Secondary Causes of Diabetes

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Disclosures

None

Overview

Classification of diabetes

Review of secondary causes of diabetes

- Pancreatic Insufficiency
- Drug induced
- Hormone hypersecretion
- Genetic syndromes

Cases

Diabetes Classification

Type 1 diabetes (T1DM)	Type 2 diabetes (T2DM)	Gestational diabetes (GDM)	Secondary Diabetes
• Autoimmune beta cell destruction • Eventually complete insulin deficiency • Early or late onset (Latent autoimmune diabetes of adulthood = LADA)	• Progressive loss of adequate beta cell insulin production • Relative insulin deficiency • Typically associated w/ insulin resistance	• Diagnosed after the first trimester • No prior hx of diabetes	• Caused by another condition, treatment, or medication • Inherited syndromes

American Diabetes Association. 2. Classification and Diagnosis of Diabetes: *Standards of Medical Care in Diabetes-2021*. Diabetes Care. 2021 Jan;44(Suppl 1):S15-S33.

Secondary Causes of Diabetes

Pancreatic insufficiency

- Structural or functional loss of beta cell function
- Cystic fibrosis related Diabetes

Increased insulin resistance and hormone hypersecretion

- Medication Induced
- Steroid induced and post transplant diabetes
- Other disease processes (Cushing's syndrome, Acromegaly, PCOS, Glucagonoma)

Genetic Syndromes:

- MODY
- Neonatal diabetes
- Mitochondrial diabetes

Pancreatic Insufficiency

- Loss of pancreatic function and lack of T1DM associated autoimmunity
- Causes:
  - Pancreatitis (most common cause)
  - Trauma to the pancreas or surgery
  - Neoplasia
  - Cystic fibrosis
  - Hemochromatosis
  - Idiopathic
- Associated with loss of pancreatic enzyme and glucagon secretion
- Similar incidence of microvascular complications as other diabetes

Presentation

Suspect in patients with:

- Known pancreatic disease
- Symptoms of exocrine dysfunction
  - Steatorrhea (develops after loss of 90% glandular function)
  - Abdominal pain
  - Malabsorption
  - Unexplained weight loss
- Symptoms concerning for hemochromatosis
  - Darkening of skin
  - Transaminitis
  - Hypogonadism
- Consider imaging (CT or MRI) to look for pancreatic abnormalities or atrophy

Pancreatic Insufficiency

Evaluation

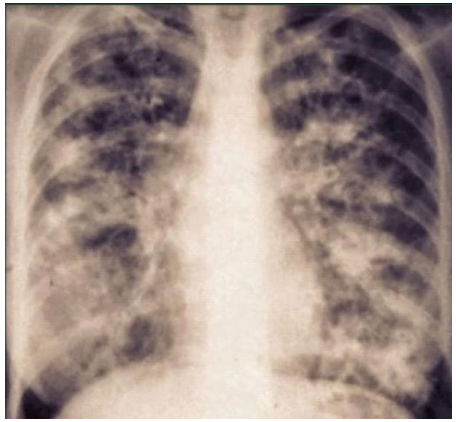
- Fasting C-peptide and glucose
- Fecal elastase
- Screening for CF when appropriate
- Screening for hemochromatosis if suspected
- Consider pancreatic imaging

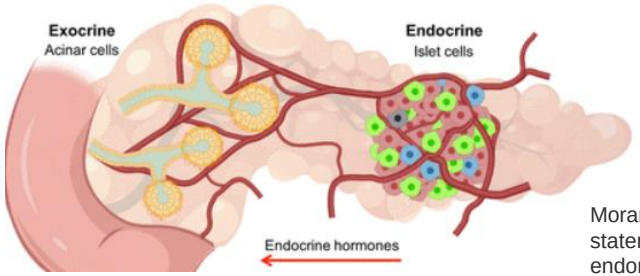
Treatment

- Insulin - may require high doses of prandial insulin
- Risk for hypoglycemia - prescribe glucagon
- Avoid GLP-1 agonists and DPP4 inhibitors with hx of pancreatitis

CFRD - Cystic Fibrosis Related Diabetes

- Thick mucus in pancreas leads to scaring and loss of function
- Progressive loss of pancreatic function → diabetes in 40-50% of adults with CF
- Infection and inflammation result in Insulin resistance
- Early diagnosis and treatment preserves lung function





Screening:

- Annual OGTT beginning by age 10 without known CFRD
- 2H 75g glucose tolerance test with glucose >200
- After diagnosis annual screening for complications (similar to T1DM)

Moran A, Brunzell C, Cohen RC, et al. Clinical care guidelines for cystic fibrosis-related diabetes: a position statement of the American Diabetes Association and a clinical practice guideline of the Cystic Fibrosis Foundation, endorsed by the Pediatric Endocrine Society. *Diabetes Care*. 2010;33(12):2697-2708. doi:10.2337/dc10-1768

CFRD Treatment

Insulin improves nutritional status and promotes desired weight gain

- Most patients require basal and bolus insulin and benefit from using ICR
- Insulin pump may be an option
- Acute illness or glucocorticoid treatment may result in 2-4 fold increase in insulin which may take 4-6 weeks to normalize after recovery

Non-insulin medications are not recommended

Carbohydrate/calorie restriction not recommended

Goal HbA1c <7% with some individualization

Patients should be seen q 3 mo by multidisciplinary team

Moran A, Brunzell C, Cohen RC, et al. Clinical care guidelines for cystic fibrosis-related diabetes: a position statement of the American Diabetes Association and a clinical practice guideline of the Cystic Fibrosis Foundation, endorsed by the Pediatric Endocrine Society. *Diabetes Care*. 2010;33(12):2697-2708. doi:10.2337/dc10-1768

Insulin Resistance and Hormone Hypersecretion

Medication Induced

- Non-steroid medications
- Steroid induced diabetes
- Post transplant diabetes

Secondary to other syndromes/diseases

- PCOS
- Cushing's syndrome/disease
- Acromegaly
- Glucagonoma

Risk of weight gain, diabetes and receptor affinities of selected first- and second-generation antipsychotics

	Risk of weight gain	Risk of diabetes*	D_2 dopamine	$5HT_{2c}$ serotonin	$5HT_{1a}$ serotonin	M_3 muscarinic	α_2 adrenergic	H_1 histamine
Role in weight regulation			✓	✓				✓
Role in insulin secretion			✓		✓	✓	✓	
First-generation antipsychotic								
Chlorpromazine	+++	+++	++++	++++	+	++++	+	++++
Perphenazine	+	+	++++	++++	+	+	+	+++
Haloperidol	++	+	++++	++	–	+	+	+/–
Second-generation antipsychotic								
Clozapine	+++	+++	+++	+++	++	+++	++	+++
Olanzapine	+++	+++	+	+++	+	+++	+	+++
Quetiapine	++	++	+	+	+	+	+++	++
Risperidone	++	++	+++	++++	++	–	++++	++
Ziprasidone	+	+	+++	++++	++++	–	++	+
Aripiprazole	+	+	++++	+++	++++	–	++	+
Paliperidone	++	+	+++	++++	+	–	+++	++
Lurasidone	+	+	++++	++	++++	–	N/A	–

Holt RIG. Association Between Antipsychotic Medication Use and Diabetes. *Curr Diab Rep*. 2019;19(10):96. Published 2019 Sep 2. doi:10.1007/s11892-019-1220-8

Steroid Induced Hyperglycemia

- Glucocorticoids (GCs) are used for chronic treatment of inflammatory conditions and after organ transplant
- Increased insulin resistance by:
  - Altering activity of 11 beta HSD that converts cortisone to cortisol
  - interfering with GLUT4 transporter (decreased glucose uptake in tissues)
  - Promotes liver gluconeogenesis
  - Impacts on adipose tissue that increase insulin resistance
- Diagnostic criteria is the same for T2DM
- Causes disproportionate post-prandial vs. fasting hyperglycemia
- Patients started on GCs should have a baseline glucose and be instructed on home monitoring
  - BG 2 hours after lunch may be most reliable in patients treated with intermediate acting GCs dosed daily in am

Tamez-Pérez HE, Quintanilla-Flores DL, Rodríguez-Gutiérrez R, González-González JG, Tamez-Peña AL. Steroid hyperglycemia: Prevalence, early detection and therapeutic recommendations: A narrative review. *World J Diabetes*. 2015;6(8):1073-1081.

Post-Transplant Diabetes Melitus

- Definition = patients with post transplant hyperglycemia regardless of pre-existing DM
- Screen for hyperglycemia when patient is on a stable immunosupressive regimen without acute infection
- OGTT is preferred screening
  - HbA1c may not be accurate due to anemia, blood transfusions, and new onset of diabetes
- Insulin is the treatment of choice during hospitalization
- Can resume home DM meds at discharge if previously well controlled and not contraindicated
  - Limited data on what agents should be used
  - DPP4 inhibitors have shown safety in small studies and do not interfere with immunosuppressants
  - NPH is a good option on patients on daily prednisone

American Diabetes Association. 2. Classification and Diagnosis of Diabetes: *Standards of Medical Care in Diabetes-2021*. Diabetes Care. 2021 Jan;44(Suppl 1):S15-S33.

Treatment of Steroid Induced Hyperglycemia

Mild hyperglycemia (BG <200)

- May be treated with insulin sensitizing agents or incretins
- DPP4 inhibitors particularly useful
- Limited ability to titrate

Moderate/severe hyperglycemia (BG >200)

- Insulin preferred for immediate onset and ability to titrate
- Hyperglycemic effect of prednisone is about 12 hours so kinetics of NPH make it a good option
  - NPH 0.1 unit/kg for every 10 mg of prednisone (maxed at 0.4 unit/kg) given at the time as glucocorticoid
  - In patients already on MDI add NPH to existing insulin regimen
- If already on basal bolus regimen can increase prandial insulin
  - Typical requirement is about 70% prandial and 30% basal

Clore JN, Thurby-Hay L. Glucocorticoid-induced hyperglycemia. Endocrine Practice. 2009 Jul-Aug;15(5):469-74.

Hypercortisolemia

Cushing's Syndrome = hypercortisolemia from any cause

- Iatrogenic
- ACTH mediated (pituitary cause = Cushing's Disease)
- Autonomous cortisol production by the adrenal glands

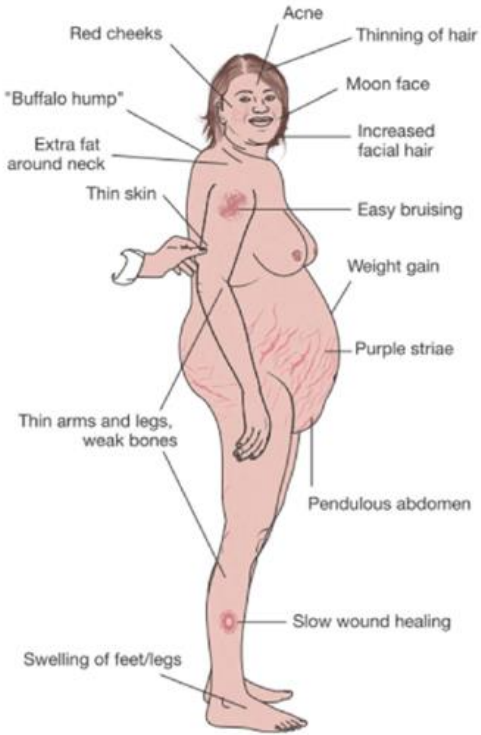
Exam:

- Plethora, facial fullness, prominent dorsal cervical and supraclavicular fat pads
- Ecchymoses, violaceous striae, hirsutism, acne, hair loss
- Central adiposity, proximal muscle weakness

History

- Unexplained weight gain
- VTE, depression/mood disturbance
- Hyperglycemia, HTN
- Fragility fractures, easy bruising
- Irregular menses or hypogonadism
- Use of exogenous GCs (injection, topical/intranasal w/ HIV meds, oral, etc)

Cushing's Syndrome Findings



- Hypertension
- Poor short-term memory
- Irritability
- Fatigue
- Poor concentration
- Menstrual irregularity
- Glucose intolerance
- Headaches
- Insomnia
- Recurrent infection
- Depression

Brue T, Castinetti F. The risks of overlooking the diagnosis of secreting pituitary adenomas. Orphanet J Rare Dis. 2016 Oct 6;11(1):135. doi: 10.1186/s13023-016-0516-x. PMID: 27716353; PMCID: PMC5052978.

Evaluation of Hypercortisolemia

First step = establish hypercortisolemia

- Am cortisol may be normal so not good for screening
- Screening options
  - 1mg dexamethasone suppression test (DST)
    - Dex at 11 pm followed by 8 am cortisol and dex level
    - Normal = cortisol less than 1.8 with adequate dex level
  - 24H urine free cortisol
    - Abnormal if >50 mcg/day
    - Avoid if significant kidney disease, correct for urine volume and Cr
  - late night salivary cortisol x 2

Next step = check ACTH to see if ACTH-mediated

- Low ACTH = adrenal cortisol production
- High/normal ACTH = pituitary or ectopic production

If testing normal, may repeat or try different test if clinical suspicion is high

…or refer to endocrine

Acromegaly and Diabetes

GH excess = acromegaly (onset as adult)

- Causes insulin resistance and increased gluconeogenesis

Clinical features:

- Change in appearance or teeth spacing
- Increased hat/ring/shoe size
- Increased sweating (hyperhidrosis)
- Impaired glucose tolerance
- Joint pain/carpal tunnel syndrome
- OSA
- Cardiac disease (CHF, hypertrophy)

…again needs endocrine referral

Screening:

- IGF-1 (at Quest)- if elevated this is concerning for acromegaly
- OGTT screens for IGT or T2DM

Ferraù F, Albani A, Ciresi A, Giordano C, Cannavò S. Diabetes Secondary to Acromegaly: Physiopathology, Clinical Features and Effects of Treatment. *Front Endocrinol (Lausanne)*. 2018;9:358. Published 2018 Jul 6. doi:10.3389/fendo.2018.00358

Polycystic Ovary Syndrome (PCOS)

- Prevalence in the US is 4-12% of women
- Diagnosed with Rotterdam criteria (need 2/3)
  - Androgen excess (biochemical or clinical)
  - Ovulatory dysfunction
  - Polycystic ovaries
    - 12 or more follicles 2–9 mm in diameter and/or an increased ovarian volume >10 mL (without a cyst or dominant follicle) in either ovary
- Exclude other conditions
  - Thyroid disease, hyperprolactinemia, congenital adrenal hyperplasia, and in severe presentation hypercortisolemia, androgen secreting tumor)

Legro RS, Arslanian SA, Ehrmann DA, et al. Diagnosis and treatment of polycystic ovary syndrome: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2013;98(12):4565-4592.

PCOS and Diabetes

- PCOS is associated with 5-10 x increased risk of developing T2DM
- In those with PCOS:
  - Prevalence of IGT = 30-35%
  - Prevalence of T2DM = 3-10%
- Screen with OGTT (if not possible then HbA1c)
- Re-screen every 3-5 years or sooner based on factors like weight gain and symptoms of hyperglycemia
- Treat IGT or T2DM with
  1. Lifestyle modification
  2. Metformin
  3. Agents that can promote weight reduction (GLP-1 agonists or SGLT-2 inhibitors)

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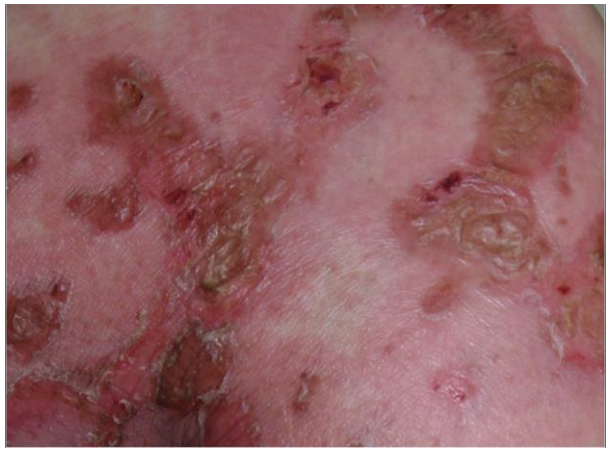
Glucagonoma



NME
- presenting symptom in ~70%
- Affects groin, buttock, lower legs
- Pruritic and painful
- Sore smooth tongue and cracked lips

- Pancreatic neuroendocrine tumor with unregulated glucagon secretion
- 75-80% are malignant with half presenting with metastatic disease
- Presentation:
  - Hyperglycemia or diabetes
  - Weight loss
  - Anemia
  - hypoalbuminemia
  - Necrolytic migratory erythema (most characteristic clinical sign)
- If suspected needs specialty evaluation for biochemical evaluation

	Gene	Inheritance	Clinical features
MODY	*GCK*	AD	GCK-MODY: stable, nonprogressive elevated fasting blood glucose; typically does not require treatment; microvascular complications are rare; small rise in 2-h PG level on OGTT (<54 mg/dL [3 mmol/L])
	HNF1A	AD	HNF1A-MODY: progressive insulin secretory defect with presentation in adolescence or early adulthood; lowered renal threshold for glucosuria; large rise in 2-h PG level on OGTT (>90 mg/dL [5 mmol/L]); sensitive to sulfonylureas
	HNF4A	AD	HNF4A-MODY: progressive insulin secretory defect with presentation in adolescence or early adulthood; may have large birth weight and transient neonatal hypoglycemia; sensitive to sulfonylureas
	HNF1B	AD	HNF1B-MODY: developmental renal disease (typically cystic); genitourinary abnormalities; atrophy of the pancreas; hyperuricemia; gout
Neonatal diabetes	*KCNJ11*	AD	Permanent or transient: IUGR; possible developmental delay and seizures; responsive to sulfonylureas
	INS	AD	Permanent: IUGR; insulin requiring
	ABCC8	AD	Permanent or transient: IUGR; rarely developmental delay; responsive to sulfonylureas
	6q24 (*PLAGL1, HYMA1*)	AD for paternal duplications	Transient: IUGR; macroglossia; umbilical hernia; mechanisms include UPD6, paternal duplication or maternal methylation defect; may be treatable with medications other than insulin
	GATA6	AD	Permanent: pancreatic hypoplasia; cardiac malformations; pancreatic exocrine insufficiency; insulin requiring
	EIF2AK3	AR	Permanent: Wolcott-Rallison syndrome: epiphyseal dysplasia; pancreatic exocrine insufficiency; insulin requiring
	EIF2B1	AD	Permanent diabetes: can be associated with fluctuating liver function (138)
	FOXP3	X-linked	Permanent: immunodysregulation, polyendocrinopathy; enteropathy X-linked (IPEX) syndrome: autoimmune diabetes, autoimmune thyroid disease, exfoliative dermatitis; insulin requiring

AD, autosomal dominant; AR, autosomal recessive; IUGR, intrauterine growth restriction; OGTT, oral glucose tolerance test; UPD6, uniparental disomy of chromosome 6; 2-h PG, 2-h plasma glucose.

Monogenic Diabetes Syndromes

- Neonatal diabetes (occurs <6 months of age)
  - 80-85% due to monogenic cause
- Maturity onset diabetes of the young (MODY)
  - Due to one of more than 14 genetic mutations impacting insulin secretion
- Screen children and young adults with presentation not characteristic of T1DM or T2DM with family hx
  - Negative autoantibodies and no signs of insulin resistance
  - Autosomal dominant inheritance
- If suspected refer to Endocrinology
- Diagnosis of MODY impact management
  - GCK mutation- not progressive and usually doesn't require treatment
  - HNF1A mutation – sulfonylureas are preferred treatment
  - HNF1B mutation – associated with renal disease

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Case 1

- 32 y/o male presents for 2 week hospital follow up after admission for necrotizing pancreatitis presenting with TG 2000 after heavy drinking
- Previously healthy, wt 100 kg, HbA1c 5.3
- Discharged home on pancreatic enzymes, Levemir 40 units nightly, and low dose sliding scale TID before meals
- Blood glucose log shows fasting 70-90, other times 200s
- Patient requests changing to oral medications and injections are not convenient

Case 1 - Continued

- Diagnosis?
  - Hx of severe pancreatitis now on pancreatic enzymes = diabetes due to pancreatic insufficiency
  - Can confirm with fasting C-peptide and BG
- Treatment?
  - Treat as T1DM
  - Requires insulin, cannot change to only oral medications
  - Prescribe glucagon
  - Avoid DPP4 inhibitors and GLP-1 agonists
  - Will need diabetes education and
  - May benefit from CGM and in the future possible insulin pump

Case 2

- 68 y/o woman with hx of HTN and preDM (on metformin) who was started on prednisone 20 mg daily for rheumatoid arthritis 2 weeks ago as she did not have adequate response to alternate treatments
- Weight = 100 kg, BMI 31
- Coming for routine HTN follow up with labs last week showing HbA1c of 6.0 (previously 6.2)
- She does not check blood sugar at home
- On ROS she reports new polyuria and polydipsia

Case 2- Continued

- What do you suspect?
  - Should screen for steroid induced hyperglycemia
  - In office POC blood glucose is 210 about 2 hours after lunch
- But HbA1c has improved….
  - HbA1c reflects avg BG over the past 3 months and prednisone was started 2 weeks ago
- Treatment?
  - Prescribe home glucose testing supplies for more data and close follow up

Case 2- Continued

- 1 week later her blood glucose log shows:

Pre-breakfast	Pre-lunch	Pre-dinner	Bedtime
90	221	201	180
130	235	264	190
142	240	210	186
128	210	195	175
168	184	165	220
120	192	203	153
136	214	198	185

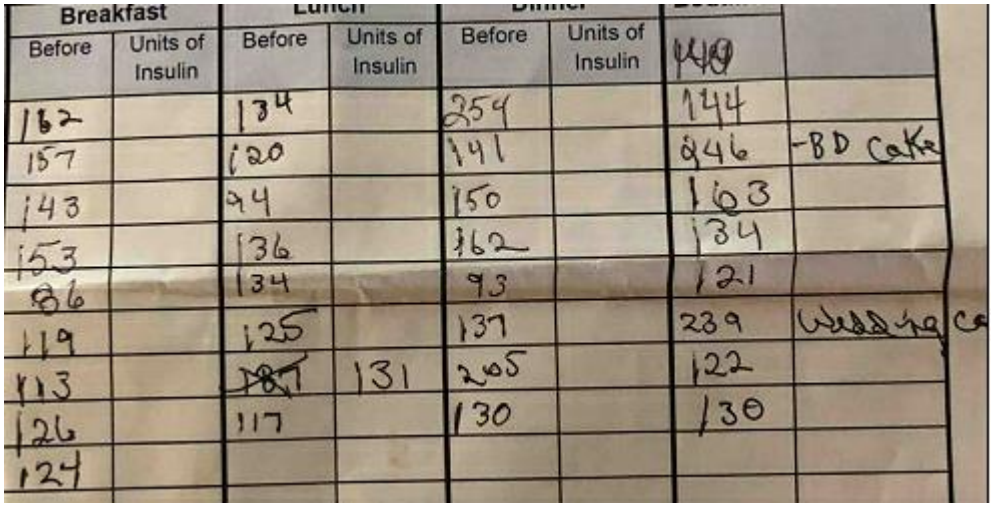
Case 2- Continued

- 1 week later her blood glucose log shows:
- Treatment?
  - Consider adding once daily NPH
    - 0.1 unit/kg for every 10 mg prednisone
    - 0.1 x 100 kg x 2 = 20 units of NPH
    - Let's be conservative since she is insulin naïve and older
    - Reduce to 15 units every morning w/ prednisone 20 mg
  - Refusing daily injection
    - DPP4-inhibitor – may need renal dosing
    - Sulfonylurea if normal kidney function
    - SGLT-2 inhibitor if no contraindications

Pre-breakfast	Pre-lunch	Pre-dinner	Bedtime
90	221	201	180
130	235	264	190
142	240	210	186
128	210	195	175
168	184	165	220
120	192	203	153
136	214	198	185

Case 2 - Continued

- She chooses to start NPH 15 units every morning
- One week later blood sugars are mostly at goal
- She agrees to notify you prior to andy changes in her prednisone dose



Breakfast		Lunch		Dinner			
Before	Units of Insulin	Before	Units of Insulin	Before	Units of Insulin		
162		134		254		144	
157		120		141		246	-BD Cake
143		94		150		163	
153		136		162		134	
86		134		93		121	
119		125		137		239	
113		87	131	205		122	
126		117		130		130	
124							

Case 3

- 31 y/o female with previous diagnosis of PCOS (on combined OCP) and spironolactone presenting for evaluation of weight gain.
- Weight 120 kg, BMI 41, BP 162/96
- HbA1c 2 weeks ago was 7.4 and she was started on metformin but discontinued due to diarrhea
- Weight is up 60 lbs since the pandemic started. She attributes this to decreased activity after rib fracture while sleeping.
- She has worse acne despite trying 2 different OCPs with GYN and increasing spironolactone
- Reports irregular menses for 2 years prior to starting OCP (they were regular until age 28)
- She is frustrated that her lifestyle modifications have not been successful and inquires about bariatric surgery

Case 3 - Continued

- What to look for on exam?
  - Plethora, facial fullness, prominent dorsal cervical and supraclavicular fat pads
  - Ecchymoses, violaceous striae, hirsutism, acne, hair loss
  - Central adiposity, proximal muscle weakness
- She has all the symptoms except for muscle weakness
- Next steps?
  - Testing for hypercortisolemia vs. endocrine referral
- Testing?
  - She is on a combined OCP so dexamethasone suppression test will be less accurate
  - Check 24 hour urine free cortisol and or late night salivary cortisol

Case 3 - Continued

- Results:
  - 24 hour urine free cortisol – 304 (normal <50)
  - LNSC x2 both >3 times higher than the ULN
- Patient is referred to endocrinology
- Further testing reviels low-normal ACTH and repeat UFC elevated
- Pituitary MRI shows 9 mm adenoma
- She undergoes successful transsphenoidal surgery with resolution of hypercortisolemia
- At follow up 3 months after surgery
  - Down 30 lbs and feeling much better
  - BP has normalized
  - HbA1c is 6.2

References

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