Unusual Forms of Diabetes and a Glycare Update

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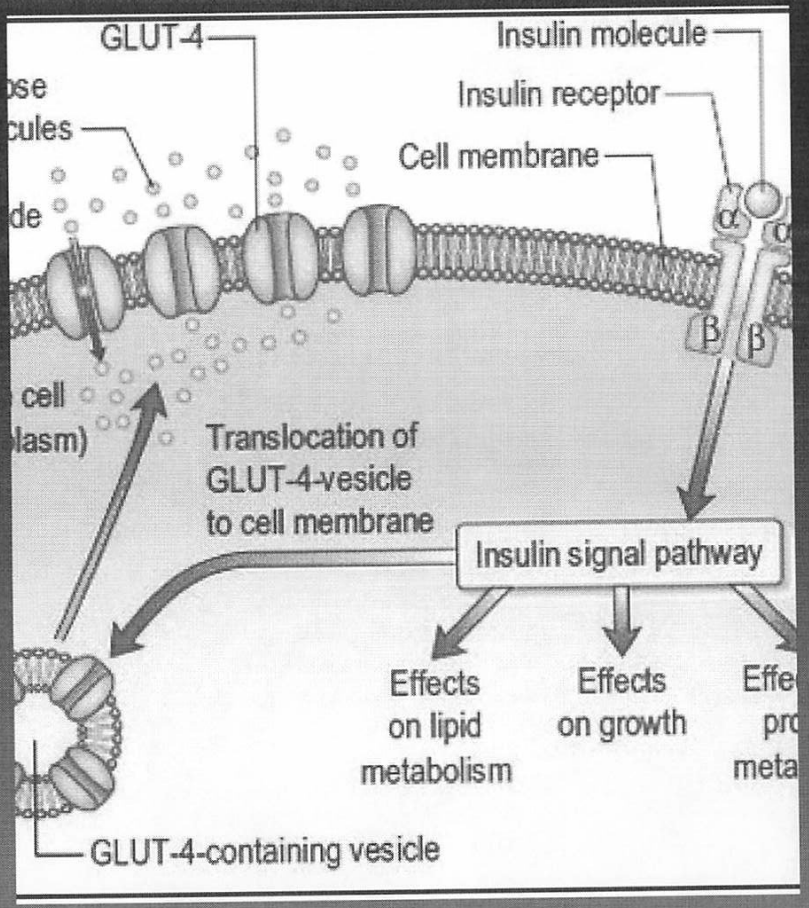
Outline and Learning Objectives

- review the etiological classification of diabetes mellitus
- learn to recognize, diagnose and treat (where possible) the unusual forms of diabetes
- emphasis on recognizing the MODY syndromes, the Insulin Resistance Syndromes A and B, LADA, and anti-GAD associated syndromes
- a few remarks about Glycare before closing

Etiologic Classification of DM

- Type 1 DM
- Type 2 DM
- Genetic Defects of Beta Cell Function (MODY et al)
- Genetic Defects of Insulin Action (Type A Insulin Resistance and others)
- Immune Mediated Diabetes (Type B Insulin Resistance syndromes, anti GAD syndromes, Anti Insulin Receptor Ab syndromes)
- Diseases of Exocrine Pancreas
- Endocrinopathies
- Drug or Chemical Induced

review of insulin action



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- other unusual genetic syndromes

LADA or Type 1.5 Diabetes

- genetic features of type 1 and type 2 diabetes
- heterogeneous group of patients with variable — titers of anti-GAD or ICA Abs, BMIs, and frequency of progression to “outright” type 1 DM
- clinical presentation includes— a “seemingly” type 2 individual w poor response to initial therapy w metformin/sulfonylureas, family history or personal hx of autoimmune disease, and who, over time, appears to act like a type 1
- CASE REPORT

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MODY (maturity onset diabetes of the young)

- clinically heterogeneous group of disorders characterized by noninsulin-dependent DM diagnosed at a young age w autosomal dominant transmission and lack of autoantibodies
- the genetic defects involved control pancreatic beta cell development, function, regulation— causing impaired glucose sensing, function, regulation

MODY (maturity onset diabetes of the young)

- MODY 3 (HNF1A) - 50-60%
- MODY 2 (glucokinase gene abnl) — 15-30%
- MODY1 (HNF4A) -10%

MODY 3

- due to mutations in HNF1A which regulates, or is a weak transactivator of the insulin gene in beta cells
- mutations can lead to abnormal insulin secretion, and can also result in a low renal threshold for glucose
- clinically, these patients may "look" like type 1 patients initially, with insulin sensitivity, and occasionally even presenting w DKA, but they have a remarkable sensitivity to sulfonylureas, and 70% are successfully treated w SFU monotherapy

MODY 2

- due to mutations in Glucokinase which phosphorylates glucose to glucose -6-P and probably acts as a glucose sensor
- defects in the gene and GCK results in a higher threshold for glucose stimulated insulin secretion
- hyperglycemia is stable, mild, typically not associated w complications, and these patients are often treated w diet alone

MODY 1

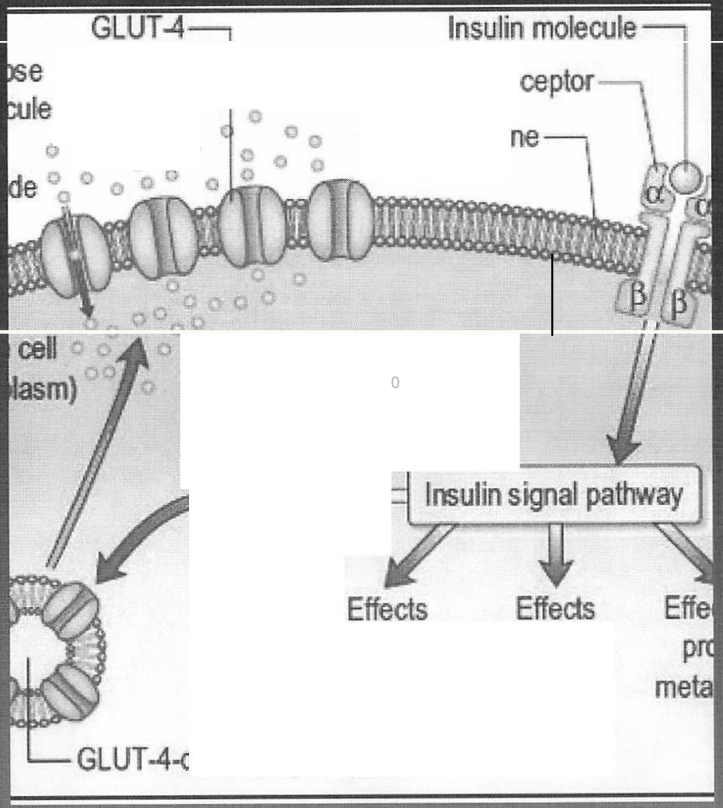
- due to mutations in HNF4A, which appears to regulate HNF1A
- reduced insulin response to glucose — unlike MODY 2, the hyperglycemia is progressive, and they will have less of a response to SFUs over time and may eventually require insulin

MODY
(maturity onset diabetes of the young)

- diagnosis made by genetic testing for mutations in HNF4A, GCK, HNF1A

index of suspicion raised with: fam ilia l OM w autosomal dominance, onset <25, non obese, negative ICA or anti GADs...

review of insulin action



Type A Insulin Resistance

- due to defects in the gene coding for the insulin receptor (INSR)
- part of a spectrum which also includes Donohue and Rabson Mendenhall Syndrome
- it is considered on the “milder” end of the spectrum because it doesn’t become apparent until adolescence and is generally not life threatening

Type A Insulin Resistance

- clinical features are far more apparent in women: late menarche, or oligomenorrhea, ovarian cysts, acanthosis nigricans is marked, hirsutism, and these patients are not obese — often have very lean appearance, esp. in extremities — may be managed with efforts to reduce insulin requirements (low carbohydrate diet) and improve insulin resistance

other genetic forms of diabetes

- as mentioned before, Leprechaunism, Donohue Syndrome, Rabson Mendenhall Syndrome — may all be related to genetic defects in INSR gene, Williams syndrome as well
- Wolfram syndrome (DIDMOAD) — DI, DM, Optic Atrophy, Deafness) — genetic defect in endoplasmic reticulum of pancreatic beta cells
- index of suspicion — a child or young adult with growth delay, growth disorder, distinctive appearance (unusual), and hyperglycemia —> pediatric genetics consult
- MIDD (maternally inherited diabetes and deafness) due to a defect in pancreatic mitochondrial DNA which leads to a defect in insulin secretion and sensorineural hearing loss, cardiac conduction defects, Gestational DM, neuropathy

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Immune Mediated Diabetes

- **Insulin Resistance Syndrome Type B** — not due to defects in the insulin receptor, but due to an autoantibody to the insulin receptor
- extreme insulin resistance, hyperglycemia, polyuria, polydipsia, (rarely hypoglycemia) weight loss, severe hyperandrogenism, widespread acanthosis nigricans —
- often occurs on a background of rheumatologist illness — lupus, Sjogren's, or is a paraneoplastic manifestation of malignancy
- historically treatment was with immunosuppression (steroids), but now includes protocols aimed at pathological antibody production — rituximab, cyclophosphamide, or cyclosporine etc. and immunosuppression - steroids, azathioprine
- before treatment these patients may require THOUSANDS of units of insulin per day!
- CASE REPORT

Immune Mediated Diabetes

- **Cerebellar Ataxia, Stiff-Man Syndrome —**
- these are two neurologic disorders that results from autoimmune destruction/compromise of nerve sheaths/myelin
- associated with very high titers of anti-GAD antibodies and can be associated w type 1 DM
- (CASE REPORT)

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Diseases of the Exocrine Pancreas

Chronic Pancreatitis

Trauma/Surgery

Neoplasia

Cystic Fibrosis

Hemachromatosis

others

Diseases of the Exocrine Pancreas

- diabetes associated w pancreatitis may develop quite gradually
- may initially respond to therapies for T2DM, but will ultimately require insulin therapy
- CF patients may have insulin resistance from infection and glucocorticoids, but also insulin deficiency due to chronic pancreatitis
- because CF patients are living longer, as many as 15 % will develop DM

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DM caused by Endocrinopathies

- Acromegaly
- Cushing's Syndrome
- Glucagonoma
- Pheochromocytoma
- Somatostatinoma
- others

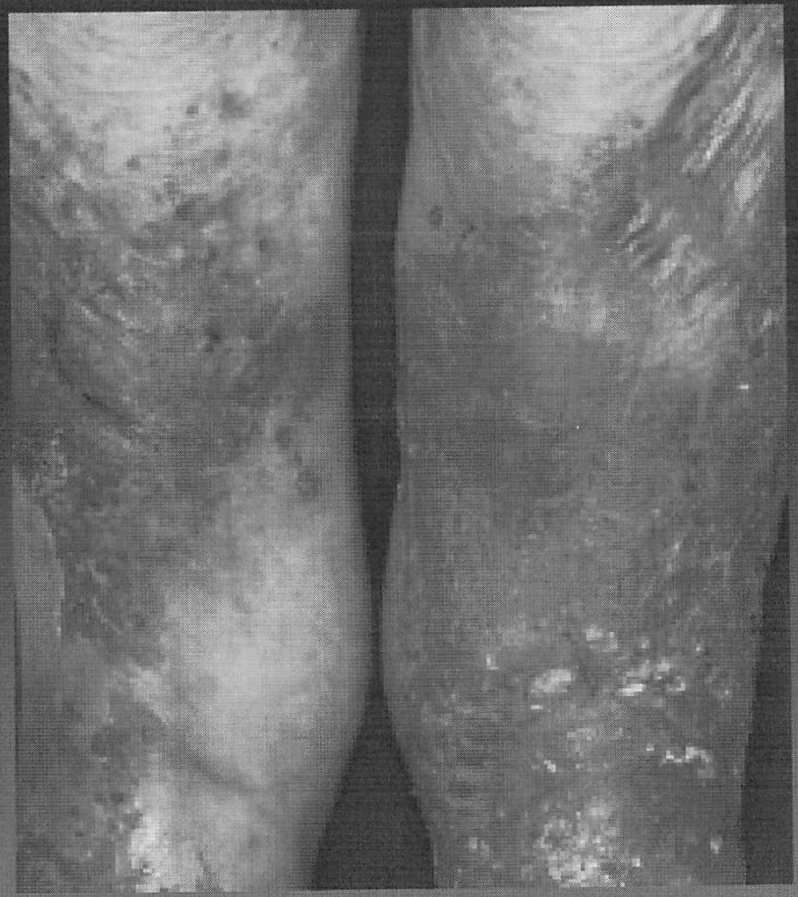
DM caused by Endocrinopathies

- Acromegaly
- **Cushing's Syndrome (more and more seen in the endocrine literature about occult Cushing's as the cause of "unexplained" hypertension or hyperglycemia)— if suspicious— recommend the overnite dexamethasone suppression test— 1mg at bedtime and the next morning an 0800 cortisol (should be lower than 1.7 mcg/dl)**
- Glucagonoma
- Pheochromocytoma
- Somatostatinoma
- others

DM caused by Endocrinopathies

- Acromegaly
- Cushing's Syndrome
- **Glucagonoma — high suspicion if previously no diabetes— and hyperglycemia, characteristic skin rash (necrolytic migratory erythema), weight loss, thromboembolism, anemia**
- Pheochromocytoma
- Somatostatinoma
- others

necrolytic migratory erythema



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Drug/Chemical Induced DM

- glucocorticoids
- diazoxide
- thiazides
- antipsychotics
- alpha interferon
- anti-epileptics
- **anti-retroviral therapy for HIV — protease inhibitors cause insulin resistance by interfering with GLUT4 glucose transporters..**
- others

Conclusions

review of the atypical or unusual causes of diabetes/hyperglycemia

heightened index of suspicion should be maintained to properly diagnose and treat those with diabetes

correct classification ensures correct therapy

Location - ALBI					
Encounter Type - Inpatient					
				Baseline 05/18-09/18	
				GlyCare 05/20 -09/20	
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	Avg BS	Improvement		Severe Hyperglycemic	B= 68 Events; 13.6 Events per month
Baseline 01/18 - 12/18	195			(>= 500 mg/dl)	G= 12 Events; 2.4 Events per month
GlyCare 01/20-12/20	170	15%			
				Severe Hypoglycemic	B=13 Events; 2.6 Events per month
Order Comments	Avg BS	# of Patients		(<= 30 mg/dl)	G= 1 Event
Order entered by rule: [Glucose< 60]	110	81			
Order entered by rule: [Glucose > 300]	220	106			
Order entered by rule: [2 Glucose> 200 in 24 hr]	169	409		Hypoglycemia	B=242 Events; 48.4 Events per month
				(31-54 mg/dl)	G=11 Events, 2.2 Events per month
Grand Total	170	596			
Patient-day method. Glucose data were normalized to patient-day. An average POC-BG level was computed for each inpatient patient-day by summing together the measurement occasions for a given patient-day and dividing by the number of measurements that occurred on that day. These patient-day averages were then aggregated to the hospital level, and averaged to compute the patient-day-weighted mean POC-BG level for each hospital.					
An Individual Hypoglycemic Event is defined as the initial occurrence and up to 4 hours after the individual occurrence as a single event.					
An Ind1v1dual Hyperglycem1c Event is defined as an initial occurrence throughout a 24-hour period as a single event.					