Identification and Treatment of Type 1 Diabetes in AI/AN Populations

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Objectives

To review and discuss:

1. The Natural History of and Laboratory Tests for Diagnosis of Type 1 Diabetes
2. Laboratory Tests that Differentiate Type 1 from Type 2 Diabetes
3. Important Considerations in AI/AN patients with Type 1 Diabetes
4. Current Treatment Guidelines
5. One Recommended Change You Can Make in Your Practice.
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The Causes of Diabetes

- Defective insulin production by pancreas (1 & 2)
- Excess glucose production
- Reduced glucose uptake
- Resistance to the action of insulin (2)
Type 1 Diabetes: Family Risks

- Most cases of Type 1 DM are sporadic; only 10 percent to 15 percent of affected individuals have a first-degree relative with Type 1 DM at the time of diagnosis.
- The risk of developing Type 1 DM is 5 percent if a first-degree family member is also affected with Type 1 DM, compared with a general population risk of 0.4 percent – i.e., about a 20-fold increase.
- The offspring of a father with Type 1 DM has a 4-6 percent chance of becoming diabetic, whereas the risk for an offspring of a Type 1 mother is 2-3 percent.
- This may reflect a higher spontaneous early abortion rate both the fetus and the mother carry the Type 1 genes.
Type 1 Diabetes: Family Risks

**Concordance Rates With Types of Diabetes:**

- Type 1 Diabetes in Identical Twins: 50%
- Type 2 Diabetes in Identical Twins: 70-90%
- Type 1 Diabetes in Siblings with 1 parent affected: 5%
- Type 2 Diabetes in Siblings with 1 parent affected: 30%

This indicates that there is a powerful environmental component(s) interacting with the genetic component to confer risk of Type 1 Diabetes.
Natural History of Type 1 Diabetes

Genetic Predisposition → Environmental Factor(s) → Detectable Immunologic Abnormalities → Normal Insulin Release → Declining Insulin Release → Severe Insulin Deficiency

Possible Intrauterine Precipitating Factors(s) → Process Arrested: Non-Diabetic Individual

Process Arrested: LADA or Prediabetic Individual → Overt Diabetes

Type 1 Diabetes: Auto-antibodies

• At clinical onset of Type 1 DM, less than 10 percent residual ϒ-cell mass remains and humoral and cellular abnormalities are present.

• In humans, islet cell infiltration by lymphocytes (mainly CD8+ cells) is found in patients newly-diagnosed with the disease.

• As a result of T-cell lymphocyte-mediated attack, islet cell cytoplasmic antibodies (ICAs) are formed against proteins in the ϒ-cell.
Type 1 Diabetes: Auto-antibodies

- 90 percent of persons with newly diagnosed type 1 diabetes have one or more associated autoantibodies
- Commonest of these are:
  - Islet cell ab (ICA)
  - Insulin ab (IAA)
  - Glutamic Acid Decarboxylase 65 ab (GAD65)
  - PTP-related Islet Antigen 2 ab (IA-2A)
  - Zinc Transporter 8 Ab (ZnT8A)
- One Positive Ab confers a 5-year risk of 5 percent for Type 1 Diabetes
- Four Positive Abs confers a 5-year risk of 80 percent for Type 1 Diabetes

Siljander HT et al. Diabetes 58:2835-2842, 2009
Type 1 Diabetes: Environmental Factors

Actual Precipitant(s) Unknown - Factors for which there is some supporting evidence include:

- Exposure to viruses (rubella, mumps, coxsackie B) or other microbial pathogens
- Early exposure to cow’s milk
- Diminished breast milk consumption
- Early exposure to cereals, with or without wheat gluten
- Lack of Vitamin D supplementation in infancy
- “Clean” Environment

Possible mechanisms for these include:

- “mimicry” of components of the islet cell by components of these agents, such that the immune response turns on the islet component
- Inadequate immune system priming early in life to train it to distinguish “self” from “non-self”

### Genetics of Type 1 DM and HLA Haplotypes

**Susceptibility:**

**High**
- DRB-1: 0401, 0402, 0405, 0301
- DQA-1: 0301, 0501
- DQB-1: 0302, 0201

**Moderate**
- DRB-1: 0801, 0101, 0901
- DQA-1: 0401, 0101, 0301
- DQB-1: 0402, 0501, 0303

**Protection:**

**High**
- DRB-1: 1501, 1402*, 0701
- DQA-1: 0102, 0101, 0201
- DQB-1: 0602, 0503, 0303

**Moderate/Weak**
- DRB-1: 0401, 0403, 0701, 1101
- DQA-1: 0301, 0201, 0501
- DQB-1: 0301, 0302, 0201

* Found more commonly in Native Americans
Genetics of Type 1 DM and HLA Haplotypes

• Type 1 Diabetes is also associated with other auto-immune endocrine diseases, e.g., Hashimoto’s thyroiditis, adrenal insufficiency, etc.

• A patient with type 1 DM has about a 30 percent lifetime risk of autoimmune thyroid disease (>90 percent of which will be Hashimoto’s disease leading to hypothyroidism), a 4 percent risk of adrenal insufficiency and a 1 percent or lower risk of premature gonadal failure, hypoparathyroidism or pernicious anemia and others.

Atypical Forms of DM that May Resemble Type 1

ADA Etiologic Class III – Types A-H

A. Genetica Defects of β-cell function:
   MODY types 1-6 and Mitochondrial DNA

B. Genetic Defects in Insulin Action:
   Type A insulin resistance, Lipoatrophic DM, Rabson- Mendenhall Syndrome, Leprechaunism

C. Exocrine Pancreatic Disorders:
   Pancreatitis, Trauma, Pancreatectomy, Neoplasia, Cystic fibrosis, Hemochromatosis, Tropical calcific pancreatitis, Cassava toxicity

D. Secondary to Endocrinopathy:
   Acromegaly, Cushing’s Syndrome, Glucagonoma, Pheochromocytoma, Hyperthyroidism, Somatostatinoma, Aldosteronoma
Atypical Forms of DM

ADA Etiologic Class III – Types of A-H (continued):

E. Drug of Chemical Induced:

- Vacor,
- Pentamidine,
- Nicotinic Acid,
- Glucocorticoids,
- Thyroid hormone,
- Diazoxide,
- β-Adrenergic agonists,
- Thiazides,
- Dilantin,
- α-Interferon

F. Infections:

- Congenital Rubella,
- Cytomegalovirus

G. Immune Mediated:

- Stiff-Man Syndrome,
- Anti-insulin receptor antibodies

H. Other Genetic Syndromes:

- Down’s Syndrome,
- Klinefelter’s Syndrome,
- Turner’s Syndrome,
- Wolfram’s Syndrome,
- Friedreich’s Ataxia,
- Huntington’s Chorea,
- Laurence-Moon-Biedl Syndrome,
- Dystrophia Myotonica,
- Porphyria,
- Prader-Willi Syndrome
Atypical Forms of DM

• ADA Etiologic Class IV:

Gestational Diabetes Mellitus (GDM)

- Defined as diabetes mellitus first recognized during pregnancy
- Most will be true GDM
- Some will be previously unrecognized Type 2 DM
- A very few will be evolving Type 1 DM
- Rarely, atypical (Class IV) DM will be picked up at this time.

Therefore, diabetes must be re-evaluated and reclassified after delivery.
Prevention of Type 1 DM

No intervention has been conclusively shown to be effective in preventing Type 1 DM

- European Nicotinamide Diabetes Intervention Trial ‘ENDIT’ – treatment of >500 high risk subjects with high-dose nicotinamide was ineffective;

- Diabetes Prevention Trial (DPT) – treatment of high-risk subjects with oral or parenteral insulin was ineffective;

- Avoidance of cow’s milk products – inconclusive, probably ineffective;

- Multiple infections in early childhood and preschool daycare have shown a protective effect against Type 1 DM.

- Canadian/European and French Cyclosporin studies showed insufficient benefit to justify cyclosporin toxicity.

- Trials with azathioprine, linomide, BCG vaccine and oral insulin were ineffective.

- Protégé Study – Phase 3 trial with anti-CD3 antibody tepluzimab. Some beneficial results, but primary outcome measure was not met.

- Trials with anti-CD20 ab rituximab and anti-T lymphocyte abatacept have shown early promise.

Metabolic Consequences of Type 1 DM

Severe Insulin Deficiency

- Hyperglycemia
  - Osmotic Diuresis
    - Dehydration
    - Acidosis
    - Electrolyte Imbalance

- Free Fatty Acid Release
  - Ketone Production
    - Acidosis

- Muscle Catabolism
  - Protein Breakdown
    - ↓Glucose Uptake

CLASSICAL ACUTE CLINICAL PICTURE

= Liver  = Fat  = Blood  = Urine  = Muscle
Classical Acute Clinical and Laboratory Picture of Type 1 DM Diabetic Ketoacidosis (DKA)

Symptoms
- Polyuria
- Dizziness
- Polydipsia
- Blurred Vision
- Drowsiness
- Weight Loss
- Polyphagia

Signs
- Confusion
- Cachexia
- Ketotic fetor
- Hyperventilation
- Low temp
- Dry mucus membranes
- Postural BP ↓
- Low JVP
- Clamminess

Laboratory Data
- Hyperglycemia
- Low pH
- Hyperkalemia
- Hyponatremia (may be ‘pseudo’)
- Low HCO₃
- Low pCO₂
- High BUN:Creat
- Anion gap
- High ketones
- Glycosuria

Coma and Death
Unique Features of Non-Immunologically Mediated “Pseudo-Type 1 DM”

**Pseudo-Type 1 DM:**
- All Islet Cell Types are damaged

**Net Result:** Loss of both insulin and glucagon = very brittle diabetes and usually exocrine insufficiency & malabsorption.

**Type 1 DM:**
- Beta Cell is specifically targeted for destruction

**Net Result:** Loss of insulin production only
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2. *Laboratory Tests that Differentiate Type 1 from Type 2 Diabetes*

3. Important Considerations in AI/AN patients with Type 1 Diabetes

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5. One Recommended Change You Can Make in Your Practice.
Distinguishing Type 1 from Type 2 DM

As a practical issue, this is actually less important than it sounds.

Why?

1. Because the principle of therapy is to treat hyperglycemia with the least aggressive, most convenient modalities that will achieve stable target glycemia and to treat all detected cardiovascular risk factors.
2. Because many patients have features of both Type 1 and Type 2 diabetes in varying degrees, all of which must be addressed.
3. Because diabetes is a spectrum ranging from classic type 1 through intermediate forms to classic type 2.
4. It is often not possible to give a patient a label with certainty.
Distinguishing Type 1 from Type 2 DM

Features that do not differ between Type 1 and Type 2 DM with sufficient frequency to be diagnostically helpful:

**History/Symptoms/Signs:**
- Polyuria
- Polydipsia
- Nocturia
- Polyphagia
- Weight loss
- Dizziness
- Blurred vision
- Obesity
- Family history

**Laboratory Data:**
- Hyperglycemia
- Acidosis
- Hyperkalemia
- Low HCO₃
- High BUN: Creatinine
- Glycosuria
**Distinguishing Type 1 from Type 2 DM**

Features that differ between “Classic” Type 1 and Type 2 DM:

<table>
<thead>
<tr>
<th>Feature</th>
<th>Type 1</th>
<th>Type 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketoacidosis</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Autoantibody</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Low c-peptide</td>
<td>Yes</td>
<td>Np</td>
</tr>
<tr>
<td>Anion gap</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>High triglycerides</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Low HDL</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Hypertension</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Lean</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

Generally, the diagnosis is made when multiple classic features are present, but there is “required” number of criteria.
Distinguishing Type 1 from Type 2 DM

Exception to ketoacidosis as a reliable diagnostic criterion for Type 1 DM:

MODY in African-Americans

- 10 percent of African-Americans with youth onset diabetes
- Presents with weight loss, ketoacidosis, insulin-dependence
- Later generally follows a non-ketosis prone insulin-independent course for many years of follow up.
- 50 percent of affected patients are obese.

Ketoacidosis generally indicates severe, virtually complete, insulin deficiency, but can occur in the setting of moderately severe insulin deficiency with extreme insulin resistance.

Distinguishing Type 1 from Type 2 DM

Q: Is there a gold standard test for diagnosis of type 1 DM?
A: Yes, the stimulated c-peptide. Often, the main utility of this test is to satisfy insurance company requirements for provision of insulin pumps. *But it is seldom performed correctly!!*
Performing the stimulated c-peptide challenge correctly:
1. Why c-peptide?

Connecting peptide (c-peptide) links the A and B chains of insulin in its precursor form, proinsulin. Cleavage of c-peptide activates insulin. No synthetic insulin contains the c-peptide fragment. Its presence confirms the presence of non-synthetic insulin of pancreatic origin.
Distinguishing Type 1 from Type 2 DM

Performing the stimulated c-peptide challenge correctly:

2. How should c-peptide be maximally stimulated in order to reliably indicate endogenous insulin secretory capacity?

<table>
<thead>
<tr>
<th>Condition</th>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin therapy must be withheld</td>
<td>Insulin suppresses its own secretion by feedback</td>
</tr>
<tr>
<td>Glucose must be elevated above postprandial levels (&gt;150mg/dl)</td>
<td>Elevated glucose promotes maximum insulin secretion</td>
</tr>
<tr>
<td>Patient must be fed</td>
<td>Activates the entero-insular axis</td>
</tr>
</tbody>
</table>

The Entero-Insular Axis

- Incretin hormones GLP-1 and GIP are released by the intestine throughout the day, and their levels ↑ in response to a meal.

GLP-1=glucagon-like peptide-1; GIP=glucose-dependent insulino tropic polypeptide.
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GLP-1=glucagon-like peptide-1; GIP=glucose-dependent insulinoceptive polypeptide.
The Entero-Insular Axis (cont.)

Ingestion of food → GI tract → Release of active incretins GLP-1 and GIP → Pancreas → ▲ Insulin

DPP-IV inhibitor ‘gliptins’

<table>
<thead>
<tr>
<th>GLP-1 inhibitor</th>
<th>GIP inhibitor</th>
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<td>DPP-IV enzyme</td>
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Pancreas

Glucose dependent ▲ Insulin

▲ Glucose uptake by peripheral tissue

▼ Blood glucose in fasting and postprandial states

▼ Hepatic glucose production

GLP-1 = glucagon-like peptide-1; GIP = glucose-dependent insulinotrophic polypeptide.

DPP-IV inhibitors: sitagliptin, linagliptin, saxagliptin
The Entero-Insular Axis

GLP-1 agonists: exenatide, liraglutide, exenatide extended release.

GLP-1=glucagon-like peptide-1; GIP=glucose-dependent insulinotropic polypeptide.
Performing the stimulated c-peptide challenge correctly:

1. Withhold long-acting insulin the previous evening and on the morning of the test
2. Usual short-acting insulin dose with evening meal the night before the test
3. Patient eats breakfast and presents to Clinic one hour later
4. Capillary glucose is tested. When reading is above 150 mg/dl, patient is sent to Laboratory, where glucose and c-peptide are drawn.

Value of <0.6 nmol/L indicates Type 1 DM

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Insulin Resistance: An Underlying Cause of Type 2 Diabetes

Obesity and inactivity
Genetic abnormalities
Aging
Medications
Rare disorders
Type 2 diabetes
Hypertension
Dyslipidemia
Atherosclerosis
PCOS
Clinically Useful Parameters to Identify Insulin Resistance

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<th>Parameter</th>
<th>Sensitivity</th>
<th>Specificity</th>
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<td>97%</td>
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<td>Impaired Glucose Tolerance</td>
<td>26%</td>
<td>95%</td>
</tr>
<tr>
<td>High Fasting Insulin</td>
<td>66%</td>
<td>83%</td>
</tr>
<tr>
<td>High Insulin 2 hours post 75g Glucose</td>
<td>71%</td>
<td>86%</td>
</tr>
<tr>
<td>Fasting Triglyceride &gt;130 mg/dl</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Low HDL</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Triglyceride: HDL Ratio &gt;3</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>BMI &gt; 25 kg/m2</td>
<td>60%</td>
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# Clinically Useful Parameters to Identify Insulin Resistance in Patients with Type 1 DM

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Coexistence of Insulin Resistance with Type 1 DM – “Superimposing Type 2”

Having Type 1 DM **precludes** expression of the genetic and environmental risk factors of the insulin resistance of type 2 DM

OR

Having Type 1 DM **allows** expression of the genetic and environmental risk factors of the insulin resistance of type 2 DM
Coexistence of Insulin Resistance with Type 1 DM – “Superimposing Type 2”

• Therefore, it is important to consider that many AI/AN patients with Type 1 DM can develop the metabolic features of Type 2 DM, which should be treated. Insulin sensitization can therefore be an important component of treatment of Type 1 AI/AN patients, especially as they age.
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Principles of Insulin Therapy

1. The simplest regimen that achieves glycemic control should be employed:

2. Initiation and adjustment of insulin should be based on appropriate available glucose monitoring data;

3. Sliding-scale insulin alone is *NEVER* a suitable prescription and should not be permitted on quick orders;

4. The insulin that is administered now is dosed based on historical data of glucose at a later time point;
Use of ‘Sliding-Scale’ Insulin Alone Is Strongly Discouraged

- Evidence does not support this technique without basal insulin
- Hazards of sliding-scale insulin use exceed the advantages of its convenience
- Leads to rapid changes in BG levels resulting in exacerbation of both hyperglycemia and hypoglycemia
- Possible iatrogenic diabetic ketoacidosis in patients with T1DM
Normal Secretory Pattern of Insulin
Maintaining Physiologic Insulin Delivery: Basal-Bolus

- **Basal insulin**
- **Mealtime insulin (bolus)**
- **Supplemental or ‘stress’ insulin**
Dosing Short-Acting Insulin

Insulin

- Breakfast: Insulin ‘A’ given here
- Lunch: Glucose for ‘A’ measured here
- Dinner
- Bedtime
Dosing Short Acting Insulin

Breakfast
- Insulin ‘A’ given here
- Glucose for ‘A’ measured here

Lunch

Dinner
- Insulin ‘B’ given here
- Glucose for ‘B’ measured here

Bedtime
Normal Secretory Pattern of Insulin
Insulin

Options for Basal Insulin (controlling BG in fasting state)

Analogs
- Detemir
- Glargine

Human
- NPH

Options for Nutritional Insulin (controlling BG when there is caloric intake)

Analogs
- Aspart
- Glulisine
- Lispro

Human
- Regular

NPH and Detemir are only once a day insulin in low dosage, usually 30 units or less.
Adjustment of Insulin According to Glucose Readings

Glargine: 35 units; Aspart: 10 - 10 - 10 - 0
Normal Secretory Pattern of Insulin

Glargine: 38 units; Aspart: 12 - 10 - 14 - 0
Additional Considerations in Management of Type 1 DM

1. In patients with coexistent features of insulin resistance, consider the benefits of using insulin sensitizers – pioglitazone sensitizes up to 35 percent, metformin 15-20 percent and effects are additive.

2. Insulin dosing should not be determined based on post-prandial readings alone. The pre-prandial glucose is the dose-determining value for safety reasons.

3. Supplemental dosing of short-acting insulin postprandially is strongly discouraged, most especially in Type 1 DM – it is a form of “stacking” with risk of late hypoglycemia.
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One Recommended Change You Can Make in Your Practice

Four to Choose From:

1. If performing the stimulated c-peptide challenge for diagnosis of type 1 DM, be sure to hold insulin, feed patient and verify glucose above 150 mg/dl in order to get a valid result.

2. Consider the potential benefits of insulin sensitizer use in type 1 DM patients with clinical and laboratory evidence of concomitant insulin resistance.

3. Avoid sliding-scales in ambulatory patients, ensure that there are no quick-orders for sliding-scale insulin in your Pharmacy menu. Dose both short-acting and long-acting insulins proactively against their desired action point.

4. Stacking is for chairs and pancakes, but not for insulin.
The End

Questions or Comments?