

Initial Evaluation for Type 1 Diabetes (T1DM)

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Definition, Assessment, and Diagnosis

Definition of diabetes mellitus

- Group of disorders affecting glucose metabolism characterized by hyperglycemia
- Can result from insulin insufficiency or insulin resistance or both
- Causes derangements in carbohydrate, lipid and protein metabolism

Diagnosing diabetes in childhood and adolescence

- Criteria based on blood glucose levels in the presence or absence of symptoms
- To make a diagnosis of diabetes:
 - Polyuria, polydipsia, polyphagia + weight loss + random venous blood glucose >200 mg/dl (ketonuria may lag behind), or
 - No symptoms + *random* venous blood glucose >200 mg/dl on two occasions - (may want to obtain oral glucose tolerance test (OGTT) to confirm), or
 - No symptoms + *fasting* venous blood glucose >125 mg/dl on two occasions (Fasting refers to no caloric intake for at least eight hours.)
- American Diabetes Association (ADA) guidelines
 - Oral Glucose Tolerance Test (OGTT)
 - 1.75 g/kg (max 75 g) of glucola after overnight fast
 - *Venous* blood glucose at zero (0) and two (2) hours
 - Normal results for OGTT
 - Fasting blood glucose <100 mg/dl
 - Two hour post challenge <140 mg/dl
 - Abnormal OGTT
 - Fasting blood glucose >100 but <126 (impaired fasting glucose- IFG)
 - Two hour blood glucose >140 but <200

- Impaired glucose tolerance (IGT)
 - Usually occurs before the fasting blood glucose levels are affected
- Fasting blood glucose >125 = diabetes
- Two hour blood glucose >200 = diabetes
- Hemoglobin A1c \geq 6.5% is diagnostic of diabetes. The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.
- Pre-Diabetes
 - Intermediate states between normoglycemia and diabetes are distinct entities - basal vs. dynamic states
 - Impaired glucose tolerance (IGT)-dynamic
 - Impaired fasting glucose (IFG)-basal
 - IGT and IFG can be associated with the metabolic syndrome.
 - High risk for development of diabetes
 - Can be seen as intermediate stages in any type of diabetes, such as type 1, 2, CF- related diabetes, gestational, maturity-onset diabetes of the young (MODYs), etc.
 - Can have normal HbA1c levels

Type 1 Diabetes: Pathogenesis, Epidemiology, Classification, Recommendations

Pathogenesis

- T-cell mediated islet β -cell destruction, which can be slowly progressive or “fulminant”
- Absolute insulin deficiency after “honeymoon” or remission period
- 85-90% of new patients with T1DM have specific serological markers of autoimmunity
 - GAD65 antibodies
 - ICA-512 antibodies
 - Insulin antibodies (IAA)
 - Zinc transporter 8 (ZnT8) autoantibodies
- Interaction of multiple genes: HLA DQA and DQB genes which can be predisposing or protective
- Triggers
 - Congenital rubella-proven
 - Possibly chemical, viral, enteroviruses, food proteins, gluten, casein
- Process begins months to years before the clinical manifestations

Epidemiology

- More than 50% of new onset type 1 diabetics are diagnosed before the age of 15.
- T1DM accounts for more than 90% of childhood and adolescent diabetes in most western countries.
- Annual incidence varies tremendously between countries.
 - United States
 - Rate of approximately 18-32/100,000 (0-14 yr)
 - Incidence in Caucasian > African American > Latinos
 - Type 2 diabetes mellitus is still relatively infrequent; however, the highest rates were observed among adolescent minority populations.
 - Incidence of T1DM compared to that of the United States
 - Finland - almost triple
 - Canada - double

- France - half
- Argentina - one third
- Well-documented rise in incidence noted in many countries
 - Some reports demonstrate a disproportionate rise in those younger than 5.
 - Seasonal variation has been shown with peak during the winter months.
 - No recognizable pattern of inheritance
- Risk of diabetes
 - Identical twin = 36%
 - Sibling and “fraternal” twin = 4% by the age of 20 and 9.6% by the age of 60
 - General population = 0.5%
 - Risk higher for probands diagnosed at younger age
 - Risk in offspring of diabetic fathers is 3.6-8.5% versus 1.3-3.6% in children of diabetic mothers

Classification

- Determination of correct diagnosis has therapeutic and educational implications.
- If the patient exhibits the typical presentation of T1DM with polyuria, ketonuria, hyperglycemia, and weight loss but antibodies are negative, consider the following classifications:
 - Type 1B (idiopathic type 1 diabetes)
 - Type 2 diabetes
 - Monogenic diabetes (MODYs)
- Regardless of the type, child with severe fasting hyperglycemia, metabolic derangements and/or ketonemia, will require insulin therapy initially.
- Other types of diabetes should be considered in a child with
 - Autosomal dominant family history of diabetes
 - Conditions like deafness, optic atrophy or syndromic features
 - Marked insulin resistance or small insulin requirement after honeymoon period
 - Past exposure to drugs that are toxic to islet cells or cause insulin resistance (steroids, chemotherapy)
- MODY (monogenic diabetes)
 - Autosomal dominant history of diabetes
 - Non-ketogenic
 - Onset before age 25
 - HNF-4 α gene mutation (MODY1)
 - Glucokinase gene mutation (MODY2)
 - *HNF-1 α gene mutation (MODY3)-most common in the general population*
 - Insulin promoter factor-1 mutation (MODY4)
 - HNF-1 β mutation (MODY5)
 - NeuroD1 gene mutation (MODY6)
- MODY3- suspect in patients who have:
 - Very small insulin requirements
 - Detectable c-peptide levels 3 years after diagnosis
 - No ketosis
 - Good response to sulfonylureas
- Neonatal diabetes
 - Insulin requirement in the first 3-6 months of life (1 in 400,000 births)
 - IUGR
 - Transient/ permanent
 - Permanent cases associated with specific genetic mutations

- Mitochondrial diabetes
 - Maternally inherited diabetes
 - Associated with sensorineural deafness
 - Progressive non-autoimmune beta cell failure
- Cystic fibrosis related diabetes
 - CFRD- adolescents, young adults
 - Poor prognosis
 - Increased morbidity and mortality if untreated
 - Insulin therapy is necessary.
- Drug-induced diabetes
 - Dexamethasone, other glucocorticoids - Diabetes may be reversible.
 - L-asparaginase-reversible
 - Cyclosporin- usually permanent
 - Tacrolimus-usually permanent
 - Atypical antipsychotics (olanzapine, risperidol, quetiapine, and ziprasidone)-may be reversible
- Stress hyperglycemia
 - Reported in up to 5% of children presenting to the ED
 - Associated features
 - Acute illness/ injury
 - Trauma
 - Febrile seizures
 - Fever > 39° C
 - Reported incidence of progression to overt diabetes is 0-32%
 - Those without serious illnesses more likely to develop diabetes
 - Presence of islet cell antibodies and insulin autoantibodies are highly predictive of type 1 diabetes.

Recommendations (ADA/ISPAD)

- Diagnosis of diabetes is based on blood glucose measurements obtained by venipuncture and the presence or absence of symptoms.
- An oral glucose tolerance test (OGTT) may be useful for the diagnosis of non-type 1 diabetes.
- Severe hyperglycemia detected under stressful conditions may be transitory and require treatment but should not be regarded as diagnostic of diabetes.
- Measurement of auto-antibodies: ICAs, ZnT8, GAD, IA-2, IAAs and/or HbA1c may be helpful in some situations.

This guideline was developed to improve health care access in Arkansas and to aid health care providers in making decisions about appropriate patient care. The needs of the individual patient, resources available, and limitations unique to the institution or type of practice may warrant variations.

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