ENDOCRINE PANCREAS

Islets of Langerhans:
1. Alpha cells: Glucagon
2. Beta cells: Insulin
3. Delta cells: Somatostatin
4. D1 cells: Vasoactive Intestinal Polypeptide (VIP)
5. F cells: Pancreatic Polypeptide (PP)
6. G cells: Gastrinoma

1. Glucagonoma

2. Insulinoma
   Insulin aids the conversion of carbohydrate to energy for intracellular energy. It is an anabolic hormone with salt retention properties. It stimulates the appetite and may be atherogenic in large amounts. It maintains glucose in the normal range.
   Spontaneous hypoglycemia. 80% are benign. Usually single and small tumors. Second most common pancreatic tumor to be found in MEN 1.
   DX: Must document elevated insulin and C-peptide level with low glucose level and symptoms. Fasting hypoglycemia (BG less than 50) and elevated insulin and c-peptide levels. Important that typical symptoms be present, since many normal people have glucose levels under 50. Patients often have to awaken at night to eat. Abdominal scans often find nothing. Intraoperative ultrasound may help. Oral glucose tolerance test is NOT diagnostic for this since half of all people have low blood sugars during testing, often with symptoms. TX: surgery. Can try octreotide to palliate, especially cases with liver metastases. Also, diazoxide may help and chemotherapy may palliate.
   The most common differential diagnosis of hypoglycemia includes reactive (post-prandial) hypoglycemia secondary to an over-zealous insulin response to high carbohydrate foods. This often is a precursor for type 2 diabetes mellitus. Other diagnoses that need to be considered include anxiety; medications; malnutrition; insulin or sulfonylurea abuse; hypothyroidism; glucocorticoid insufficiency; renal insufficiency; hepatic insufficiency. Other non-glucose related processes that may mimic the catecholamine symptoms or general symptoms include neurologically mediated hypotension, seizures, cardiac problems.

3. Somatostatinoma
   Rare. Widely distributed throughout the body. Somatostatin inhibits release and action of gastrin, CCK, secretin, VIP, motilin, GIP, insulin, glucagons. Usually asymptomatic. No specific syndrome. Often malignant. TX: surgical, possibly chemo tx.
4. **VIPoma**

   VIP usually inhibits gastrin and stimulates pancreatic bicarbonate secretion. Severe watery diarrhea and decreased gastric acidity. GI loss of potassium and bicarbonate. Often malignant with metastases at diagnosis. Tx: surgery; chemo tx; octreotide for palliation.

5. **Pancreatic polypeptide**

   Inhibits gallbladder contraction, pancreatic enzyme secretion, gastric acid secretion weakly. No syndrome or symptoms. Possibly a marker for other pancreatic tumors.

6. **Gastrinoma**

   Gastrin usually produced by gastric antrum and duodenum (and fetal pancreas) and stimulates gastric acid secretion. Most common pancreatic tumor associated with MEN 1. Syndrome: peptic ulcer disease, increases gastric acidity (Zollinger-Ellison Syndrome). Secretin test to confirm diagnosis. May be a small tumor. Can be malignant occasionally with liver metastases. Tx: Surgery; Proton-pump inhibitors.

**DIABETES MELLITUS**

Fasting glucose over 125 twice or any glucose over 200 with symptoms. These are actually relatively late findings in type 2 diabetes. Fasting glucose over 100 should alert us that there very well may be an abnormality. 2 hour glucose tolerance test is diagnostic if fasting glucose is under 140 but two values are over 200. Type 1 and type 2 diabetes mellitus (DM) are very different in pathophysiology and treatment.

   Long-term complications include fatigue, blindness (retinopathy), stroke, coronary artery disease, renal failure (nephropathy)—look for proteinuria or microalbuminuria (30-300 mcg/mg albumin in a random sample), infections, neuropathy, impotence, etc.

I. **Type 1 Diabetes Mellitus**

   Autoimmune attack on the islet cells. Often find anti-islet cell antibodies (in 85% of cases). “Ketosis prone.” Genetic predisposition to autoimmune attack against the islet cells. Relatively rapid onset. There may be environmental triggers with viruses, bacteria, fungi, cow’s milk.

   Diagnosis: usually present with significant ketones. Rapid onset of polyuria, weight loss, blurred vision, fatigue, polydipsia. Tx: Diet therapy, exercise.

   Insulin, as soon as possible. Usually best off with NPH plus Lispro or Aspart or Regular before breakfast and dinner. Alternatively, N plus rapid-acting insulin before breakfast, rapid-acting insulin sometimes before lunch, rapid-acting insulin before dinner, and N at bedtime. Lispro (Humalog) and Aspart (Novolog) are quick-acting insulins about twice as rapid in onset as Regular insulin and may be used in place of Regular insulin. Glargine (Lantus) is a basal insulin with no
peak. This at bedtime plus rapid-acting insulin with meals is an excellent regimen.

Intensive treatment yielding tight control can reduce complications by as much as 70% according to the Diabetes Control and Complications Trial (DCCT). The closer the Hemoglobin A1C to normal, the less chance of complications. This study involved type 1 diabetics but it is felt that the results probably extrapolate to type 2 diabetics. The United Kingdom Prospective Diabetes Study (UKPDS) and Kumamoto study yielded similar results for type 2 diabetics.

II. Type 2 Diabetes Mellitus (Adult-Onset DM)
Pathophysiology involves insulin resistance secondary to strong genetics and central obesity. If one identical twin has this, the other has a 90% chance of developing DM. Initially, these patients have hyperinsulinemia. Continued hyperglycemia, resistance, and hypersecretion of insulin lead to further beta cell dysfunction and decompensation and decreased sensitivity to hyperglycemia. Insulin resistance syndrome: obesity, elevated cholesterol and triglycerides, low HDL, small dense LDL, hypertension, ovarian dysmetabolic syndrome (polycystic ovarian syndrome), hirsutism, acanthosis nigricans, etc.

This type has a slow onset. Most patients have had type 2 DM for 5-8 years when initially diagnosed. Ketones are not a problem, although they often have a small amount when sick due to generalized illness and not the diabetes.

Maturity Onset Diabetes of the Young (MODY): Five or more subtypes identified. Abnormal glucokinase activity is one cause. Generally young patients, not dramatically overweight. May get by with oral agents.

Tx: WEIGHT REDUCTION IF OVERWEIGHT. This can dramatically improve insulin resistance. Diabetic, low fat diet. Medications: (oral agents approved for type 2 diabetics only)

1. Sulfonylureas: glyburide, glipizide, chlorpropamide, glimepiride, etc.—Insulin secretagogues: stimulate pancreatic insulin production.
2. Biguanides: metformin—decreases hepatic glucose production. Contraindicated in CHF, active liver disease, creatinine 1.4 or higher in females and 1.5 or higher in males. Precaution: lactic acidosis, B12 deficiency.
5. Meglitinides—repaglinide, nateglinide—causes insulin release with meals.
6. Sitagliptin (Januvia); Saxagliptin (Onglyza); Linagliptin (Tradjenta): DPP-4 inhibitor: increases GLP-1 and GIP: Causes insulin release in response to

7. Exenatide (Byetta, Bydureon); Liraglutide (Victoza): GLP-1 mimetic: Causes insulin release in response to carbohydrates. Decreases inappropriate post-prandial glucagon production. Suppresses appetite.


9. Insulin (Human): N and R

10. Insulin Analogues: rapid-acting: aspart (Novolog); lispro (Humalog); glulisine (Apidra). Long-acting: glargine: (Lantus); detemir (Levemir).

11. Combinations: Insulin with any of the above agents.

12. Intensive insulin therapy (basal insulin once or twice daily and pre-meal rapid-acting insulin)

12. Insulin Pump therapy

13. Continuous glucose sensors

Intensive therapy: DCCT (type 1 diabetics) found that intensive insulin therapy with 3-4 shots daily or insulin pumps was overall much better. Carbohydrate counting is important with intensive insulin therapy. It was more physiologic. Patients also need to be taught to have some self-autonomy with their glucose therapy.

AMERICAN DIABETES ASSOCIATION recommendations:

- yearly dilated eye exam
- foot exam at each visit
- regular dental exam
- office visits 2-4 times yearly
- A1C 2-4 times yearly—goal is under 7%
- pre-meal glucose values 110 or less
- 2 hour post-prandial values 140 (160) or less
- check sensation in feet with 10 gram nylon filament
- urine microalbumin ratio yearly (LabCorp code 140285, the test will be done wrong at LabCorp unless you have this code on it);
- 24 hour urine for protein and CrCl if abnormal
- aspirin if not contraindicated
- ACE inhibitor or ARB if nephropathy or hypertensive; perhaps for all diabetics?
- flu and pneumonia vaccines

CONCEPTS: Insulin resistance syndrome:

**Metabolic syndrome (ATP III identification):**

* Abdominal obesity: waist circumference: men >40 inches, women >35 inches
* Triglycerides 150 or higher
* HDL cholesterol: men <40; Women<50.
* BP: 130/85 or higher
* FBS: 110 (?100) or higher

metabolic syndrome also may include:
*Insulin resistance and hyperinsulinemia
* Dyslipidemia with low HDL, high total cholesterol, and small dense LDL and high triglycerides
* Glucose intolerance/DM
* Elevated uric acid
* Hyperandrogenism
* Anovulation (PCOS)

Endothelial Dysfunction
Post-prandial hyperglycemia
Hepatic glucose production
Inflammation
Free fatty acids
Cytokine and Adipocytokines (adiponectin, leptin, TNF, IL-6, resistin, etc.)
Incretins: intestinal hormones: (GLP-1, GIP, Oxyntomodulin, etc.)
Is rosiglitazone associated with increased mortality?  .
Is glargine associated with increased cancer risk?

Other types of Diabetes:
   MODY (Maturity Onset Diabetes of the Young)
   LADA (Latent Autoimmune Diabetes of Adults)
       (positive GAD-65 antibody)

HOPE study and micro-HOPE:
   Ramipril 10 mg lowers risk of cardiovascular complications in diabetics

ACCORD study: initially reported as intensive A1c reduction in patients with coronary artery disease yielded an increase in mortality, but post-hoc analysis revealed that the patients who had better A1c control in the intensive therapy group did not have an increase in mortality. Also, hypoglycemia was not the cause of the increase in mortality.

NICE-SUGAR: intensive glucose control in the ICU in critically ill adults increased the risk for death by 10%.

VADT: decreased risk of cardiovascular events in adults who initiated intensive glucose control in the first fifteen years after a diagnosis of type 2 diabetes.

Intensive insulin treatment post-CABG (FURNARE and VAN DEN BERGHE)
III. Secondary Diabetes Mellitus

drugs (glucocorticoids, thiazides, pentamidine, dilantin, oral contraceptives, etc.)
alcohol: direct effect on the liver and bouts of pancreatitis
metastatic disease to the pancreas
Cushing’s syndrome, acromegaly, glucagonoma, pheochromocytoma,
thyrotoxicosis
liver disease: hemochromatosis (“bronze diabetes”)
pancreatic toxins or other infiltrative disorders

Cases:

1. 22 year old Caucasian female with glucose 400 and urine 3+ ketones. Moderately ill. DX: Probably new onset type 1 DM. Tx: Education. Regular insulin IV drip followed by SC insulin (N+R) before breakfast and dinner if tolerated. If trial of oral agents is entertained, she must be watched closely.

2. 65 year old obese female diagnosed with type 2 DM 4 years ago. Complains of tingling/burning of her feet at night at rest. This awakens her and she states the bedsheets sometimes hurt. On NPH insulin 58 units BID. Glucose at home by fingersticks around 200 in the morning. Urine: 2+ proteinuria. Tx: Change timing of fingersticks to get a more representative sampling. Consider ACE inhibitor. Collect 24 hour urine protein and CrCl. Add Regular insulin if possible. Encourage weight reduction.

3. 34 year old with “hypoglycemic” symptoms two hours after eating or if late with meals. Doesn’t awaken to eat. Medical history otherwise negative. On oral contraceptives for prevention of pregnancy. Testing: fasting glucose, insulin, c-peptide levels, liver and kidney function tests. Important to try to get glucose, insulin, c-peptide levels at least once when symptoms are occurring.

Dx:
If true hypoglycemia as documented by a venous glucose below 60 and concurrent symptoms:

If past gastric bypass surgery: possible nesidioblastosis (islet cell hyperplasia).

Rule out insulinoma, surreptitious insulin or sulfonylurea use.
Rule out inaccurate glucose meter results.
Rule out adrenal/pituitary insufficiency

Rule out malnutrition.

If hypoglycemia not documented, rule out other cause of spells:

Cardiac: NMH (neurologically mediated hypotension);
  POTS (postural orthostatic tachycardia syndrome)
  Cardiac dysrhythmia; etc.
Neurologic: Seizures, Narcolepsy, etc.
Psychologic: Anxiety/Panic attacks
Other: Mastocytosis; Myeloma/MGUS