Type 1 Diabetes-Pathophysiology, Diagnosis, and Long-Term Complications

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Objectives

- Understand the pathophysiology of Type 1 diabetes.
- Be familiar with the different classifications of diabetes.
- Be familiar with diabetic ketoacidosis and its complications.
- Be familiar with long term complications of diabetes and screening that is done to monitor these complications.

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Diabetes

- Worldwide prevalence in 2011 was 366 million
- Worldwide prevalence by 2010 will be 552 million
- In US, Canada, and Europe 5-10% of diabetes is Type 1 diabetes
- Type 1 diabetes is the main type of diabetes in childhood
- Incidence of Type 1 diabetes is increasing worldwide at a rate of 3-5% per year

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Case Study- Sarah

- Thus far, here is what we know about Sarah:
  - 3-week history of polyuria, polydipsia, and unexplained weight loss.
  - Acanthosis nigricans, BMI 32, and visceral adiposity.
  - 6-month history of oligomenorrhea, moderate acne, and hirsutism

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Case Study-Sarah

- Thus far, here is what we know about Sarah:
  - Family history of diabetes mellitus.
  - History of maternal gestational diabetes mellitus.
  - Random blood glucose of 350 mg/dL.

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Question

In distinguishing Type 1 diabetes from Type 2 diabetes, which of the following is most helpful?

a) Family history of diabetes.
b) A history of ketoacidosis at diagnosis.
c) Overweight.
d) Levels of fasting insulin and C-peptide
e) Islet cell antibodies

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Islet Cell Autoantibodies

- Islet cell autoantibodies (ICA)
- Glutamic acid decarboxylase autoantibodies (GADA)
- Insulinoma associated 2 autoantibodies (IA-2A)
- Insulin autoantibodies (IAA)
- Zinc transporter autoantibodies (ZnT8A)

Islet Cell Autoantibodies

- Insulin autoantibodies more common in young children (< 5 years of age) who develop Type 1 diabetes.
- GAD65 autoantibodies more common in adults developing Type 1 diabetes
- Antibodies in 1st relatives of Type 1 diabetics can predict risk of developing disease:
  - ≥ 2 autoantibodies risk of > 90% over 10 years
  - 1 autoantibody risk of 20% over 10 years

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Question

Which of the following best describes the difference in pathophysiology of Type 1 vs Type 2 diabetes?

a) Individuals with type 1 diabetes are insulin deficient while those with type 2 diabetes are primarily insulin resistant.

b) Individuals with type 1 diabetes are insulin resistant while those with type 2 diabetes are primarily insulin deficient.

c) Individuals with both type 1 and type 2 diabetes are primarily insulin deficient.

d) Individuals with both type 1 and type 2 diabetes are primarily insulin resistant.

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Type 1 Diabetes

Genetic Susceptibility
(HLA DR3/DR4, DQ8/2)

↓ Environmental Trigger

Insulitis/β-cell injury

↓

Progressive loss of β-cell mass
eventually leading to glucose intolerance/diabetes

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Pathophysiology

- Genetic Susceptibility: HLA genotypes DR and DQ
- Environmental Triggers (virus, vaccines, diet, hygiene)
- Cell-mediated (T-cell) response leading to beta cell destruction
- Humoral (B-cell) response leading to autoantibody formation

Question

Sarah is found to have islet autoantibodies. Which of the following is the best classification of her diabetes?

a) Type 1a diabetes mellitus.
b) Type 1b diabetes mellitus.
c) Type 2 diabetes mellitus.
d) Other specific types of diabetes.
e) None of the above.

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Classification of Diabetes Mellitus

	T1A	T1B	Diabetes 1.5	T2
Genetics	Polygenic	?	Polygenic?	Polygenic
Age	Any age	Any age	Children and adolescents	Any age
Autoimmunity	Yes	Absent	Present	Absent
Presentation	Often acute	?	Variable	Variable
Acanthosis	No	No	Maybe	Maybe
Insulin Needed	Yes	Yes	Maybe	Maybe

Adapted from Table 1: Canivell S, Gomis R. Diagnosis and classification of autoimmune diabetes mellitus. Autoimmunity Reviews 13 (2014:403-407.

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Question

Given Sarah's diagnosis, which of the following is the most appropriate treatment option?

a) Diet and exercise.
b) Weight loss.
c) Metformin.
d) Insulin.
e) None of the above.

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Basal Insulin

- Half of total daily insulin units.
- Long-Acting Insulin:
  - Glargine (Lantus):
    - Onset 1-2 hrs, Duration 2-22 hrs, Gone 24 hrs.
  - Detemir (Levemir):
    - Onset 1-2 hrs, Duration 2-20 hrs, Gone 20hrs

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Bolus Insulin

- **Rapid-acting insulin types**
  - insulin lispro (Humalog)
  - Insulin aspart (Novolog)
  - Insulin glulisine (Apidra)

Onset 10-15 minutes, Main effect 30-90 minutes, Gone 3-4 hours

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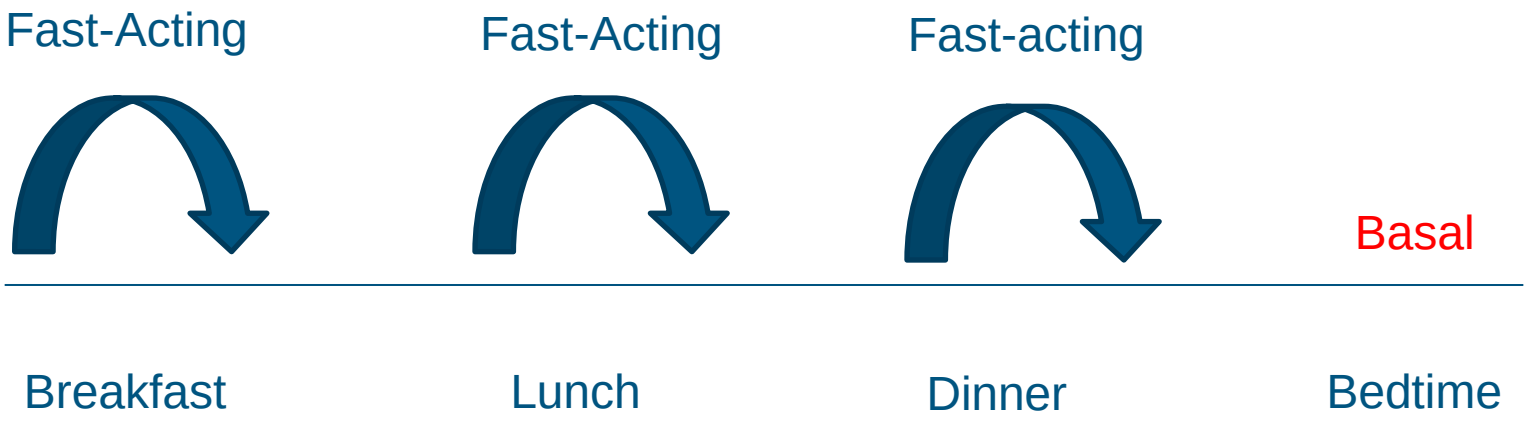
Insulin



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Sarah

Sarah is treated with insulin, taught how to count carbohydrates for all meals and snacks, and shown how to test her blood glucose before meals, snacks, and bedtime. Her family received age-appropriate educational resources from the American Diabetes Association.

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Question

However, one month after her initial diagnosis, she starts to experience frequent episodes of hypoglycemia. Considering her duration of her diabetes, what is the most likely cause of her hypoglycemia?

a) Somogyi effect.
b) Honeymoon phase.
c) Dawn phenomena.
d) Munchausen by proxy syndrome.
e) None of the above.

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Honeymoon Phase

- Residual β-cell function improves after initiation of insulin therapy leading to frequent hypoglycemia.
- Need to decrease insulin doses.
- Minority of children (< 5%) even maintain normal glucose levels without insulin therapy.
- Duration last several months but may last as long as 1-2 years.

Early Morning Hyperglycemia

- Dawn Phenomenon:
  - Surge of stress hormones at 4-5 am.
  - Cortisol
  - Glucagon
- Somogyi Effect:
  - Rebound hyperglycemia due to early morning hypoglycemia.
  - Stress hormones (glucagon, cortisol, catecholamines).

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Sarah

Two months after her initial diagnosis, Sarah develops a febrile illness and begins vomiting. In addition to being pale, Sarah's parents note she is extremely thirsty, lethargic, and having trouble breathing. She is brought to the local emergency department where she is noted to be dehydrated, tachycardic, and experiencing Kussmaul respirations.

Question

Given her history and clinical presentation, you suspect which of the following?

a) Pylonephritis.
b) Diabetic Ketoacidosis.
c) Septicemia.
d) Severe hypoglycemia.
e) None of the above.

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Question

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Diabetic Ketoacidosis

- Severe insulin deficiency leads to:
  - Hyperglycemia.
  - Fat breakdown (fatty oxidation)➔ ketone formation.
  - Stress hormone response (eg, glucagon, catecholamines)➔ worsening hyperglycemia.

Severe hyperglycemia, ketone formation lead to dehydration, metabolic acidosis, electrolyte abnormalities

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Diabetic Ketoacidosis Definition

- Hyperglycemia
- Venous pH < 7.3
  - mild 7.21-7.3
  - moderate 7.11-7.2
  - severe < 7.1
- Bicarbonate level < 15 mmol/L

DKA Epidemiology

- Type 1 DM diagnosis: 15-67% in North America.
- Type 2 diagnosis children/adolescents: Up to 1/3.
- Risk Factors:
  - Children < 4 years.
  - No first-degree relative with Type 1 DM.
  - Lower socioeconomic status.
  - Poor metabolic control.
  - Psychiatric disorders.
  - Difficult family circumstances.

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DKA and Cerebral Edema

- Mortality rates from DKA range from 0.15% to 0.31%.
- Cerebral edema is the cause of 57% to 87% of these deaths.
- Mechanism is not well understood (osmotic changes vs vasogenic edema).
- Usually occurs 4-12 hours after onset of treatment.

Risk factors: New-onset, younger age, longer duration of symptoms, high BUN, more severe acidosis, failure for rise in Na as glucose decreases.

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Question

Sarah's parents ask about the long term complications of diabetes. Which of the following occur in individuals with type 1 diabetes or type 2 diabetes?

a) Microvascular disease (nephropathy, retinopathy, neuropathy).
b) Macrovascular disease (coronary artery disease, peripheral vascular disease, strok).
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Nephropathy

- Annual screening at start of puberty or at age of ≥ 10 years, whichever is earlier, once patient has had diabetes for 5 years.
- Spot urine sample albumin-to-creatinine ratio.
- ACE inhibitor should be considered with elevated albumin-to-creatinine ratio confirmed on 2 additional specimens from different days.

Hypertension

- Blood pressure checked at each visit.
- If systolic or diastolic blood pressure > 90% for age, sex, height:
  - Weight control through diet and exercise.
  - Medication should be considered if blood pressure goal not reached in 3-6 months.
- Medication should be given if SBP or DBP persistently ≥ 95% or > 130/80.

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Dyslipidemia

- If there is known family history of hypercholesterolemia or early cardiovascular events or if family history unknown, check fasting lipid panel > 2 years of age.
- If family history of no concern, obtain fasting lipid panel at puberty or ≥ 10 years of age.
- In children at or after puberty, obtain fasting lipid panel soon after diagnosis.
- Annual lipid panel if markers abnormal on initial screen. If LDL < 100 mg/dL, repeating lipid panel every 5 years is reasonable.

Dyslipidemia

- Initial therapy may consist of Step 2 AHA diet (saturated fat < 7% total calories and < 200 mg cholesterol per day) and optimizations of glucose control.
- If ≥ 10 years, LDL > 130 mg/dL, and has one or more CVD rks factor, may consider starting statin.
- Goal LDL < 100 mg/dL.

Retinopathy

- Initial dilated eye examination should be considered for patient at start of puberty or at age ≥ 10 years once patient has had diabetes for 3-5 years.
- After initial examination, annual follow up recommended.

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Celiac Disease

- Occurs in 1-16% of Type 1 diabetics.
- Symptoms include diarrhea, weight loss, poor weight gain, growth failure, abdominal pain, erratic blood glucose levels.
- Measure IgA and IgA tissue transglutaminase or IgA endomysial antibodies soon after diagnosis.
- Positive screening results should be referred to gastroenterologist for confirmation with endoscopy and biopsy.
- Biopsy confirmed cases should be placed on gluten-free diet.

Hypothyroidism

- Autoimmune thyroid disease occurs in 17-30% of Type 1 diabetics.
- Consider checking thyroid antibodies and TSH soon after diagnosis of Type 1 diabetes.
- If screening normal, consider rechecking every 1-2 years unless there are concerns sooner (eg, goiter, poor growth).

References

1) Diagnosis and classification of autoimmune diabetes mellitus. Gomis, R, Canivell, S. Autoimmunity Reviews, 13 (2014): 403-407.
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