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Pathophysiology of Type 1 and Type 2 Diabetes

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No conflicts to disclose

Objectives

1. Describe the estimated prevalence of Type 1 and Type 2 Diabetes
2. Discuss the pathophysiology of Type 1 vs. Type 2 Diabetes
3. Review presenting symptoms of diabetes
4. Discuss the diagnostic criteria for diabetes
5. Briefly review the management of diabetes

CONTENTS

- **Incidence and Prevalence**
- Etiology and Pathogenesis
- Signs/Symptoms
- Diagnostic Criteria
- Management

Incidence of Diabetes

- One of the most common chronic diseases in the school-aged child

- 27 cases/100,000 pop/year (SEARCH study) (Diabetes, 2014)

- Affects >190,000 (1 out of 433) youth aged <20 years
  - 21.1% increase in T1D over 8 years
- Factors: Age, race/ethnicity, geography, secular changes, seasonality

Secular changes in T1D incidence:
Incidence of diabetes in children under age 10 years in Norway, 1925–1995.

Gale E A Diabetes 2002;51:3353-3361

Geographical Variations in T1D Incidence

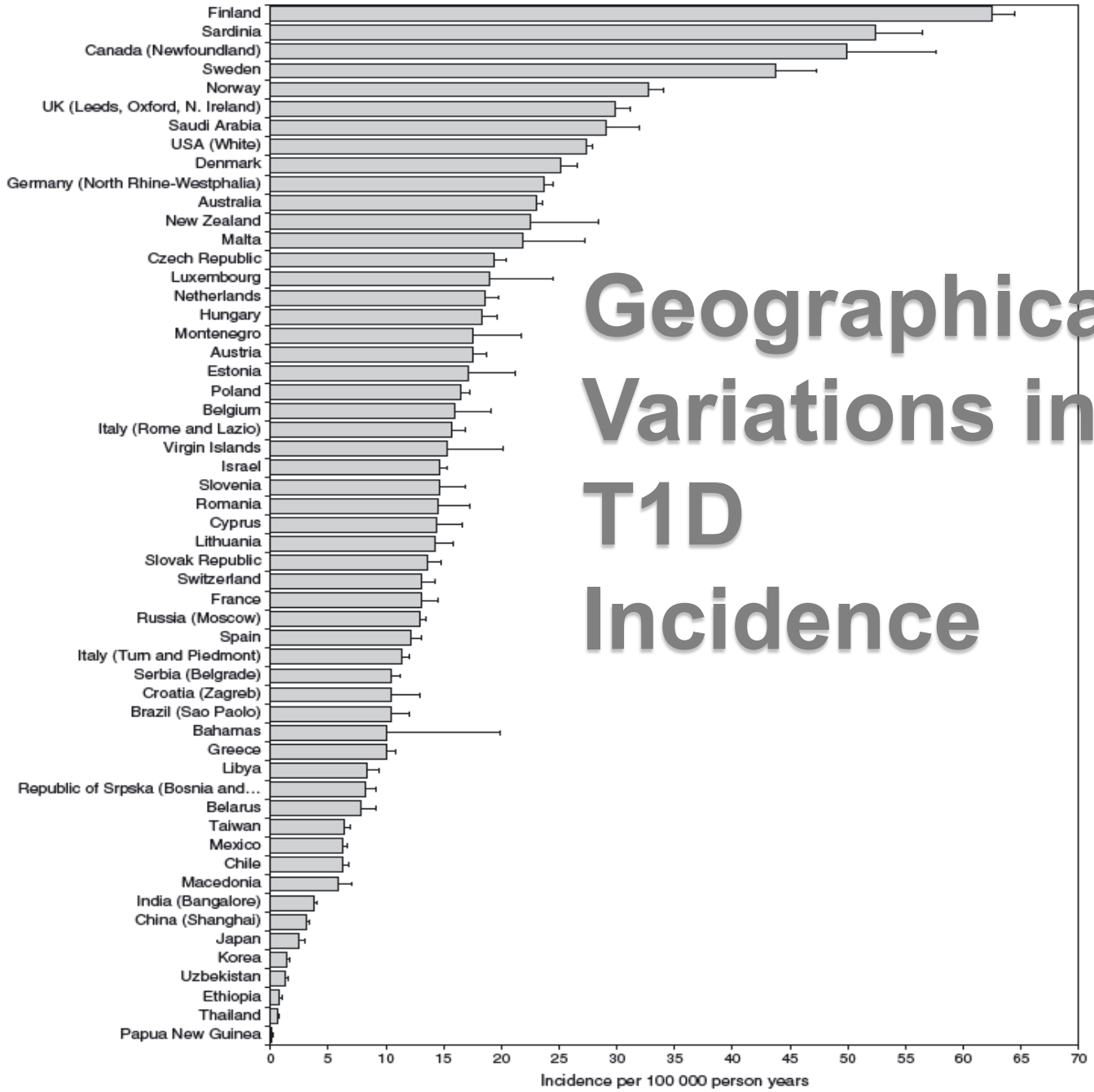
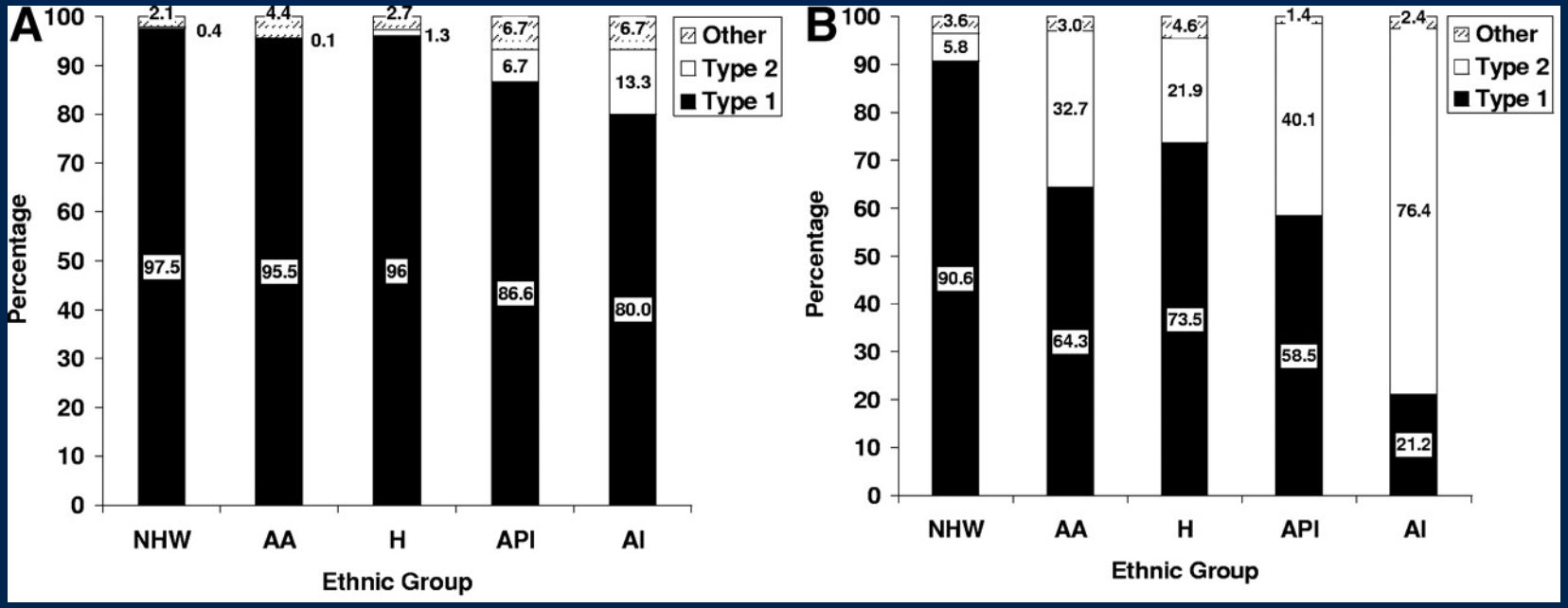


Fig. 1. Global mean annual incidence rates of type 1 diabetes in children and adolescents aged 0–14 yr. Only countries in which the study period included data from 2000 onwards are shown [adapted from the International Federation atlas (39)].

Type-specific proportions of prevalent cases of diabetes

0-9 years old

10-19 years old



SEARCH for Diabetes in Youth Study Group et al.
Pediatrics 2006;118:1510-1518

PEDIATRICS®

Prevalence of Type 2 Diabetes

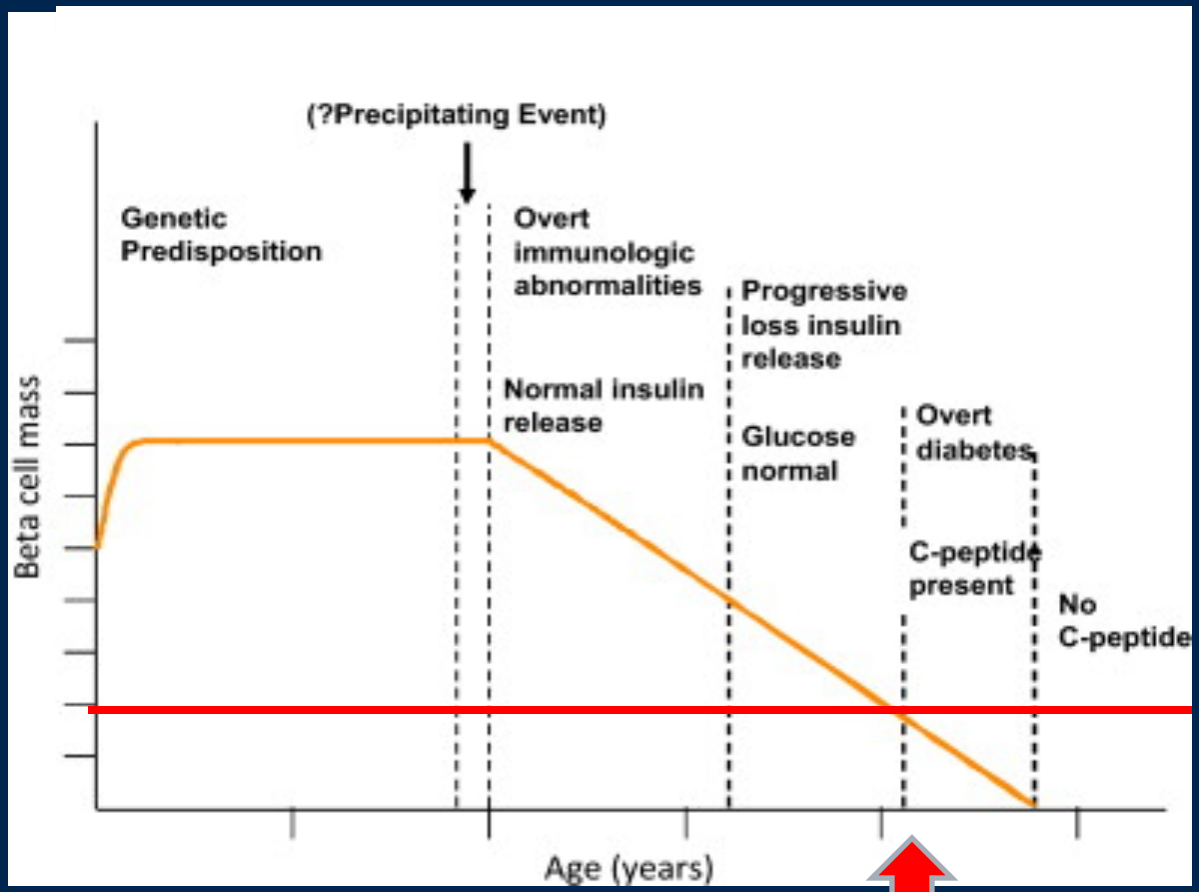
- Rising prevalence occurring parallel with increasing prevalence of Obesity
  - 1990s – T2DM represented ~ 3% of Pediatric Diabetes
  - 2003 – T2DM represented ~ 20% of pediatric diabetes
  - Increase in prevalence by 30.5% in youth between 2001 and 2009 (SEARCH study)

CONTENTS

- Incidence and Prevalence
- **Etiology and Pathogenesis – Type 1 Diabetes**
- Signs/Symptoms
- Diagnostic Criteria
- Management

Type 1 Diabetes – immune-mediated β-cell destruction, leading to insulin deficiency and lifelong insulin requirement

Eisenbarth Model of Stages in T1D Development



G.S. Eisenbarth
NEJM 1986

DIABETES

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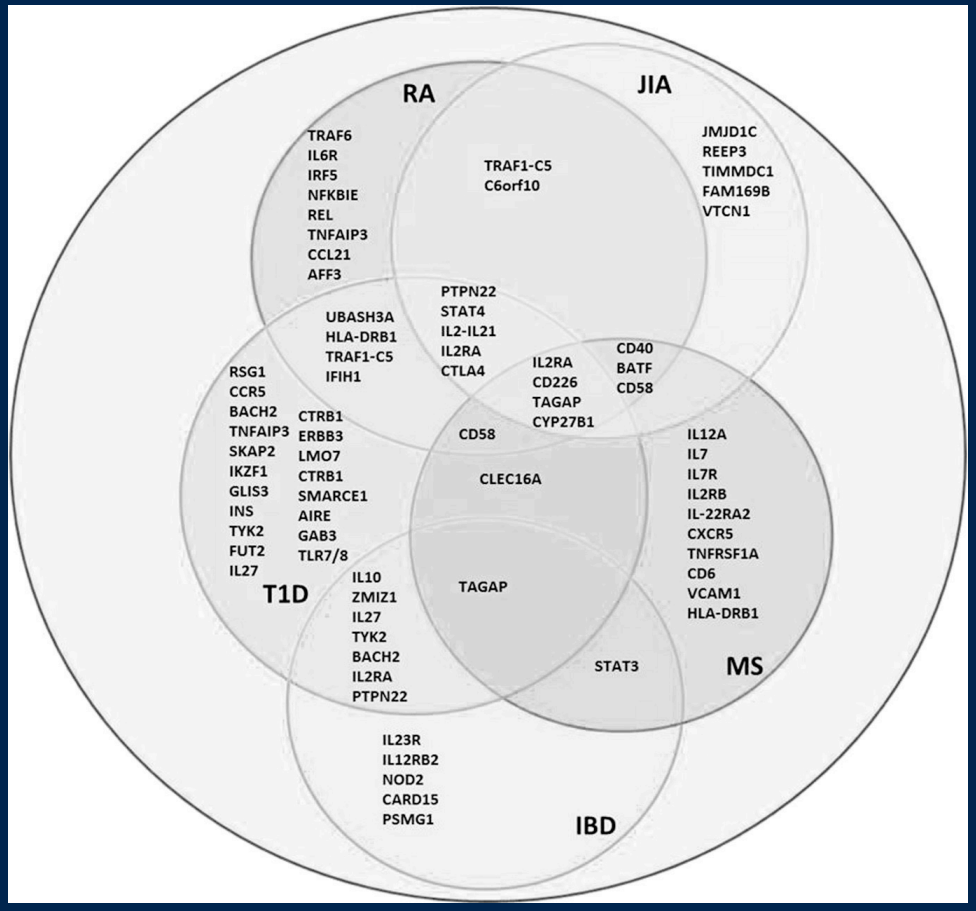
Familial Aggregation

- General population: 0.4%
- Siblings of patients: 6%
- Children of male patient: 6-9%
- Children of female patient: 1.3-4%
- Monozygotic twins of patients: 50-70%

Genetic Factors involved in T1D

- HLA Haplotypes
- Insulin Gene
- PTPN22
- Cytotoxic T-lymphocyte associated protein 4 (CTLA-4)
- Interleukin-2 receptor subunit alpha (IL2RA)
- Protein tyrosine phosphatase, non-receptor type 2 (PTPN2)
- Interferon-induced helicase (IFH1)
- Small ubiquitin-like modifier 4 protein (SUMO4)
- Basic leucine zipper transcription factor 2 (BACH2)

Genetic basis of association with other autoimmune diseases



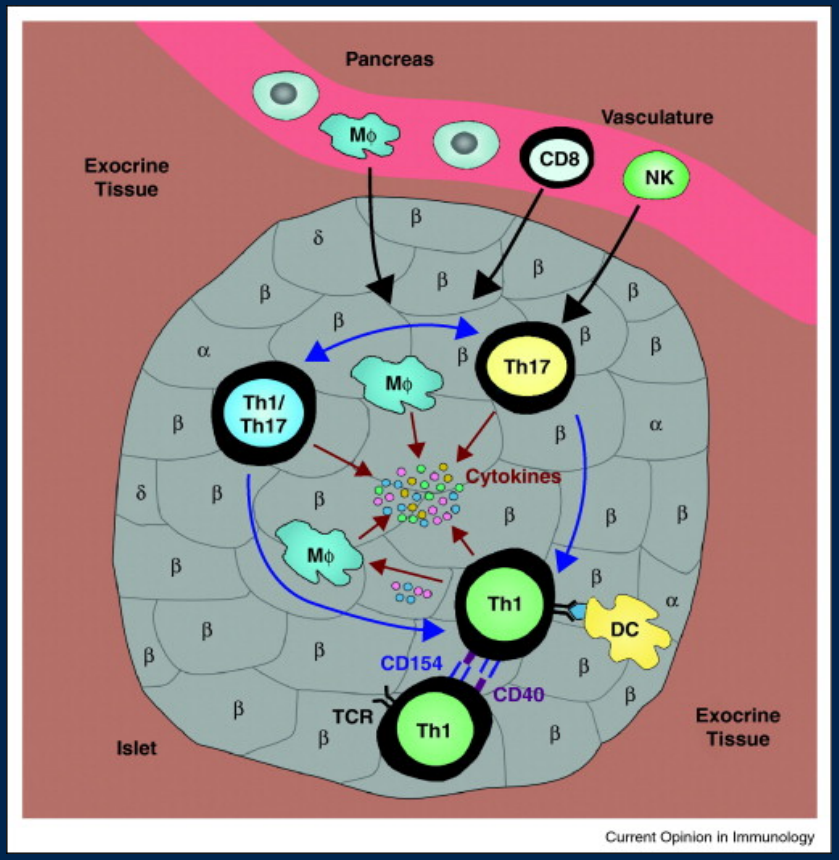
Challenges

- Complex genetic effects
  - Imprinting (insulin gene)
- Acquired genetic polymorphisms (e.g. by retrovirus)
- Epigenetics
- Gene-gene interactions
- Interaction between genes and environment (e.g. genes related to vitamin D metabolism)
- Studies on non-Caucasian ethnic groups
- Heterogeneity of T1D

Environmental Factors

- Viruses
- Cow's milk v breastfeeding:
- Diet, bacteria
- Vitamin D
- Effect of obesity/overweight
- Hygiene hypothesis
- Vaccines: No!

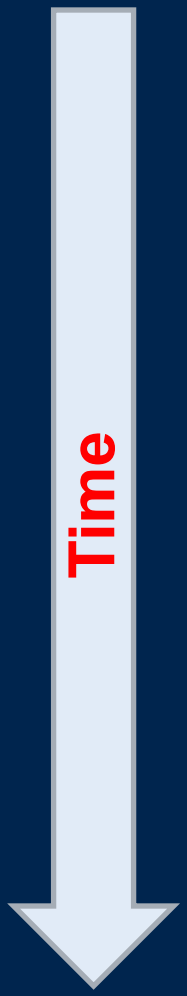
Pathogenesis of Type 1 Diabetes



- Auto-reactive T cells
- Insulitis
- Beta-cell death

Haskins et al. Current Opinion in Immunology, 2011

Measures of beta-cell function loss



Beta-cell dysfunction:

↓ Beta-cell glucose sensitivity

↓ Insulin-to-proinsulin ratio

↓ First phase of insulin secretion

↓ Insulin and C-peptide secretion

Metabolic abnormality:

↑ HbA1c

↑ Postprandial glucose

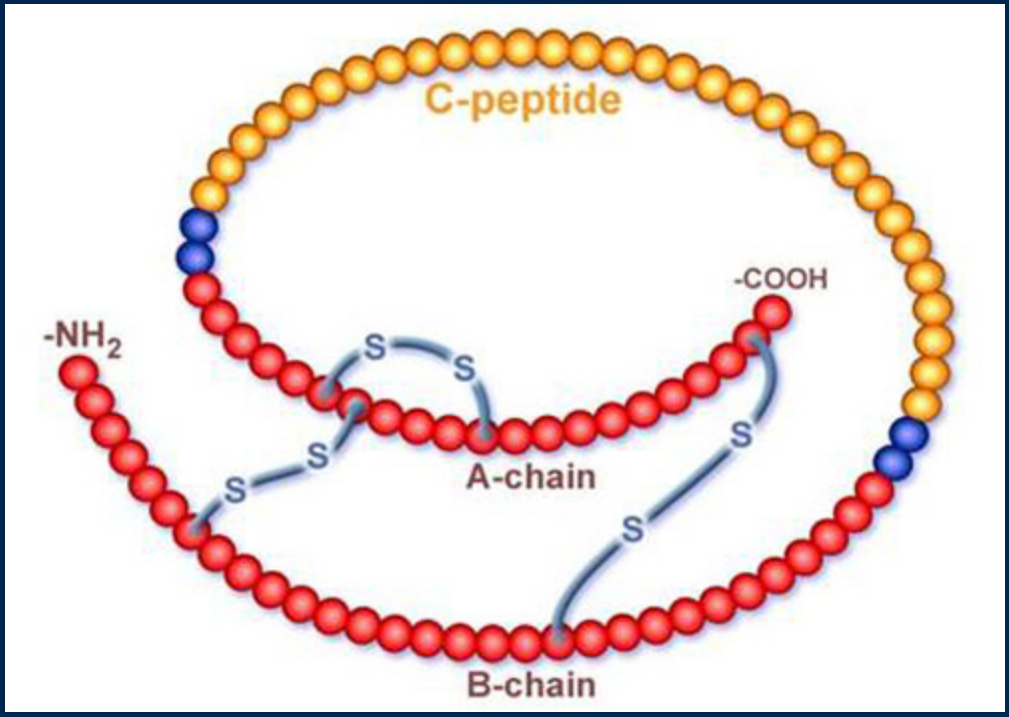
↑ Fasting glucose

Clinical correlates:

↑ Exogenous insulin requirements

Diabetic ketoacidosis

C-peptide is co-secreted with insulin



Anti-islet autoantibodies (Aab)

- Markers (not causative) of beta-cell destruction
  - Diagnosis
  - Prediction
- >=1 expressed in 90-95% of T1D cases
  - Islet cell antibody (ICA)
  - Biochemical:
    - Insulin (IAA)
    - Glutamic acid decarboxylase (GAD65)
    - Thyroxine phosphatase-like protein (ICA512/IA-2)
    - Zinc transporter (ZnT8-Arg and –Trp)

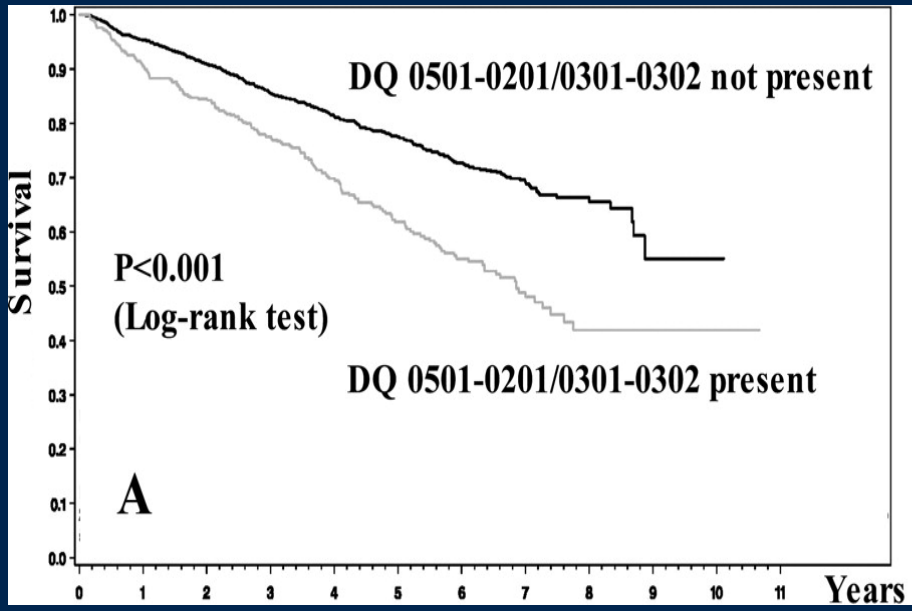
Anti-islet autoantibodies predict T1D

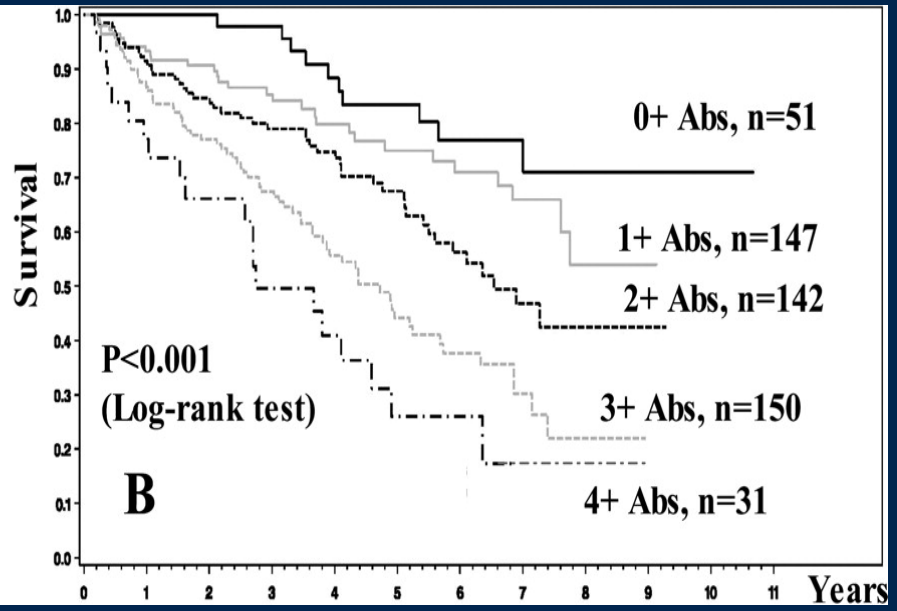
- Appear even years before diagnosis
- Higher T1D risk with:
  - Higher number positive:
    - >=2 positive: 70% T1D risk in 7 yrs
  - Higher titer
  - Certain specificities and combinations
  - Genetic background:
    - Monozygotic twins
    - Relatives

Progression to T1D in relatives of patients

Higher risk in DQ2/DQ8 relatives

Highest risk in DQ2/DQ8 relatives with multiple +Aabs





Redondo M J et al. J Clin Endocrinol Metab 2006;91:1705-1713

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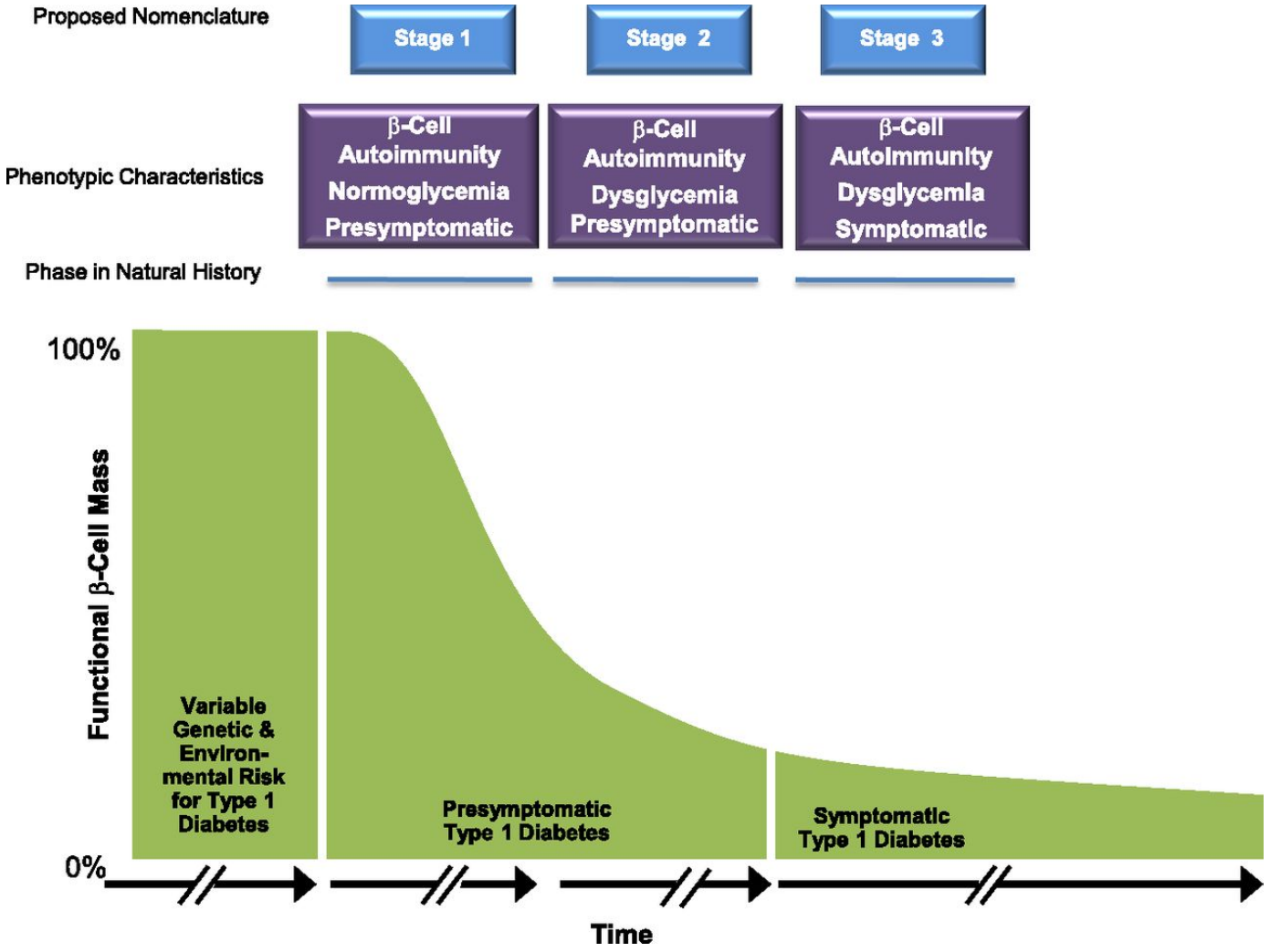
Early stages of type 1 diabetes



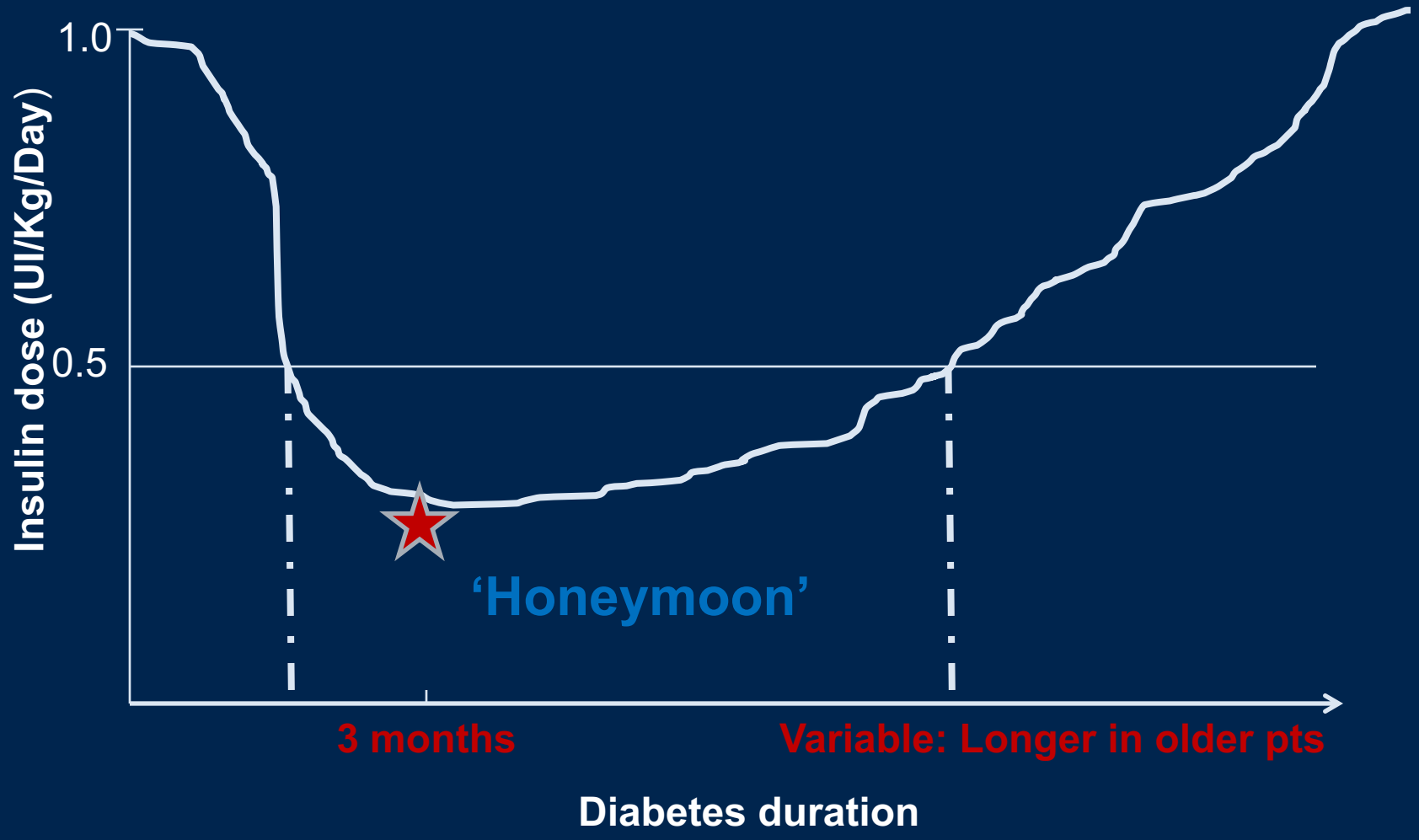
Richard A. Insel et al. Dia Care 2015;38:1964-1974

THE ENDOCRINE SOCIETY

JDRF IMPROVING LIVES. CURING TYPE 1 DIABETES.

American Diabetes Association.

Exogenous insulin requirements after T1D onset



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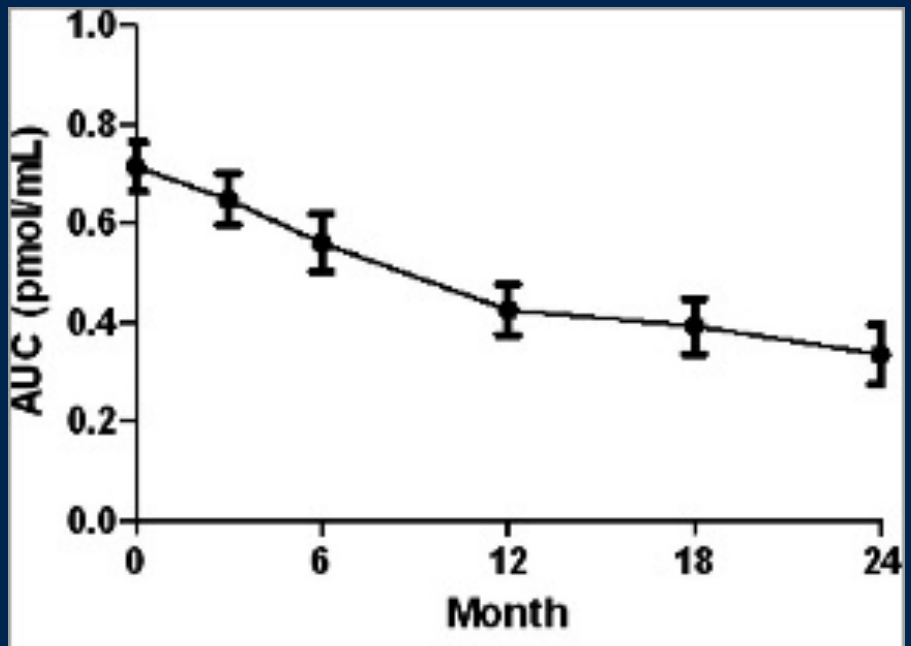
Partial Remission Period ('honeymoon')

- **Definition:**
  - Temporary partial beta-cell functionality after initiation of therapy (Glucotoxicity resolving?)
  - Total daily insulin (TDI)<0.5 U/kg/day; TDI-adjusted A1c<9%
- **Benefits of "honeymoon":**
  - Easier to treat diabetes:
    - Better Hb1c
    - Lower postprandial hyperglycemia
    - Less hypoglycemia
  - Predicts less long-term chronic complications

C-peptide decline after onset



Month	Standard Deviation
0	0.34
3	0.35
6	0.39
12	0.34
18	0.37
24	0.37

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- Type 2 Diabetes – insulin resistance with failure of β-cell compensation and a relative insulin deficiency

Risk Factors for Childhood-onset T2DM

- Obesity
- Positive Family history
- Specific racial and ethnic groups
- Female gender
- Conditions associated with insulin resistance

Risk Factors for Childhood-onset T2DM -Obesity

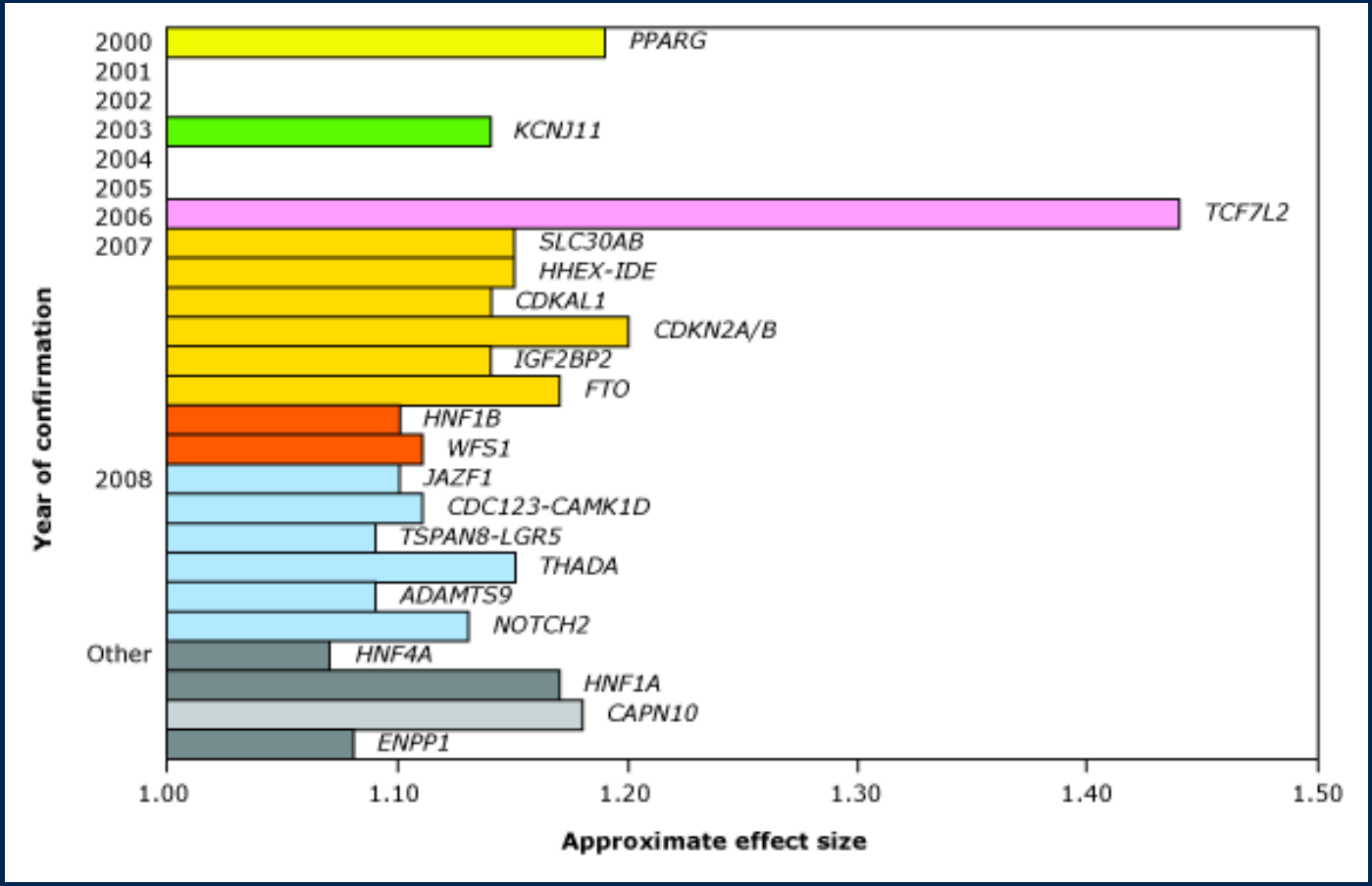
- - BMI ≥95th%
- SEARCH study showed that nearly 80% of youth with T2DM were obese and an additional 10% were overweight
- - Predisposes to T2DM by increasing peripheral resistance to insulin-mediated glucose uptake

Risk Factors for Childhood-onset T2DM – Genetic Susceptibility

- Risk of T2DM is significantly increased in close relatives of an affected patient
- 50-75% of children/adolescents have at least one affected parent
- In monozygotic twins, the other twin has a 90% chance of developing diabetes

- Several candidate genes have been linked to T2DM
  - Involved in pancreatic development, insulin synthesis, secretion, or action

Genetic Loci Associated with T2DM



Risk Factors for Childhood-onset T2DM – Ethnicity

- More common in Native American, African American, Asian American, and Pacific Islander Children

Risk Factors for Childhood-onset T2DM – Female Gender

- Girls are 1.3-1.7 times more likely than boys to develop T2DM during adolescence

- Possibly due to increased risk of insulin resistance, as seen in girls with PCOS

Risk Factors for Childhood-onset T2DM – conditions associated with insulin resistance

- Low Birth Weight
- Gestational Diabetes
- Polycystic Ovarian Syndrome

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Clinical Presentation

- Polyuria, polydipsia, and weight loss with dehydration
- 25% are in clinically apparent DKA (diabetic ketoacidosis)
  - Occasionally children with T2DM can present with DKA (~5-12% frequency for initial presentation)

Laboratory Evaluation

- Elevated serum glucose – fasting >126, random >200
- Glycosuria – renal threshold 185 mg/dl
- Blood or urine ketone bodies
- Pseudo-hyponatremia
- Elevated triglycerides
- Hemoglobin A1C

DKA Presentation

- Initial presenting signs: polyuria, polydipsia, weight loss, dehydration, abdominal pain, Kussmaul respirations
- Labs:
  - **(D)** Hyperglycemia – glucose > 200
  - **(K)** Ketosis – ketones in serum or urine
  - **(A)** Acidosis – pH <7.3, bicarbonate < 15
  - Other labs can include: pseudohyponatremia, elevated WBC (infection), elevated BUN (dehydration), any level potassium

Treatment of DKA

- Measure labs and establish diagnosis
- Fluid and Electrolyte Replacement
- IV Insulin Therapy
- Monitoring

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- Signs/Symptoms
- **Diagnostic Criteria**
- Management

Diagnostic Criteria for Diabetes

- A1C ≥6.5%

OR

- Fasting plasma glucose ≥ 126 mg/dl

OR

- 2 hour plasma glucose ≥ 200 mg/dl during an OGTT

OR

- Random plasma glucose ≥ 200 mg/dl with classic symptoms of hyperglycemia (polyuria, polydipsia)

Table 1—*Criteria for the diagnosis of diabetes*

1. Symptoms of diabetes and a casual plasma glucose ≥200 mg/dl (11.1 mmol/l). Casual is defined as any time of day without regard to time since last meal. The classic symptoms of diabetes include polyuria, polydipsia, and unexplained weight loss.

OR

2. Fasting plasma glucose ≥126 mg/dl (7.0 mmol/l). Fasting is defined as no caloric intake for at least 8 h.

OR

3. 2-h plasma glucose ≥200 mg/dl (11.1 mmol/l) during an oral glucose tolerance test. The test should be performed as described by the World Health Organization, using a glucose load of 75 g anhydrous glucose dissolved in water or 1.75 g/kg body wt if weight is <40 pounds (18 kg).

HgbA1C	Average Sugar
4	60
5	90
6	120
7	150
8	180
9	210
10	240
11	270
12	300
13	330

Diagnostic Criteria for Prediabetes

- Fasting Plasma Glucose between 100 mg/dl and 125 mg/dl
- 2 hour plasma glucose between 140 mg/dl-199 mg/dl in the oral glucose tolerance test
- A1C 5.7-6.4%

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Daily Diabetes Tasks – Type 1 Diabetes

Blood Sugar Monitoring

When to check:

- Before meals
- Before bedtime
- Before and after exercise
- During illness
- Having symptoms of hypoglycemia or hyperglycemia
- 2 am when fasting blood sugars have been elevated, change in insulin doses, extra physical activity, instructed by doctor or diabetes educator

Target Blood Sugar Levels

Fasting (before meals)	Bedtime/ Overnight
90-130 mg/dl	90-150 mg/dl

Insulin Therapy

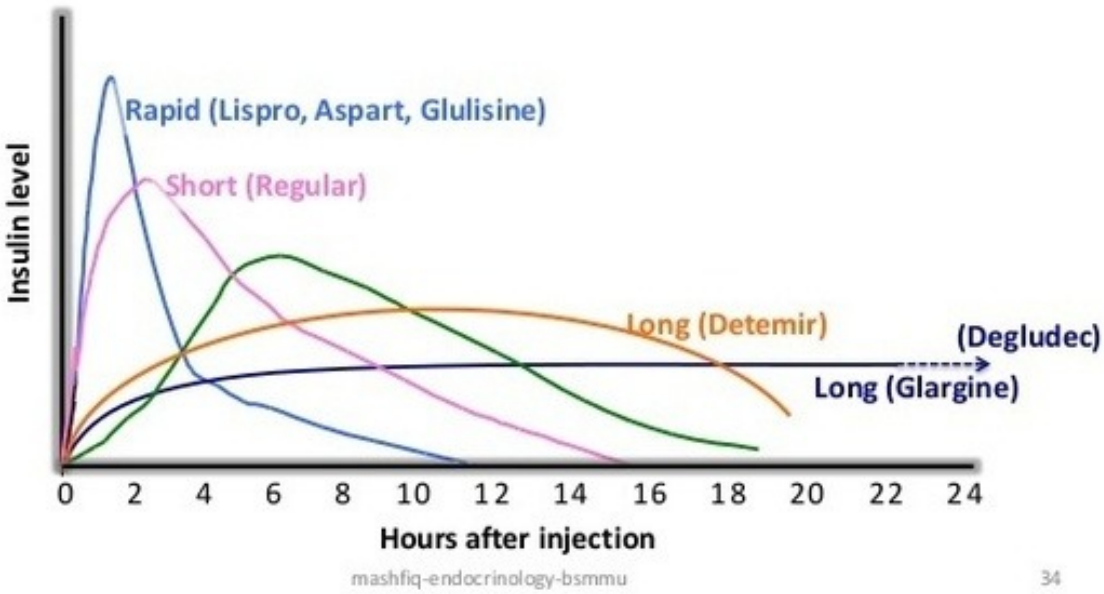
Insulin at School

- Most children will receive a dose of insulin before lunch
- At least Novolog or Humalog (short acting insulin to cover meals)
- Some children will receive their long acting insulin at lunch (Lantus, Basaglar, Tresiba)

Types of Insulin

- Long Acting:
  - Lantus
  - Basaglar
  - Levemir
  - Tresiba
- Short Acting:
  - Humalog
  - Novolog
  - Apidra
  - Fiasp

Insulin Therapy



Daily Diabetes Tasks – Type 2 Diabetes

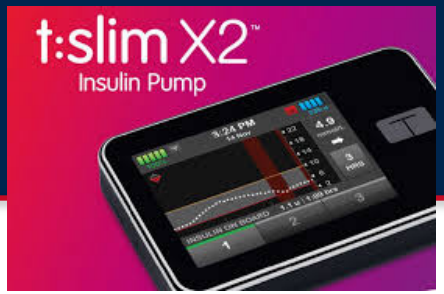
- May require blood glucose monitoring if on insulin
- Treatment
  - Lifestyle modification – diet/exercise
  - Oral Medication – Metformin
  - Insulin may be required depending on blood glucose levels
  - Victoza – GLP-1 agonist

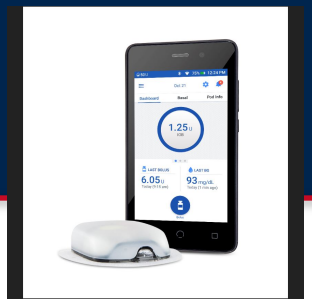
Diabetes technology

Diabetes Technology- insulin pumps

Insulin pumps

- Infusion sets and reservoirs
  - changed every 1-3 days
- Basal rate – small amount of background insulin delivered continuously at a preset rate
  - Temp rate – adjust basal rate for a pre-determined period of time
    - (exercise, illness, stress, menstrual cycle)
- Bolus – dose of insulin delivered when needed
    - (meal and/or correction)
  - Extended – feature used for certain meals such as high-fat





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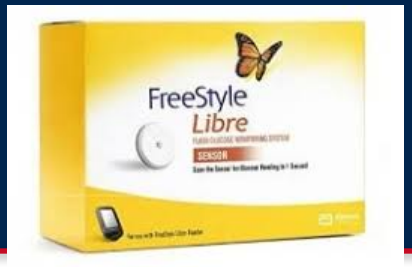
Diabetes Technology – Continuous Glucose Monitors

Continuous glucose monitoring system

- Sensor – changed every 6-7 days
- Transmitter- reusable
- Receiver – specific insulin pumps, smart phone, smart watch, Dexcom receiver



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Practice Questions

Question 1

- Which of the following is a diagnostic criteria for diabetes?

A. Fasting blood sugar of >100 mg/dl
B. Hemoglobin A1C of ≥ 6.5
C. Random plasma glucose level of > 180 mg/dl with symptoms
D. 2 hour oral glucose tolerance test reading of ≥ 180 mg/dl

Question 2

- Which of the following situations would it be appropriate to check for ketones in a patient with Type 1 diabetes?

A. 4 year old girl with a blood sugar of > 300 mg/dl
B. 8 year old boy with vomiting
C. 15 year old girl with abdominal pain and nausea
D. All of the above

Question 3

- Which of the following statements is false?

A. Type 2 diabetes can present with ketosis

B. Pancreatic antibodies are common in Type 2 diabetes

C. It is more common for a patient with Type 2 diabetes to have an affected relative than it is for a patient with Type 1 diabetes

D. Type 2 diabetes has a polygenic inheritance







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Thank you
Questions?