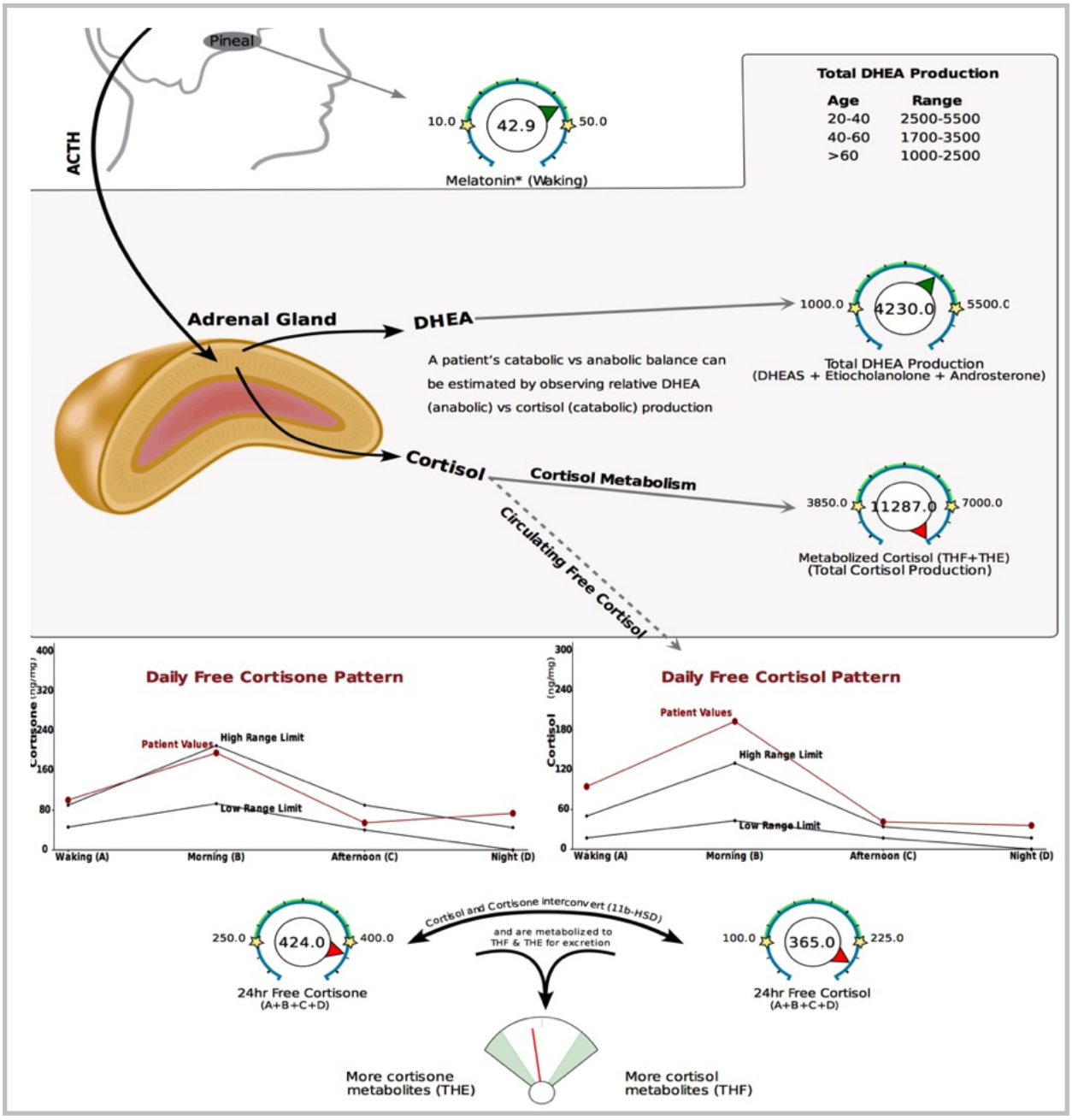
KRESSER INSTITUTE FOR FUNCTIONAL AND EVOLUTIONARY MEDICINE

HPA-D Case Studies – Part 5

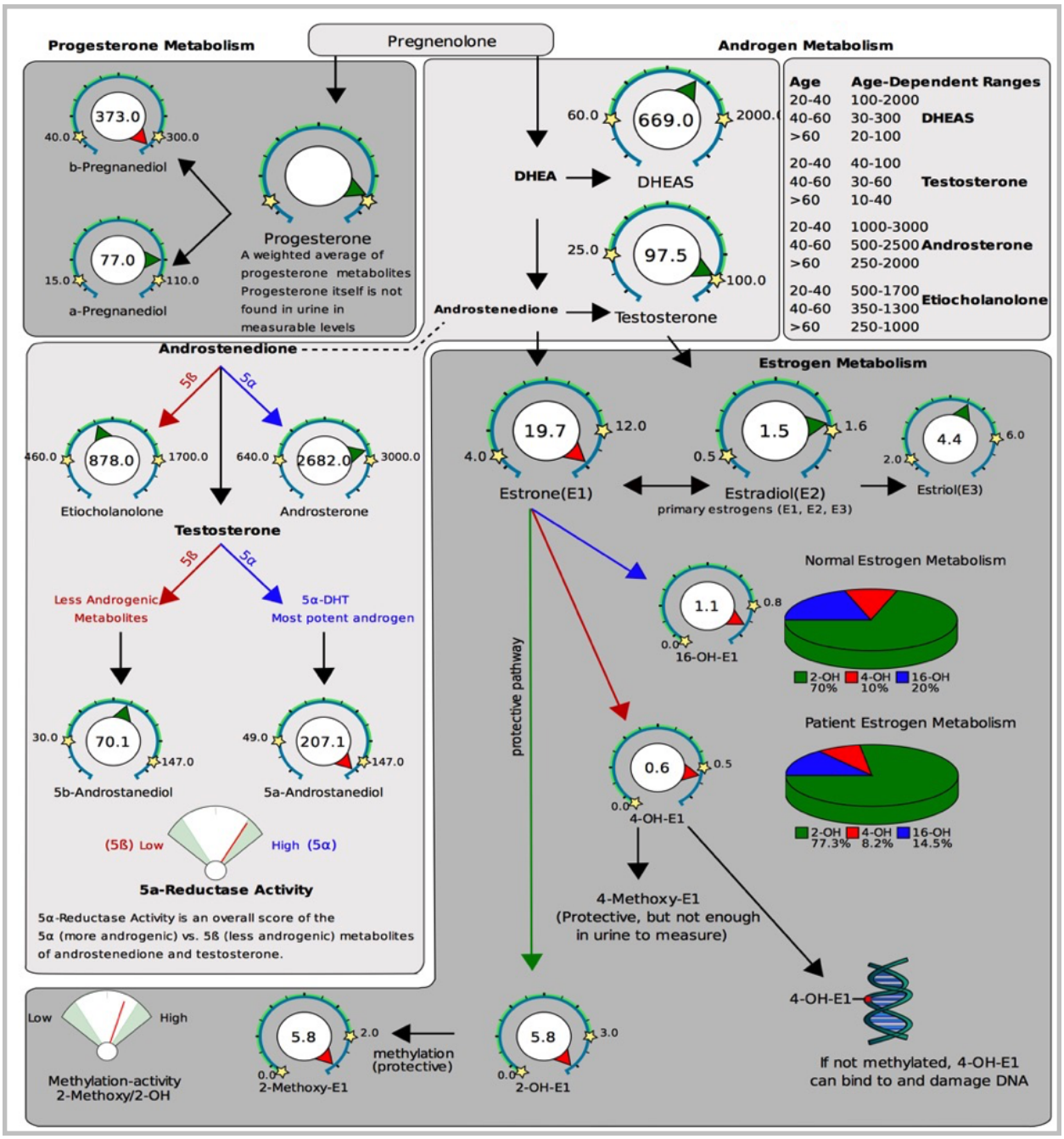
Next patient is a 30-year-old male. Chief complaint was IBS, heartburn, post-meal fatigue, and brain fog.



Free cortisol was really high at 365. Upper end of the range is 225. Diurnal cortisol rhythm was high at every time point, especially at night. Free cortisone rhythm was similar. Total free cortisone

was high, so it supports the free cortisol finding. Cortisol metabolites are very high. Upper end of the range is 7,000, and this patient was 11,287, so getting up there. Total DHEA was normal. Cortisol-to-DHEA ratio was high because of the very high cortisol. Cortisol-to-cortisone balance was normal, and the melatonin was normal.

Let's look at some other labs for this patient just to fill out the picture and give you an idea of how it all works together.



So notice on the sex hormone portion of the DUTCH test, he had borderline high androgens, 5-α androstanediol, borderline high testosterone, and high-normal DHT, which isn't pictured here. Then you have high estrone, high estrogen metabolites, and borderline high progesterone. So everything is trending high, and this is indicative of a hyperactive stress response. We want to be thinking about what could be driving that. Because we do a case review with every patient, and we have all of these different labs assessing gut and blood chemistry, we get the answer to that question right away. We often don't have to wait.

Comprehensive Stool Analysis / Parasitology x3

BACTERIOLOGY CULTURE

Expected/Beneficial flora	Commensal (Imbalanced) flora	Dysbiotic flora
4+ Bacteroides fragilis group	3+ Alpha hemolytic strep	4+ Citrobacter freundii complex
2+ Bifidobacterium spp.	2+ Gamma hemolytic strep	4+ Citrobacter freundii complex,isolate 2
NG Escherichia coli		3+ Klebsiella pneumoniae ssp pneumoniae
2+ Lactobacillus spp.		
NG Enterococcus spp.		
4+ Clostridium spp.		

NG = No Growth

BACTERIA INFORMATION

Expected /Beneficial bacteria make up a significant portion of the total microflora in a healthy & balanced GI tract. These beneficial bacteria have many health-protecting effects in the GI tract including manufacturing vitamins, fermenting fibers, digesting proteins and carbohydrates, and propagating anti-tumor and anti-inflammatory factors.
Clostridia are prevalent flora in a healthy intestine. Clostridium spp. should be considered in the context of balance with other expected/beneficial flora. Absence of clostridia or over abundance relative to other expected/beneficial flora indicates bacterial imbalance. If *C. difficile* associated disease is suspected, a Comprehensive Clostridium culture or toxigenic *C. difficile* DNA test is recommended.
Commensal (Imbalanced) bacteria are usually neither pathogenic nor beneficial to the host GI tract. Imbalances can occur when there are insufficient levels of beneficial bacteria and increased levels of commensal bacteria. Certain commensal bacteria are reported as dysbiotic at higher levels.
Dysbiotic bacteria consist of known pathogenic bacteria and those that have the potential to cause disease in the GI tract. They can be present due to a number of factors including: consumption of contaminated water or food, exposure to chemicals that are toxic to beneficial bacteria; the use of antibiotics, oral contraceptives or other medications; poor fiber intake and high stress levels.

YEAST CULTURE

Normal flora	Dysbiotic flora
1+ Geotrichum spp	

MICROSCOPIC YEAST

Result:	Expected:
None	None - Rare

The microscopic finding of yeast in the stool is helpful in identifying whether there is proliferation of yeast. Rare yeast may be normal; however, yeast observed in higher amounts (few, moderate, or many) is abnormal.

YEAST INFORMATION

Yeast normally can be found in small quantities in the skin, mouth, intestine and mucocutaneous junctions. Overgrowth of yeast can infect virtually every organ system, leading to an extensive array of clinical manifestations. Fungal diarrhea is associated with broad-spectrum antibiotics or alterations of the patient's immune status. Symptoms may include abdominal pain, cramping and irritation. When investigating the presence of yeast, disparity may exist between culturing and microscopic examination. Yeast are not uniformly dispersed throughout the stool, this may lead to undetectable or low levels of yeast identified by microscopy, despite a cultured amount of yeast. Conversely, microscopic examination may reveal a significant amount of yeast present, but no yeast cultured. Yeast does not always survive transit through the intestines rendering it unvialble.

Comprehensive Stool Analysis / Parasitology x3

DIGESTION /ABSORPTION

	Within	Outside	Reference Range
Elastase	> 500		> 200 µg/mL
Fat Stain	Few		None - Mod
Muscle fibers	None		None - Rare
Vegetable fibers	Few		None - Few
Carbohydrates	Neg		Neg

Elastase findings can be used for the diagnosis or the exclusion of exocrine pancreatic insufficiency. Correlations between low levels and chronic pancreatitis and cancer have been reported. **Fat Stain:** Microscopic determination of fecal fat using Sudan IV staining is a qualitative procedure utilized to assess fat absorption and to detect steatorrhea. **Muscle fibers** in the stool are an indicator of incomplete digestion. Bloating, flatulence, feelings of "fullness" may be associated with increase in muscle fibers. **Vegetable fibers** in the stool may be indicative of inadequate chewing, or eating "on the run". **Carbohydrates:** The presence of reducing substances in stool specimens can indicate carbohydrate malabsorption.

INFLAMMATION

	Within	Outside	Reference Range
Lysozyme*		717	<= 600 ng/mL
Lactoferrin		7.6	< 7.3 µg/mL
White Blood Cells	None		None - Rare
Mucus	Neg		Neg

Lysozyme* is an enzyme secreted at the site of inflammation in the GI tract and elevated levels have been identified in IBD patients. **Lactoferrin** is a quantitative GI specific marker of inflammation used to diagnose and differentiate IBD from IBS and to monitor patient inflammation levels during active and remission phases of IBD. **White Blood Cells** (WBC): in the stool are an indication of an inflammatory process resulting in the infiltration of leukocytes within the intestinal lumen. WBCs are often accompanied by mucus and blood in the stool. **Mucus** in the stool may result from prolonged mucosal irritation or in a response to parasympathetic excitability such as spastic constipation or mucous colitis.

IMMUNOLOGY

	Within	Outside	Reference Range
Secretory IgA*		2.7	51 - 204mg/dL

Secretory IgA* (sIgA) is secreted by mucosal tissue and represents the first line of defense of the GI mucosa and is central to the normal function of the GI tract as an immune barrier. Elevated levels of sIgA have been associated with an upregulated immune response.

Look at the patient's Doctor's Data gut results. We see low levels of some beneficial bacteria, but then we see four pluses for Citrobacter, two different species, and then a 3+ for Klebsiella pneumoniae. If we look at the inflammatory markers, we see high levels of lysozyme and high levels of lactoferrin and then low sIgA. This is definitely a gut inflammation situation, and we know that inflammation is one of the primary drivers of HPA-D.

Marker	Value	Functional Range	Lab Range
Glucose	101	75 - 90	65 - 99
Hemoglobin A1c	6.6	4.4 – 5.4	4.8 - 5.6
Uric Acid	5.2	3.7 – 6.0	3.7 - 8.6
BUN	21	13 – 18	6 - 20
Creatinine	1.00	0.85 – 1.1	0.76 - 1.27
BUN/Creatinine Ratio	21	8 – 19	8 - 19
Sodium	137	135 – 140	134 - 144
Potassium	4.8	4.0 – 4.5	3.5 - 5.2
Chloride	96	100 – 106	97 - 108
C02	25	25 – 30	18 - 29
Calcium	9.3	9.2 – 10.1	8.7 - 10.2
Phosphorus	2.8	3.5 – 4.0	2.5 - 4.5
Magnesium	2.1	2.0 – 2.6	1.6 - 2.3
Protein, total	7.0	6.9 – 7.4	6.0 - 8.5
Albumin	4.7	4.0 – 5.0	3.5 - 5.5
Globulin	2.3	2.4 – 2.8	1.5 - 4.5
A/G ratio	2.0	1.5 – 2.0	1.1 - 2.5
Bilirubin, total	0.5	0.1 – 1.2	0.0 - 1.2
Alkaline Phosphatase	79	42 – 107	39 - 117
LDH	176	140 - 180	121 - 224
AST	26	10 - 30	0 - 40
ALT	95	10 - 29	0 - 44
GGT	37	0 - 40	0 - 65
TIBC	400	250 – 350	250 - 450
UIBC	286	150 - 375	150 - 375
Iron	114	85 – 135	40 - 155
Iron saturation	29	15 – 45	15 - 55
Ferritin	309	30 - 150	30 - 400
Vitamin B-12	771	450 – 2000	211 - 946
Vitamin D, 25-hydroxy	29.6	35 - 60	30.0 - 100.0
Cholesterol, total	242	150 - 240	100 - 199
Triglycerides	56	50 – 100	0 - 149
HDL	57	55 – 85	> 39
LDL	174	0 - 175	0 - 99
T. Chol / HDL Ratio	4.2	< 3	0 - 5.0
Triglycerides / HDL Ratio	0.98	< 2	< 3.8
CRP-hs	0.7	< 1.0	0.00 - 3.00
Homocysteine	6.9	< 7.0	0.0 - 15.0

When we look at the first page of his blood chemistry report here, we see that he's pre-diabetic, insulin resistant. His fasting glucose is high. A1c is high. BUN is high, as is the BUN-to-creatinine ratio. We see ALT is elevated. Ferritin at 309 is elevated. Vitamin D is low, which is typical in diabetes. Total cholesterol of 240 I'm not necessarily worried about on its own, but his total

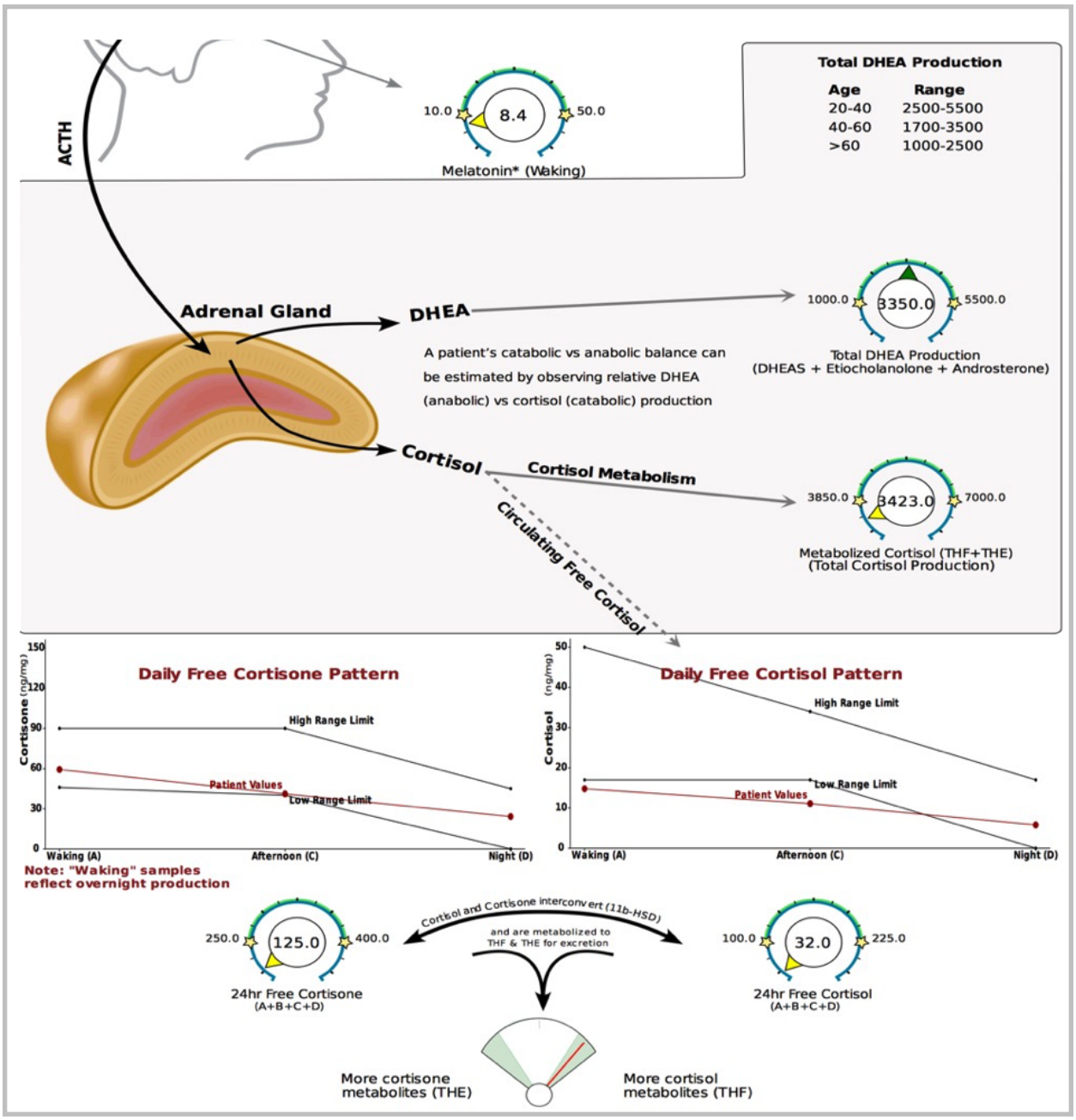
cholesterol-to-HDL ratio is high. It's higher than three, which indicates often a problem, and this patient very likely has a high LDL particle number, which I would be more concerned about.

He also has high levels of perceived stress and circadian disruption. This was a long-haul pilot of wide-body jets. He spent a lot of time sitting and definitely a lot of time crossing time zones, and his circadian rhythm was just really out of whack. So he had all four primary drivers of HPA axis dysfunction.

Protocol for high cortisol with inflammation & blood sugar dysregulation

Intervention	Dosage/Comments
HPA Balance (Vital Plan)	1 cap TID
Kavinace (Neuroscience)	1-2 caps before bed
PS (Integrative Therapeutics)	1 cap before bed
Acetyl-CH (Apex Energetics)	1 cap TID
Melatonin (Now 1 mg 2-stage release)	0.5 mg (cut tablet in half) 1 hour before bed
5-HTP (Jarrow)	50 mg 1 hour before bed
Boswellia AKBA (Pure Encapsulations)	1 cap OD or BID
Longvida curcumin (Pro-Health)	1 cap OD or BID
Metabolic Synergy (DFH)	2 caps TID
GlucoSupreme (DFH)	2 caps BID

This is a similar protocol we looked at before for high cortisol with inflammation and blood sugar dysregulation, a very complex situation and a lot of supplements. A lot of stuff going on. He wasn't going to change his job. He had seniority. He had worked many, many years to get to that level, captain and piloting these long-haul jets. He wasn't about to change his job, so we had to work within that framework. I advised him on using orange glasses, light exposure, and melatonin in accordance with his flight schedule and work schedule. Arrival at his destination is to mitigate circadian disruption as much as possible.



The next patient is a 55-year-old male. The main goal was reduce the risk of another heart attack. He had an MI in 2015 involving the LAD. His calcium score was 742 three years prior to that, and he'd lost about 70 pounds five years ago. Interestingly enough, he works as a CTO for a healthcare company, and he feels that conventional medicine is hopelessly broken. He feels like conventional MDs are too reliant on statins, so he wanted to find a way of managing this condition without statins now. We'll talk more about this when we get to the blood chemistry section, but the only population that statins have been shown to have a significant benefit for in terms of increasing lifespan, and by significant I mean statistically significant—I don't necessarily mean really

significant—is middle-aged men who have had a heart attack with pre-existing heart disease. This is one patient who may actually benefit from statins, but he didn't want to use them.

He injects testosterone. He was previously doing that three times a week, now at one to two times a week, because of supposedly low testosterone levels. I wasn't sure about that because he didn't really have labs to show for that, and some clinicians just do that empirically based on symptoms, which I do not think is a good idea. Then he lifts weights regularly.

So, if we look at his free cortisol, it's low. Diurnal cortisol rhythm is low waking, low afternoon, and normal at night. He didn't do a morning sample, which is why you only see three values here. Free cortisone rhythm was similar. Total free cortisone was low. Cortisol metabolites were low. Total DHEA was normal. Cortisol-to-DHEA ratio was low. Cortisol-to-cortisone balance, he is favoring cortisol, and his melatonin is low.

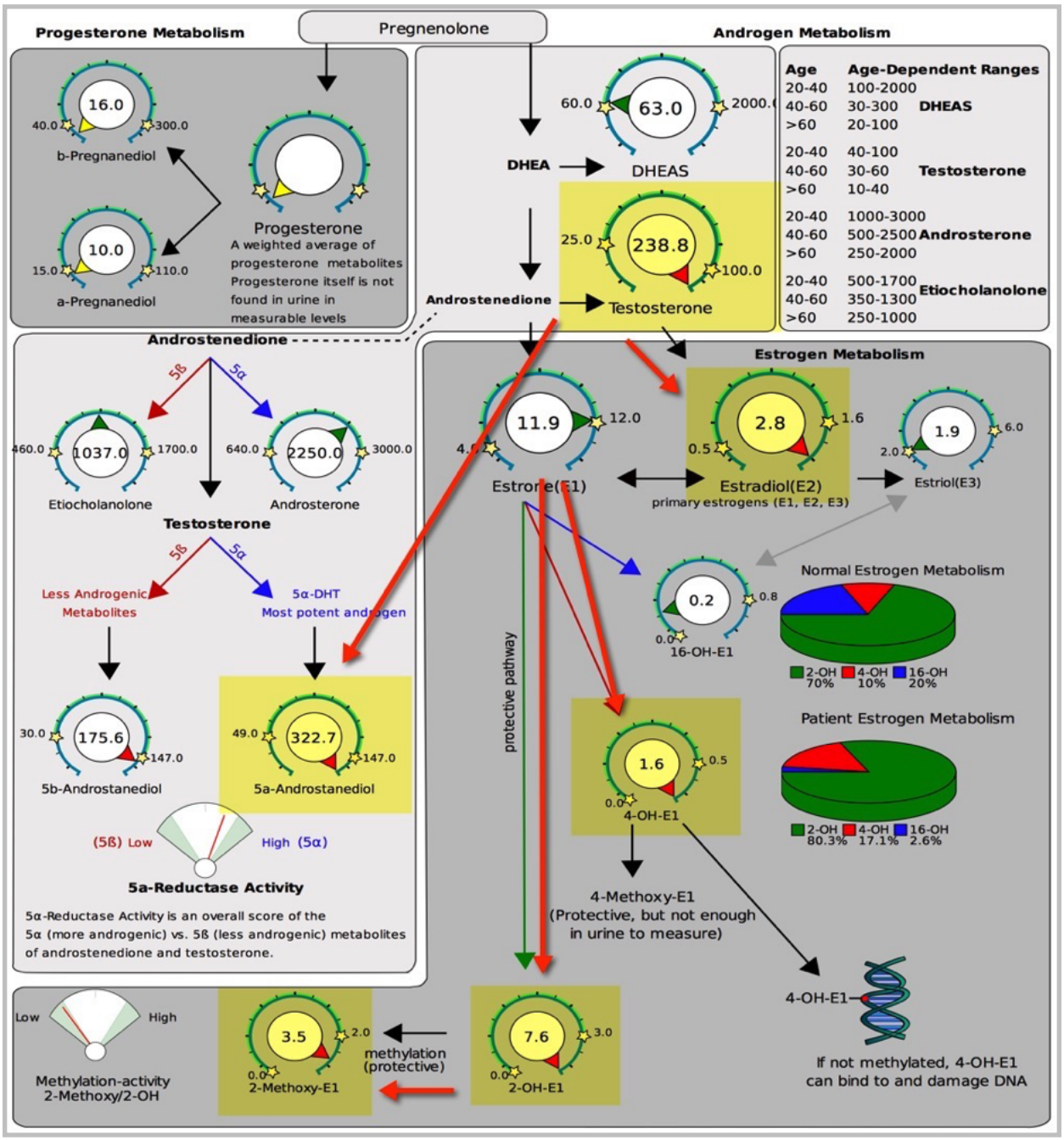
He took his samples at 5 p.m., 10 p.m., 3 a.m., and 6 a.m., so that alone should be a sign of circadian disruption. So if you pay attention to these little details, you'll catch interesting things about your patients. In this case, the 3 a.m. and 6 a.m. samples were combined to estimate a waking sample, and then no morning sample was reported.

Lipids	Total Cholesterol (mg/dL)		254			≥ 240	200 - 239	< 200	
	LDL-C Direct (mg/dL)		158			≥ 130 CHD & CHD risk eq. > 100	100 - 129 CHD & CHD risk eq. 70 - 100	< 100 CHD & CHD risk eq. < 70	
	HDL-C (mg/dL)		39			< 40		≥ 40	
	Triglycerides (mg/dL)		381			> 199	150 - 199	< 150	
	Non-HDL-C (mg/dL) (calculated)		215			≥ 160	130 - 159	< 130	
Lipoprotein Particles and Apolipoproteins	Apo B (mg/dL)		133			≥ 80	60 - 79	< 60	
	LDL-P (nmol/L)§, by NMR		1863			≥ 1360	1020 - 1359	< 1020	
	Small LDL-P (nmol/L)§, by NMR		1059			> 1000	501 - 1000	< 501	
	sdLDL-C (mg/dL)§		63			> 30	21 - 30	< 21	
	Apo A-I (mg/dL)			128		< 114	114 - 131	> 131	
	HDL-P (µmol/L)§, by NMR		27.7			≤ 34.0	34.1 - 38.0	> 38.0	
	HDL2-C (mg/dL)§			11		≤ 8	9 - 11	≥ 12	
	Apo B:Apo A-I Ratio (calculated)		1.04			≥ 0.81	0.61 - 0.80	≤ 0.60	
	Lp(a)-P (nmol/L)§		286			> 125	75 - 125	< 75	
Inflammation/ Oxidation	Fibrinogen (mg/dL)		618			< 126 or > 517	438 - 517	126 - 437	
	hs-CRP (mg/L)			1.3		> 2.9	1.0 - 2.9	< 1.0	
	Lp-PLA$_2$ (ng/mL)§		> 600			> 383	291 - 383	< 291	
	Oxidized LDL-β$_2$GPI (U/mL)§		0.5			≥ 0.2 High Risk	0.1 Moderate Risk	< 0.1 Low Risk	

Glycemic Control	Glucose (mg/dL)		132			> 125	100-125	70 - 99	
	HbA1c (%)			6.3		≥ 6.5	5.7 - 6.4	≤ 5.6	
	Estimated Average Glucose (mg/dL) (calculated)			134.1		≥ 139.9	116.9 - 139.8	≤ 116.8	
	Fructosamine (µmol/L)				288	> 346	302 - 346	< 302	
	Glycation Gap				-0.29	> 0.77	0.45 - 0.77	< 0.45	
	Postprandial Glucose Index			6.2		> 7.9	6.0 - 7.9	< 6.0	
Insulin Resistance	Leptin (ng/mL)				3	> 43	20 - 43	< 20	
	Leptin:BMI Ratio				0.10	> 1.17	0.66 - 1.17	< 0.66	
	Adiponectin (µg/mL)		6			< 10	10 - 14	> 14	
	Free Fatty Acid (mmol/L)		1.80			> 0.70	0.60 - 0.70	< 0.60	
	Ferritin (ng/mL) *				143	> 252	147 - 252	< 147	
	α-hydroxybutyrate (µg/mL)§			5.1		> 5.7	4.5 - 5.7	< 4.5	
	Oleic Acid (µg/mL)§		276			> 79	60 - 79	< 60	
	Linoleoyl-GPC (µg/mL)§				34.3	< 10.5	10.5 - 13.0	> 13.0	
	IR_1 Score (calculated)		7.8			< 8.0	8.0 - 10.0	> 10.0	
	HOMA-IR (calculated)		4.4			> 4.2	2.6 - 4.2	< 2.6	
Beta Cell Function	Insulin (µU/mL)		14			≥ 12	10 - 11	3 - 9	
	Proinsulin (pmol/L)			15		> 16	8 - 16	< 8	
	C-peptide (ng/mL)				2.8	> 4.6	3.1 - 4.6	1.0 - 3.0	
	Proinsulin:C-peptide Ratio		5.3			> 4.9	3.6 - 4.9	< 3.6	
	Anti-GAD (IU/mL)				< 5	> 5 Positive		≤ 5 Negative	

Here is a panel from True Health Diagnostics*, which we use for patients with lipid and metabolic abnormalities. As you can see, it is a sea of red. All of the lipid markers are out of range, many significantly so. Four out of four inflammatory markers were out of range. Fasting blood sugar 132 and an A1c of 6.3. Adiponectin, free fatty acids, oleic acid, linoleoyl GPC, insulin-resistance score, and HOMA-IR were all out of range. Insulin was out of range, and proinsulin-to-C-peptide ratio was abnormal. He's got blood sugar dysregulation. He's got severe inflammation. He's got high perceived stress, so that's three out of four of the key drivers, and it's concerning. If you see results like this, and you have a patient who has had a heart attack before, this is kind of like a house-is-burning-down level of intensity in terms of your focus and the patient's focus on getting this fixed up.

* **Note**: True Health Diagnostics is no longer in business. See **this post** for the latest updates.



You can see here on the hormone panel that it is pretty clear that he is injecting testosterone. His testosterone level is almost 2.5 times the upper end of the range, but he is also aromatizing a lot of that testosterone into estrogen and into estrogen metabolites that have a proliferative impact. They're associated with an increased risk of cancer. If you look at his 4-hydroxyestrone E1 levels, they are three times the upper end of the range, and that's associated with increased risk of prostate cancer. The body is trying to protect itself by methylating some of that 2-hydroxyestrone into 2-methoxyestrone, but there is so much, it can't really keep up.

If this is confusing to you, don't worry. We're not covering the sex hormones in this course. We'll do it in a later course, but you can get some—I just want to give you a taste of some of the really interesting information that you can get from the sex hormone part of this profile. In the meantime, the folks at Precision Analytical are really helpful.

Protocol for low cortisol with inflammation

Intervention	Dosage/Comments
Vital Adapt (Natura Health Products)	2 caps TID
Adrenal glandulars (Dr. Ron's)	3 capsules in the morning with breakfast
Acetyl-CH (Apex Energetics)	1 cap TID
5-HTP (Jarrow)	50 mg one hour before bed
Doc Parsley's Sleep Cocktail	One packet one hour before bed
Boswellia AKBA (Pure Encapsulations)	1 cap OD or BID
Longvida curcumin (Pro-Health)	1 cap OD or BID
Fish oil (Dr. Tobias or other)	2.4 g of EPA and 1.8 g of DHA per day

So you'd use the same protocol for this patient as the one I showed earlier for low cortisol with inflammation: Vital Adapt, adrenal glandular, acetyl-CH, 5-HTP, Doc Parsley's Sleep Cocktail, and then boswellia, curcumin, and fish oil. I'd also suggest that he consider getting off testosterone therapy.

Okay, that's it for the HPA Axis Dysfunction unit. We made it. Now I'm really excited to start with Blood Chemistry. See you then.