“Type 3” Diabetes?
Adult onset diabetes: which type is it?



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Objective

- Recognize the different types of diabetes
- Describe the features suggestive of relatively uncommon types of diabetes
- Understand how to properly diagnose different types of diabetes

Stella

- 38yo female referred for new onset diabetes (A1c 10.6%, FPG 290)
- Found during pre-op evaluation for breast nodule that seemed highly suspicious
- Reports polyuria, polydipsia and about 5lbs weight loss in the past 1month
- Reports she’s been stress eating (especially sweets) lately due to stress of potential cancer

Diagnosis of diabetes

- Fasting glucose ≥ 126mg/dL* or
- OGTT 2h glucose ≥ 200mg/dL* or
- A1c ≥ 6.5%* or
- Random glucose ≥ 200 + classic symptoms

*two (+)tests in same sample or in two separate samples

Classification and Diagnosis of Diabetes. Diabetes Care. Volume 42, Supplement 1, January 2019

Classification of DM

- Type 1 (~5%)
- Type 2 (~90%)

→ Which type does Stella have?

Bullard et al. Prevalence of Diagnosed Diabetes in Adults by Diabetes Type - United States, 2016. MMWR 2018;67:359–361.

Stella

- History of prediabetes (2-3yrs, A1c 5.7 and 5.9% with IFG), HTN (on lisinopril) and overweight/obesity (BMI 28-30)

- BP 132/78 (on lisinopril), BMI 27
- TC 160, HDL 49, TG 100, LDL 91
- Med list: metformin 1000mg BID (started last week by PCP), lisinopril 10mg/d

“Classic”

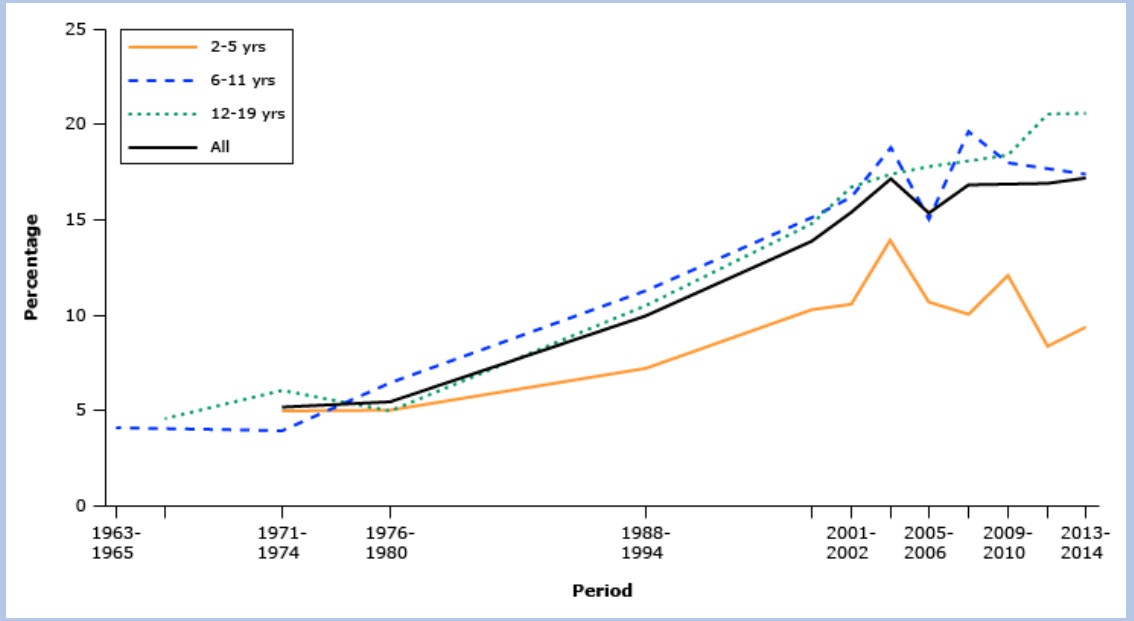
- **DM 1**
  - Early onset (before mid teens)
  - Lean
  - Insulin sensitive
  - Lack of response to noninsulin therapy
  - Symptomatic at diagnosis (DKA, 3Ps)



- **DM 2**
  - Late onset (>50yo)
  - Obese
  - insulin resistance
  - Decent response to noninsulin therapy
  - Asymptomatic at diagnosis

DM 2: Age barrier collapsed

Trends in obesity among children and adolescents aged 2–19 years, by age: 1963–1965 through 2013–2014



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- 1 in 3 new DM in youth (<18yo) is DM2
- Greater risk in certain race/ethnicity (native americans > AA > hispanics > Asians > Caucasian)

Fryar et al. *Health E-Stats July 2016 /* Silverstein et al. Curr Diab Rep. 2001;1 (1):19–27 / Dabelea et al. *JAMA*. 2014;311(17):1778-1786

Latent Autoimmune Diabetes in Adults (LADA)

- AKA: type 1.5, non-insulin requiring autoimmune diabetes, slowly progressing type 1 diabetes
- “later” onset with (+)antibodies
- 40% of DM 1 diagnosed before 20yo

SEARCH for Diabetes in Youth Study Group et al., 2007

Latent Autoimmune Diabetes in Adults (LADA)

- UKPDS: frequent (+)autoimmunity in patients who were diagnosed as DM 2

  (34% in 25-34yo and 9% in 55-65yo)
- Faster progression to insulin dependence
- Personal and/or family hx of autoimmune d/o

Desai M, Clark A. Autoimmune diabetes in adults: lessons from the UKPDS.Diabet Med. 2008 Aug;25 Suppl 2:30-4

When to suspect antibody(+) DM (DM 1 / LADA)

- Younger (< 50yo)
- Leaner (BMI < 25)
- Personal and/or Family hx of autoimmune disorder
- More acute presentation: catabolic state
- Unresponsive to noninsulin therapy
- Rapid progression of insulinopenia requiring insulin therapy.

Islet cell directed antibodies

	Sensitivity	Specificity
Glutamic acid decarboxylase (GAD65)	70-90%	99%
Insulin (IAA)*	40-70%	99%
Tyrosine phosphatase IA2 (ICA512)**	50-70%	99%
Zinc transporter 8 (ZnT8)	50-70%	99%

*may develop with exogenous insulin treatment even in the absence of autoimmune d/o

** Aka insulinoma-associated antigen (IA-2A)

Table from Gardner D et al. Greenspan's Basic & Clinical Endocrinology, Chapter17. P588

C-peptide

normal reference: 1.1-4.4ng/mL (measure when fasting glucose < 225)
*supplemental test. Estimates b-cell reserve

Clinical role	Fasting	Stimulated
Absolute insulin deficiency	< 0.24	< 0.6
Likely DM 1 / inability to achieve goal without insulin	< 0.75	< 1.8
Suggests DM 2 or MODY in pts with presumed DM 1 > 3–5y post-dx	> 0.24	> 0.6
Consider MODY/DM 2 in young onset DM at Dx	> 1.2	> 3

Modified from A.G.Jones et al. Diabet. Med. 30, 803-817 (2013)

Stella

- Lifestyle intervention recommendations
- Started on basal insulin 10units and instructed to increase by 3units q2-3days if fasting glucose >150.
- Reports nausea and diarrhea. Changed metformin IR to metformin ER tabs

Stella

- GAD/insulin ab/ZnT8 (-)
- Glucose 170, Cpeptide 2.1

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Classification of DM

- Type 1 (~5%)
  - DM 1a: abs (+)
  - DM 1b: abs (-). Idiopathic.
- Type 2 (~90%)
- Secondary diabetes (~5%)

  → Specific types of diabetes due to other causes

Bullard et al. Prevalence of Diagnosed Diabetes in Adults by Diabetes Type - United States, 2016. MMWR 2018;67:359–361.

Secondary Diabetes

- Monogenic diabetes
- Disease of exocrine pancreas
- Endocrinopathies
- Drug or chemical-induced
- Infections
- Uncommon forms of immune-mediated diabetes
- Other genetic syndromes associated with diabetes

Monogenic Diabetes

- Diabetes resulting from a single gene mutation
  (vs polygenic: DM 1 and 2)
  - Genetic defects of beta cell function
    - Neonatal DM
    - Maturity Onset DM in Youth (MODY)
  - Genetic defects in insulin resistance
    - Primary insulin signaling defects
      (generalized, partial)
    - Secondary to adipose tissue abnormalities
      (severe obesity, lipodystrophy)

Monogenic Diabetes

- 1-2% of DM
- > 80% of MODY not diagnosed
- 7-15% of DM misclassified
  - ~1% of presumed cases of DM 1
  - 4~5% of DM 2 dx < 45yo
- Risk of error high in young adults
- Often takes 10yrs before diagnosis is made

Carl-Hugo Lachance. Can J Diabetes 40 (2016) 368-375

MODY

- Maturity Onset of Diabetes in Youth
- Primary defect in b-cell function
  (insulin secretion or glucose sensing)
- Early onset (usually <25yo)
- Autosomal dominant (off spring 50% chance)

Table 1. Clinical and molecular characteristics of MODY subtypes

MODY gene	Chromosomal location	Frequency (% from MODYs)	Pathophysiology	Other features	Treatment
HNF4A	MODY 1	5	β-Cell dysfunction	Neonatal hyperinsulinemia, low triglycerides	Sensitive to sulfonylurea
GCK	MODY 2	15–20	β-Cell dysfunction (glucose sensing defect)	Fasting hyperglycemia from newborn	Diet
HNF1A	MODY 3	30–50	β-Cell dysfunction	Glycosuria	Sensitive to sulfonylurea
PDX1/IPF1	MODY 4	<1	β-Cell dysfunction	Homozygote: pancreatic agenesis	Diet or OAD or insulin
HNF1B	MODY 5	5	β-Cell dysfunction	Renal anomalies, genital anomalies, pancreatic hypoplasia	insulin
NEUROD1	MODY 6	<1	β-Cell dysfunction	Adult onset diabetes	OAD or insulin
KLF11	2p25	<1	β-Cell dysfunction	Similar to type 2 diabetes mellitus	OAD or insulin
CEL	9q34	<1	Pancreas endocrine and exocrine dysfunction	Exocrine insufficiency, lipomatosis	OAD or insulin
PAX4	7q32	<1	β-Cell dysfunction	Possible ketoacidosis	Diet or OAD or insulin
INS	11p15	<1	Insulin gene mutation	Can also present PNDM	OAD or insulin
BLK	8p23	<1	Insulin secretion defect	Overweight, relative insulin secretion defect	Diet or OAD or insulin
ABCC8	11p15	<1	ATP-sensitive potassium channel dysfunction	Homozygote: permanent neonatal diabetes; heterozygote: transient neonatal diabetes	OAD (sulfonylurea)
KCNJ11	11p15	<1	ATP-sensitive potassium channel dysfunction	Homozygote: neonatal diabetes	Diet or OAD or insulin

MODY 1-3
> 90%

MODY 1-3, 5
~ 99%

Sung-Hoon Kim. Diabetes Metab J 2015;39:468-477

MODY 2
No progression of hyperglycemia and no microvascular complication
→ *No treatment*

MODY 1, 3
Progressive hyperglycemia with complications.
Initially very responsive to *SUs*.
Becomes less responsive and progress to *insulin* therapy

MODY 5
Progressive hyperglycemia with complications.
Both defects in insulin secretion and resistance.
Poor response to SUs and early *insulin* therapy required.

	Type 2	MODY 2	MODY 3	MODY 1	MODY 5
		GCK *	HNF1A #	HNF4A #	HNF1B #
		No	No ∞	No ∞	No
	2%–4%	Yes ≈	Yes	Yes	Yes
	e and thood	Birth	Teens to young adulthood	Teens to young adulthood	Teens to young adulthood
	quency	Population frequency	Population frequency	Population frequency	Population frequency
	ive emia	Stable mild fasting glycaemia	Post-prandial hyperglycaemia initially, progressing to general hyperglycemia	Post-prandial hyperglycaemia initially, progressing to general hyperglycemia	Post-prandial hyperglycaemia initially Progressing to general hyperglycemia
		No	No	No	No
	rmal	Normal	Low but Detectable	Low but Detectable	Low but Detectable
	ormal	Normal	Very low	Normal	Normal
clinical features	disease (Thyroid, coeliac *etc.*)	mia, PCOS, Hypertension Acanthosis Nigricans	Absence of microvascular and macrovascular complications	Low renal threshold for glucose in early stages of diabetes	Macrosomia and transient neonatal hypoglycaemia	High renal involvement e.g., cysts *etc.*

Richard Carroll and Rinki Murphy. Genes 2013, 4, 522-535

When to suspect?

- DM diagnosed < 6mo of life
- DM without typical features of type 1 or 2 (negative abs, nonobese, other metabolic features, especially with strong FHx)
- Stable/mild fasting hyperglycemia (100-150mg/dL), stable A1c (5.6-7.6%), especially if nonobese

Kalyani et al. Standards of Medical Care in Diabetes. Diabetes Care 2018

Importance of correct Dx?

- Optimal treatment strategy
  - Insulin to oral (MODY 1 & 3)
  - No Tx (MODY 2)

  → improve QoL, glycemic control
- Family member screening

  →Proper genetic counseling

- Challenge due to high cost (genetic panel)

Secondary diabetes (other)

- Endocrinopathy
  - Hypercortisolism (Cushing's syndrome)
  - Acromegaly
  - Glucagonoma
  - Pheochromocytoma
  - Hyperthyroidism
  - Somatostatinoma
  - Aldostronoma
  - Other
- Pancreas
  - Hemochromatosis
  - Pancreatic cancer

Secondary diabetes (other)

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  - **- Hypercortisolism (Cushing's syndrome)**
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Hypercortisolism (Cushing's)



- Most common: Exogenous
- For endogenous, screening test
  - 1mg overnight dexamethasone suppression test
  - Midnight salivary cortisol
  - 24hr urine free cortisol

  * **<u>cannot r/o with random cortisol</u>**

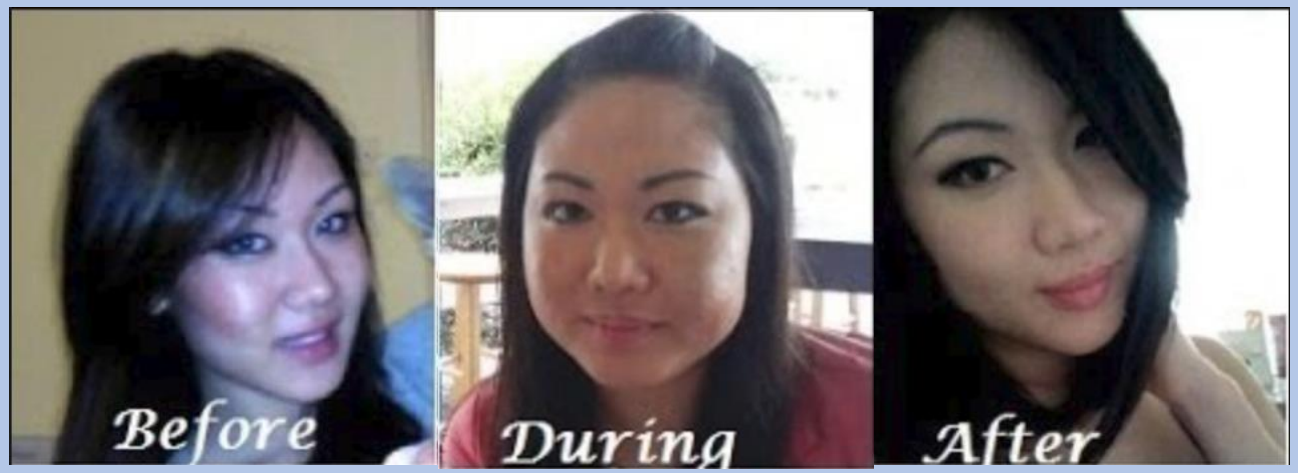
Acromegaly



- Growth hormone excess
- Most common (99%): pituitary adenoma
- Screening test: IGF-1

* **<u>Cannot r/o with random GH (growth hormone)</u>**

recognition





Secondary diabetes (other)

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Hemochromatosis

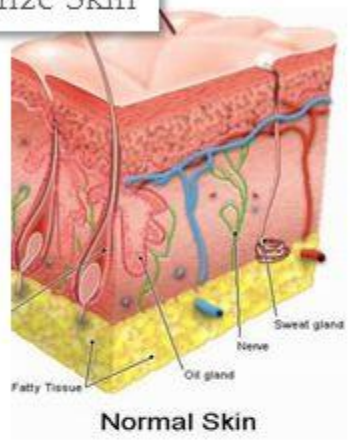
- Iron overload in parenchymal organs leading to organ toxicity
  - Hereditary
  - Secondary
  - Miscellaneous
- Incidence of hereditary
  - 1 per 200-500, most are of northern European origin

Powell et al. Semin Gastrointest Dis. 2002; 13(2):80-8

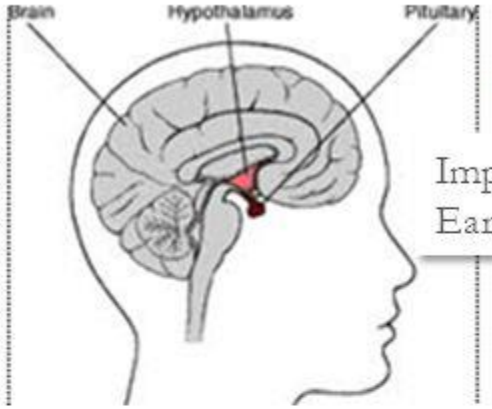
Late Symptoms – Where is Iron Deposited?

Munich RE

Bronze Skin



Normal Skin



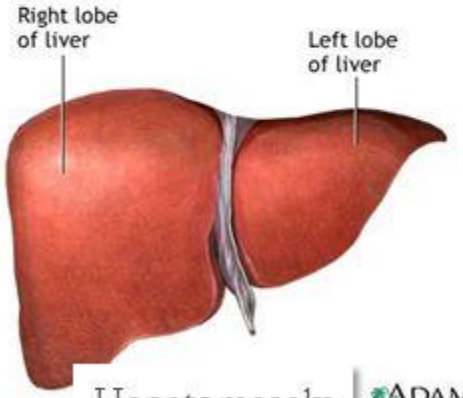
Impotence
Early menopause



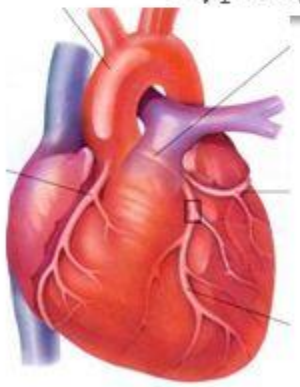
Hypothyroidism



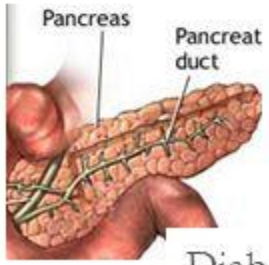
Arthritis



Hepatomegaly
^LFTs
Cirrhosis

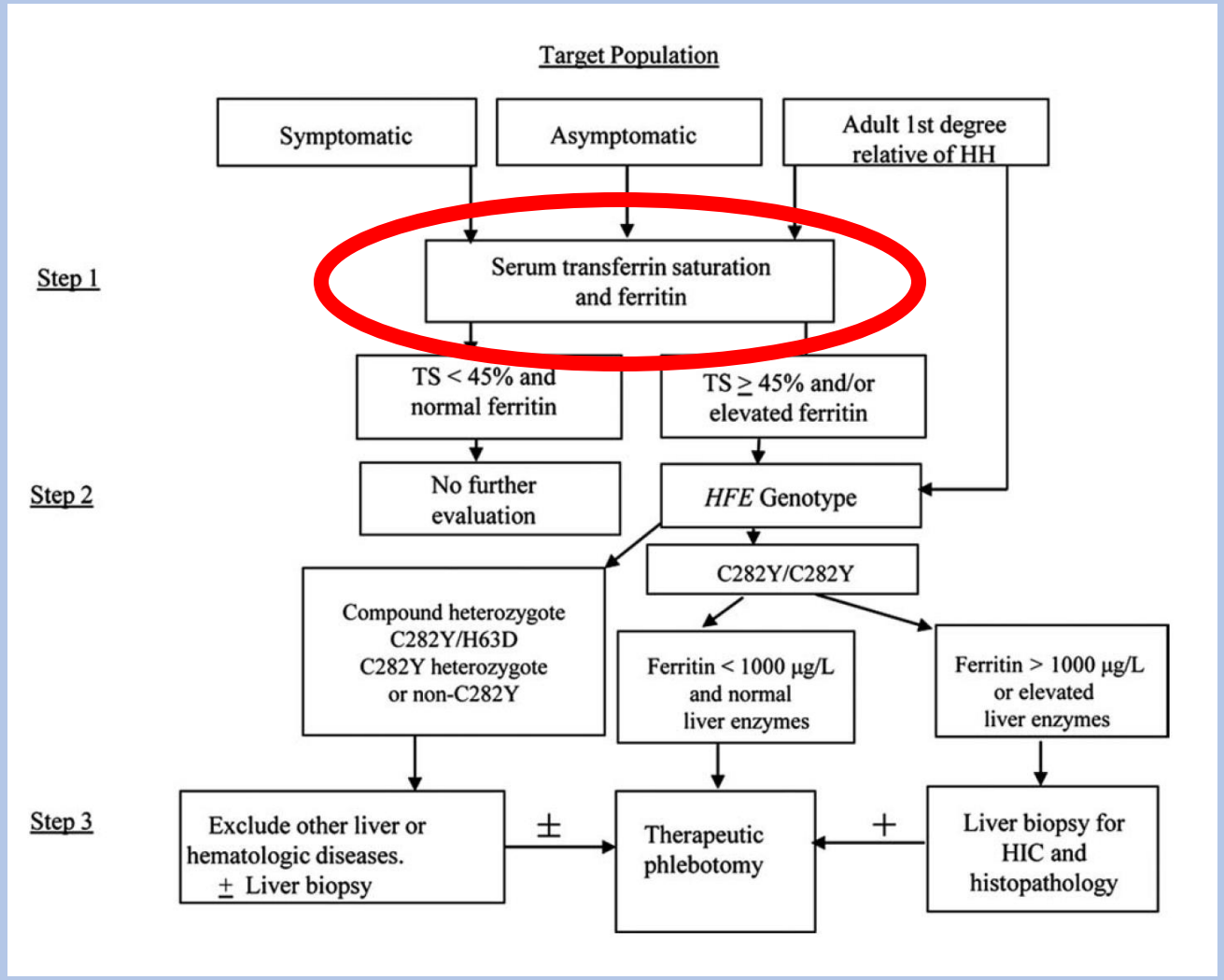


Cardiomyopathy
Arrhythmia



Diabetes

Initial test



Bacon et al. Hepatology, Vol. 54, No 1, 2011

Clinical conundrum..

- Patient with DM 2
  - Elevated AST/ALT
  - Enlarged heart
  - Hypogonadism
  - Hyperpigmented skin
  - Fatigue
  - Joint pain

Stella

- Returns following week after insulin initiation.
- Dramatic improvement in glucose (fasting 90-110s, predinner/bedtime 100-130s)
- Doing well with low carb diet. Lost another 7lbs since last visit (week)
- Self d/c basal insulin after 4days due to one time fasting glucose of 73.
- Stays on metformin ER 500mg 2tabs BID
- Still reports nausea and diarrhea.

Stella

- Advised to lower metformin to 500mg 1tab BID
- Return in 2-3weeks.
- Self d/c metformin after 1 week due to good glycemic control and persistent diarrhea.
- Maintains good glycemic control
- Lost another 10lbs
- Continues to have nausea and diarrhea….

CT of abdomen

PANCREAS: In the pancreatic head there is a 3.4 x 2.3 x 2.4 cm hypoenhancing an ill-defined mass (series 3 image 35, series 604 image 54). There is tenting of the posterior wall of the SMV suspicious for involvement (series 4 image 55). There also may be a small focus of invasion into a posterior branch in the proximal SMV (image 59 series 4). The celiac artery and branches and SMA do not appear involved. Noted is atrophy of the body and tail the pancreas with mild maintained duct enlargement measuring up to 5 mm.

Pancreatic cancer

- When to suspect
  - Rapid onset or worsening of diabetes without known cause
  - Abnormal weight loss
  - Abnormal liver/biliary studies
  - Jaundice

Summary

- Vast majority of hyperglycemia/diabetes is DM 1 & DM 2 with ~5% being secondary diabetes
- Routine screening for secondary diabetes is not cost effective and need to be considered in patients with high pre-test probability.
  - Unusual features: younger age (<40-50yo), family history, rapid progression of disease, worsening condition despite good adherence to lifestyle and treatment regimen, refractory disease despite polypharmacy
  - Recognition of clinical features (i.e., physical findings, comorbidities)
- Early recognition of these uncommon causes of hyperglycemia can change the course of disease and patient's quality of life

Questions on Diabetes or any other endocrinopathies

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