. She had a history of Lyme disease and Kawasaki disease. She had a number of autoimmune conditions such as thyroiditis and rheumatoid arthritis. You can see that her DHEA sulfate as well as etiocholanolone and androsterone are low. Note that this is an old report format prior to when they started reporting the total DHEA value on the first page.

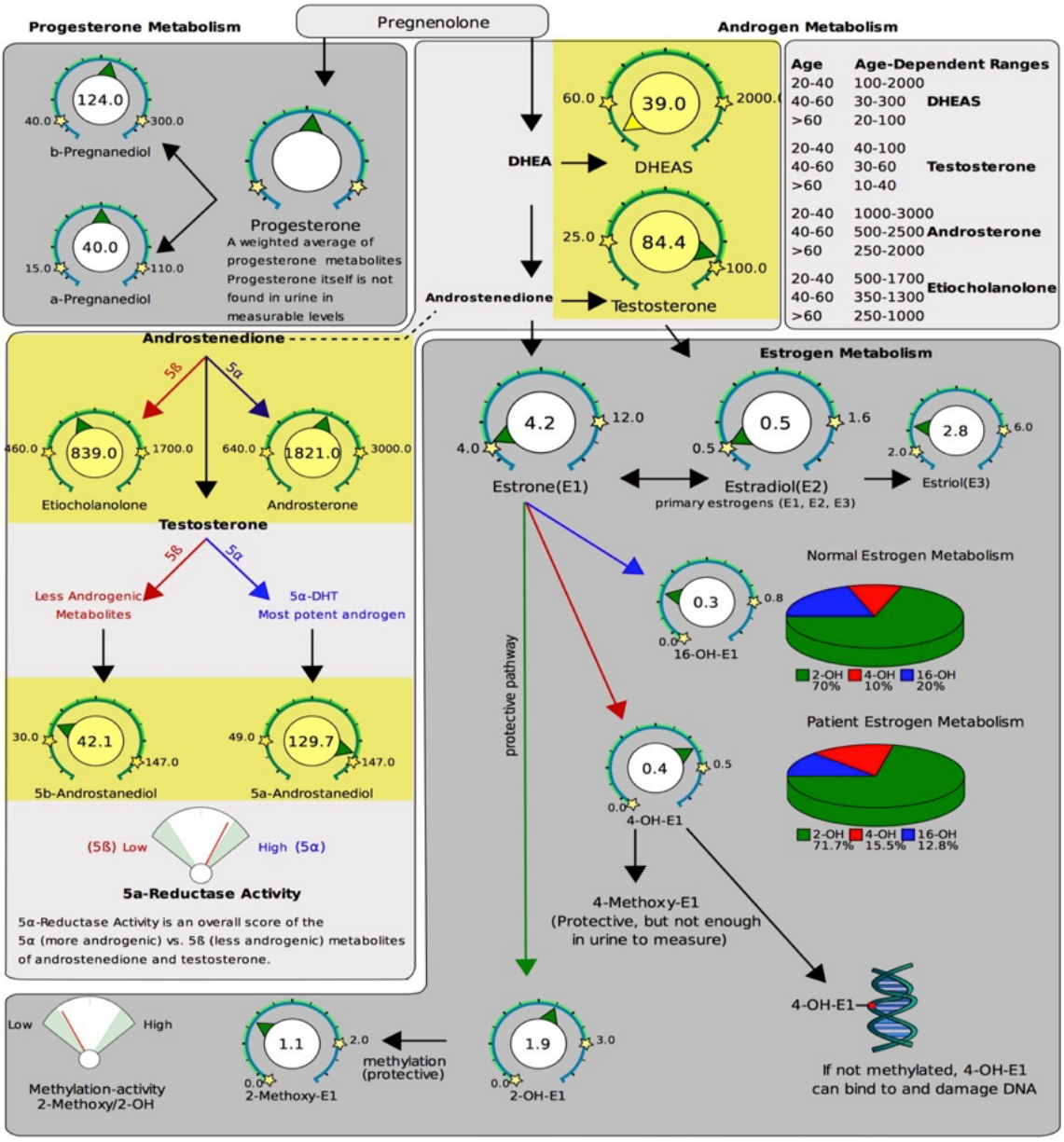

Stress
Inflammation
Stress, obesity, insulin & infection increase inflammation
Hypothalamus (brain)
CRH
AVP
Pituitary (brain)
ACTH
Adrenal
The HPA - Axis
23.0
9.0
350.0
DHEAS
Daily Total DHEAS and Free Cortisol
11.0
23.0
31
Cortisone
(inactive form)
Cortisone
Cortisol
Cortisol
(active form)
Cortisol-Cortisone Shuttle
cortisol metabolites (THF)
cortisone metabolites (THE)
2240.0
2444.0
4300.0
Metabolized Cortisol (THF+THE)
Age-Dependent DHEAS Ranges
Age DHEAS
Female 20-40 30-350
Female 40-60 10-100
Female >60 5-50
Male 20-40 100-2000
Male 40-60 30-300
Male >60 20-100

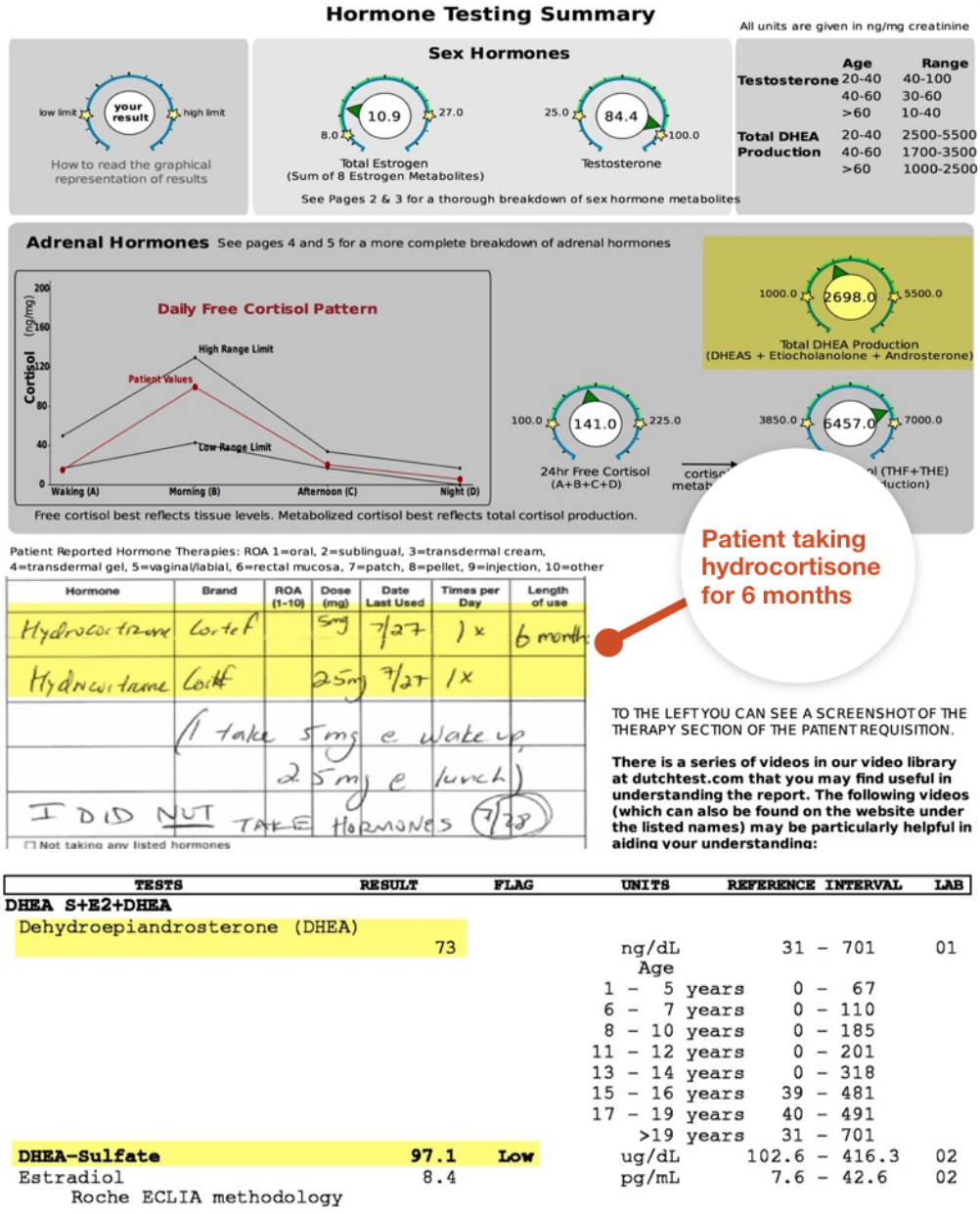

Daily Free Cortisol Pattern
Cortisol (ng/mg)
150
120
90
60
30
0
Waking
Morning
Afternoon
Night
Reference
Range
Patient



This is a 46-year-old patient with chronic neck and shoulder pain, digestive issues, and possible MS diagnosis. Both free and metabolized cortisol are normal, but her metabolized cortisol is at the far low end of the range. Her total DHEA and DHEA sulfate are low, as are her androgen metabolites, 5β- and 5α-androstanediol, and her testosterone. She hasn't slept well since her first pregnancy six years ago, and she has a very stressful job and two young kids.

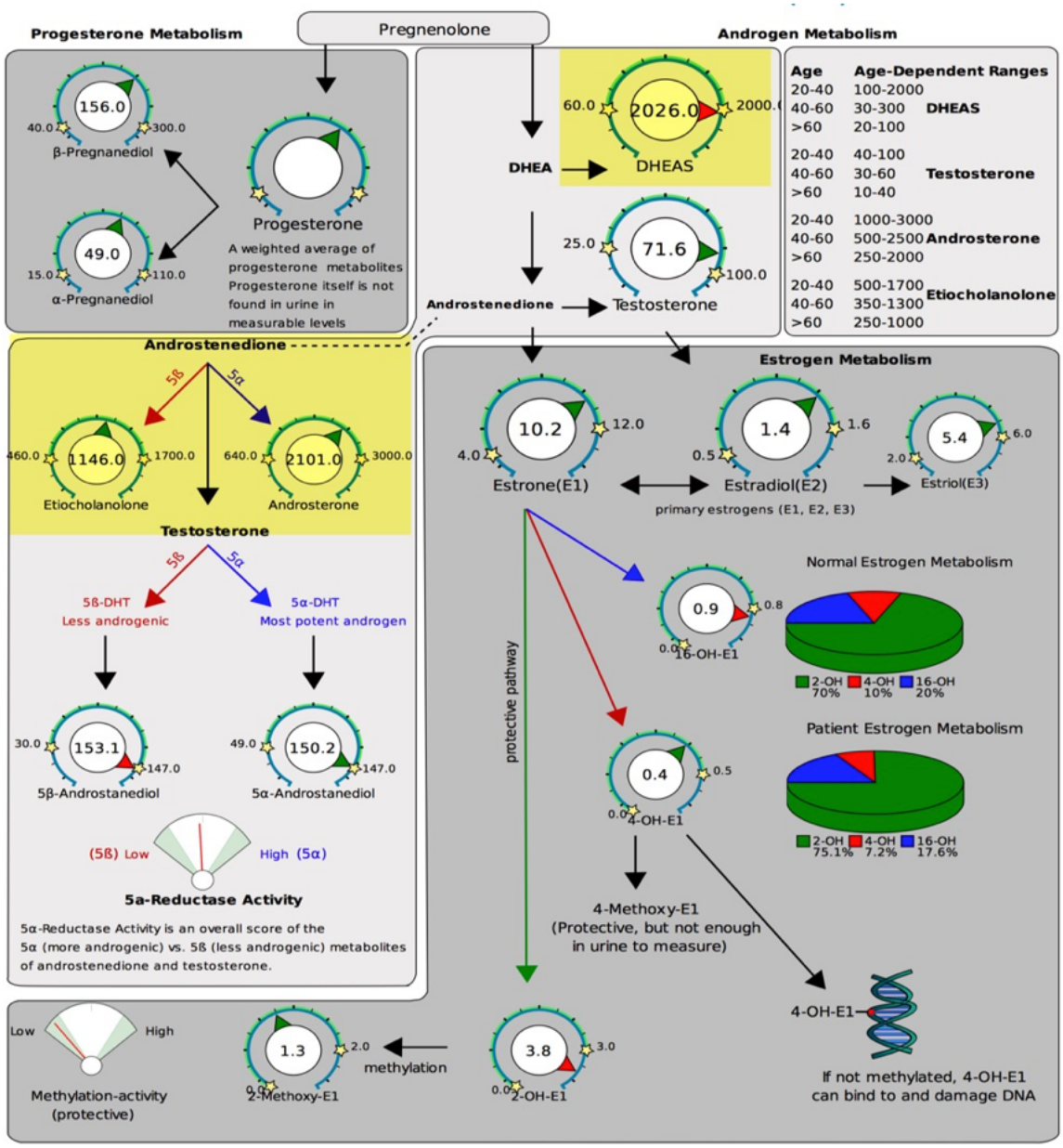
All right, let's talk about normal total DHEA with low or high DHEA sulfate. This isn't a common presentation, but I've seen it enough times to feel like it is worth pointing out. One reason you may want to run the full comprehensive panel instead of the adrenal panel is to get this additional info on DHEA and its metabolites. Just as there is sometimes discordance between free and metabolized cortisol, you'll sometimes see discordance between total DHEA and DHEA sulfate.

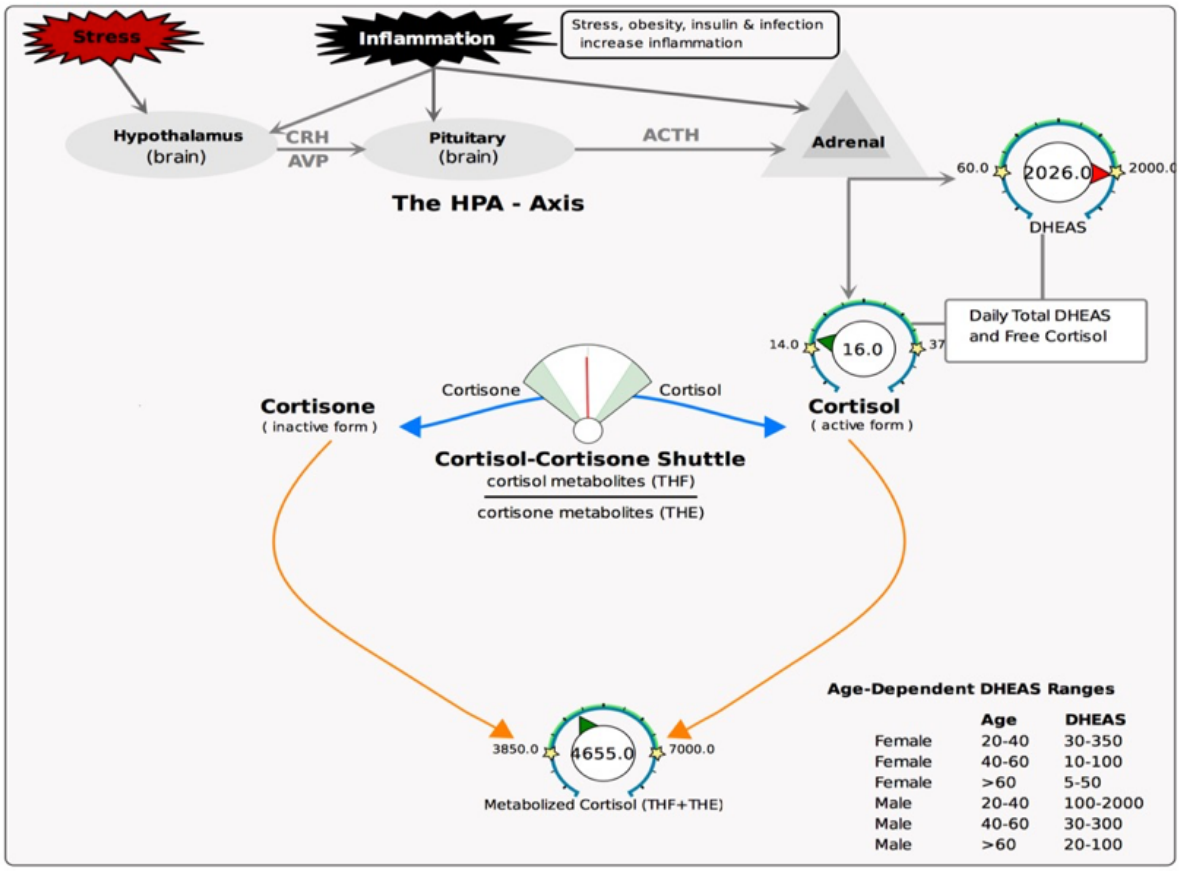

Progesterone Metabolism
Pregnenolone
Androgen Metabolism
124.0
40.0
300.0
b-Pregnanediol
Progesterone
A weighted average of progesterone metabolites Progesterone itself is not found in urine in measurable levels
40.0
15.0
110.0
a-Pregnanediol
60.0
39.0
2000.0
DHEA
DHEAS
25.0
84.4
100.0
Androstenedione
Testosterone
Age
Age-Dependent Ranges
20-40 100-2000
40-60 30-300 DHEAS
>60 20-100
20-40 40-100
40-60 30-60 Testosterone
>60 10-40
20-40 1000-3000
40-60 500-2500 Androsterone
>60 250-2000
20-40 500-1700
40-60 350-1300 Etiocholanolone
>60 250-1000
Androstenedione
5ß
5α
460.0
839.0
1700.0
640.0
1821.0
3000.0
Etiocholanolone
Androsterone
Testosterone
5ß
5α
Less Androgenic Metabolites
5α-DHT
Most potent androgen
30.0
42.1
147.0
49.0
129.7
147.0
5b-Androstanediol
5a-Androstanediol
(5ß) Low
High (5α)
5a-Reductase Activity
5α-Reductase Activity is an overall score of the 5α (more androgenic) vs. 5ß (less androgenic) metabolites of androstenedione and testosterone.
Estrogen Metabolism
4.2
4.0
12.0
Estrone(E1)
0.5
0.5
1.6
Estradiol(E2)
primary estrogens (E1, E2, E3)
2.8
2.0
6.0
Estriol(E3)
Normal Estrogen Metabolism
0.3
0.0
0.8
16-OH-E1
2-OH 70%
4-OH 10%
16-OH 20%
protective pathway
Patient Estrogen Metabolism
0.4
0.0
0.5
4-OH-E1
2-OH 71.7%
4-OH 15.5%
16-OH 12.8%
4-Methoxy-E1
(Protective, but not enough in urine to measure)
4-OH-E1
If not methylated, 4-OH-E1 can bind to and damage DNA
Low
High
Methylation-activity
2-Methoxy/2-OH
1.1
0.0
2.0
2-Methoxy-E1
methylation (protective)
1.9
0.0
3.0
2-OH-E1

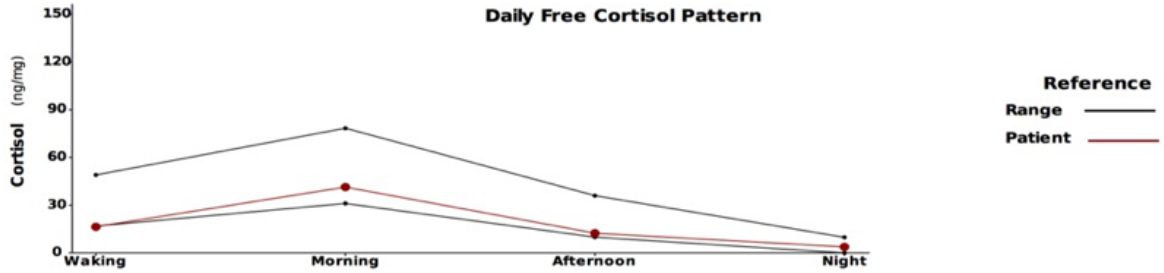


This patient is a 38-year-old male with ulcerative colitis. His total DHEA is normal, and he has normal etiocholanolone, androsterone, 5β- and 5α-androstanediol, and normal testosterone, but check out his DHEA sulfate. It is quite low. This was confirmed by follow-up serum testing of DHEA and DHEA sulfate, as the result on the bottom right of the slide indicates. You can see that we ran a lab for DHEA and DHEA sulfate. His DHEA is normal, and his DHEA sulfate was low at 97.1. The two primary causes of low DHEA sulfate are inflammation and glucocorticoid use, and in this case, the patient had both. He had IBD, which is an inflammatory gut condition, and he had been taking low-dose hydrocortisone for six months to deal with that and some of his other inflammatory

symptoms, so this is what was impairing the sulfation of DHEA and leading to low DHEA sulfate even when his total DHEA levels were normal.

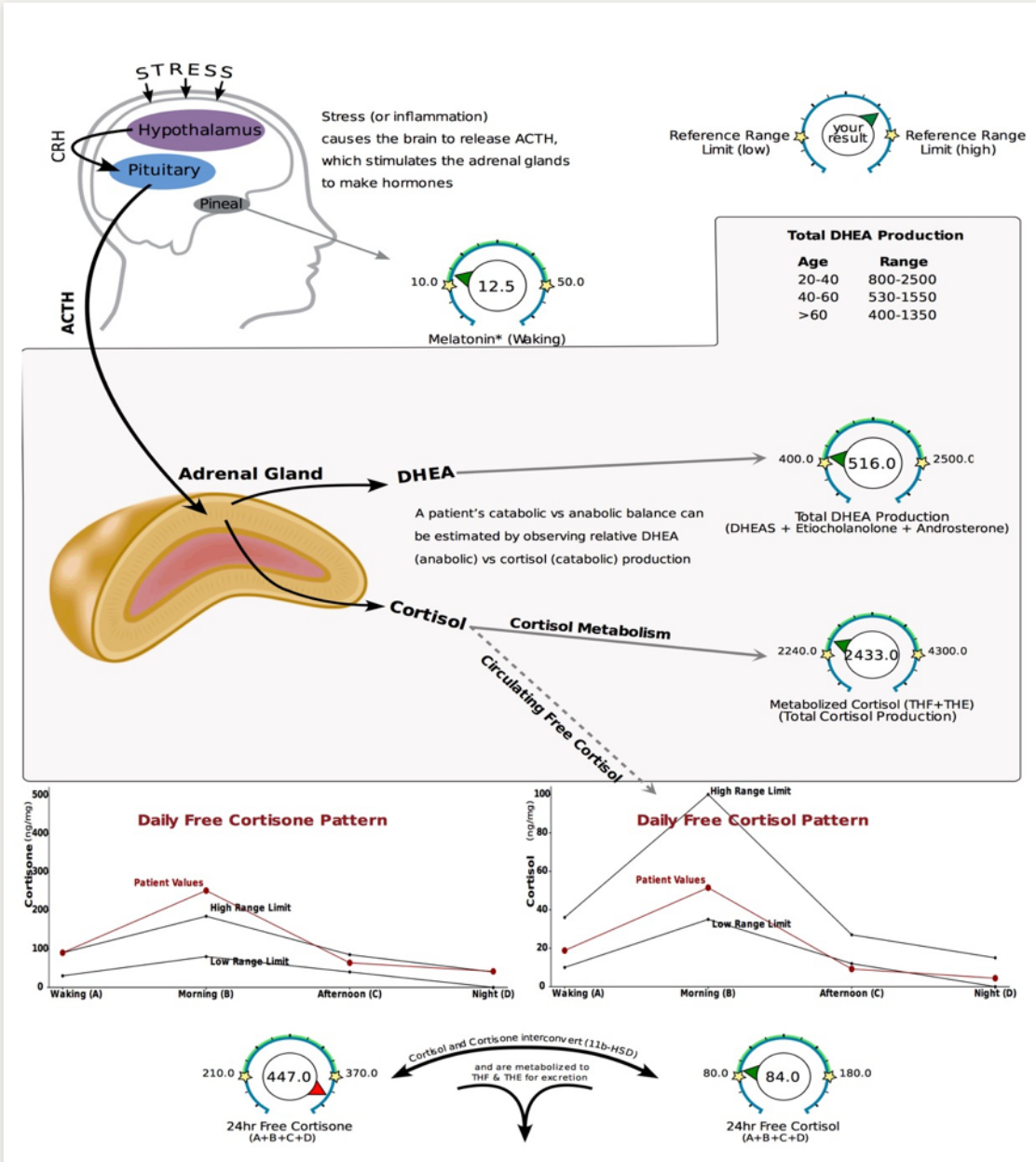






Here is the opposite scenario. DHEA sulfate is high, but total DHEA is normal. This is a 39-year-old male with chief complaint of digestive stress. When you see slightly elevated DHEA sulfate, as you're seeing here, and all of the other markers are normal, it is probably not pathological. If DHEA sulfate is significantly elevated and total DHEA is normal, possible causes would be things that upregulate sulfation such as a high-protein diet, some liver detox supplements or botanicals, and methylation supplements.

Okay, let's talk about cortisol-cortisone imbalances. Remember, cortisol is the more active form of the hormone, and cortisone is the less active form. These are interconverted back and forth, primarily by 11β-HSD. Factors that favor more cortisone include hyperthyroidism; human growth hormone; estradiol; good sleep; drugs such as ketoconazole; adaptogenic herbs such as magnolia, scutellaria, and ziziphus; and hormones such as testosterone. Factors that favor more cortisol include hypothyroidism, inflammation, visceral obesity, high insulin, excess sodium, and licorice, which increases the half-life of circulating cortisol.



Here is an example of high free cortisone and low-normal free cortisol. Total cortisol metabolites are low-normal, but tetrahydrocortisone is actually low. First, cortisone provides another look at cortisol production. If cortisol is normal or low but cortisone is high, mentally I pull the cortisol level up a bit in my mind. Likewise, if cortisol is normal or high but cortisone is very low, I would mentally pull cortisol down a bit.

Second, this indicates that a large amount of free cortisol is being inactivated into cortisone in the kidney. Free cortisone is not high from high levels of circulating free cortisone. It is from circulating free cortisol that gets shuttled into cortisone in local tissue of the kidney. If a person had high

circulating cortisone, you would expect high cortisone metabolites, but in this patient, the cortisone metabolites are low.

This patient is a 52-year-old female in perimenopause with rheumatoid arthritis, hypothyroidism, and digestive issues. As discussed before, poor thyroid function can lead to sluggish clearance of cortisol and cortisone into their terminal metabolites.

Ordering physician: Chris Kresser
DOB:1974-02-02
Gender: Female

Collection Times:
2015-04-04 05:00PM
2015-04-04 09:00PM
2015-04-05 04:00AM
2015-04-05 08:00AM
2015-04-05 12:25AM

Category	Test		Result	Units	Normal Range
Creatinine					
	Creatinine A (Waking)	Below range	0.44	mg/ml	0.5 - 3
	Creatinine B (Morning)	Within range	0.66	mg/ml	0.5 - 3
	Creatinine C (Afternoon)	Below range	0.44	mg/ml	0.5 - 3
	Creatinine D (Night)	Within range	0.51	mg/ml	0.5 - 3
Daily Free Cortisol and Cortisone					
	Cortisol A (Waking)	Within range	17.1	ng/mg	10.8 - 39.3
	Cortisol B (Morning)	Within range	51.9	ng/mg	24.5 - 87
	Cortisol C (Afternoon)	Below range	6.3	ng/mg	6.8 - 20.8
	Cortisol D (Night)	Above range	8.4	ng/mg	0 - 7.6
	Cortisone A (Waking)	Below range	40.2	ng/mg	47.2 - 142.9
	Cortisone B (Morning)	Below range	64.6	ng/mg	103.7 - 267.5
	Cortisone C (Afternoon)	Low end of range	51.2	ng/mg	46.5 - 135.5
	Cortisone D (Night)	Within range	36.1	ng/mg	0 - 52.3
	Cortisol-24hr (AUC)	Within range	16.0	ug	11 - 31
	Cortisone-24hr (AUC)	Below range	46.0	ug	49 - 131
Cortisol Metabolites and DHEAS					
	a-Tetrahydrocortisol (a-THF)	Within range	152.0	ng/mg	90 - 320
	b-Tetrahydrocortisol (b-THF)	Below range	456.0	ng/mg	750 - 1450
	b-Tetrahydrocortisone (b-THE)	Below range	921.0	ng/mg	1300 - 2560
	Metabolized Cortisol (THF+THE)	Below range	1530.0	ng/mg	2240 - 4300
	DHEAS	Low end of range	24.0	ng/mg	23 - 350
Melatonin (*measured as 6-OH-Melatonin-Sulfate)					
	Melatonin* (Waking)	Within range	20.7	ng/mg	10 - 50

Here is the opposite scenario where 24-hour free cortisol is within range, but free cortisone is low. Total cortisol metabolites are low, but cortisone metabolites are significantly lower in relation to cortisol metabolites. This patient is a 41-year-old female with fatigue and digestive issues as the main complaints. She was on thyroid medication, and the dose was too high. This was causing a facetious hyperthyroid condition, and it led to inactivation of cortisol to cortisone, which, as I mentioned, is observed in hyperthyroid states.