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Diabetes Classification and Stages

Kathy Sentena, PharmD, Oregon State University Drug Use Research and Management Group

Diabetes affects an estimated 12% of the United States population based on 2023 data.[1] That equates to approximately 29.1 million people diagnosed with diabetes and 31.3 million people that are 65 years or older with prediabetes.[1] Diabetes is most commonly classified as type 1 or type 2 diabetes, gestational diabetes, and other types caused by pancreatic disorders or medications.[2] More recently, type 1 diabetes (T1D) has been further defined by delineating Stages 1-3.[2]

The clinical presentation of diabetes occurs over time. Knowing the presymptomatic stages, risk factors and hyperglycemia symptoms helps to identify people before the classic symptoms of diabetes (i.e., frequent urination, blurred vision, unexplained weight loss) develop. Additionally, by determining the appropriate diagnostic category, providers can recommend treatment options to prevent or slow the progression of diabetes.[3] This newsletter will present the types and stages of diabetes and recommendations for early management.

Types of Diabetes

The most common types of diabetes are presented in **Table 1**. The type of diabetes is dependent upon underlying pathophysiology leading to hyperglycemia. Accurate diagnosis is important for treatment and to prevent progression and risk of associated cardiovascular (CV), cardiometabolic, retinopathy, nephropathy and other complications caused by prolonged hyperglycemia.[3] In prediabetes and type 2 diabetes (T2D) early identification allows for modification of lifestyle factors (e.g., weight management and physical activity) to assist in glucose management and minimization of related complications.[3]

Table 1. Types of Diabetes[2]

Diabetes Type	*Description*	*HbA1c*
Prediabetes	Elevated glucose levels but below diagnostic threshold for diabetes	5.7-6.4%
Type 2 Diabetes	Nonautoimmune progressive loss of insulin secretion often associated with insulin resistance	≥ 6.5%
Type 1 Diabetes	Autoimmune beta-cell destruction. Islet autoantibodies against insulin can be identified before overt diabetes. Absolute endogenous insulin deficiency results	≥ 6.5%

Type 1 Diabetes Disease Continuum

The identification of islet autoantibodies allows practitioners to identify T1D before symptoms are present. There are 3 stages of T1D disease progression (**Table 2).** Adults who develop the stages of T1D may have a less classic presentation or slower progression than children and may be misclassified as having T2D. Presymptomatic screening for T1D can be done by testing for autoantibodies against insulin (IA), glutamic acid decarboxylase (GAD), islet antigen 2 (IA-2) or zinc transporter 8 (ZnT8).[2]

Table 2. Stages of Type 1 Diabetes[2]

Stage	Characteristics	Glucose Levels	Timeline to Stage 3 diabetes
Stage 1	- Autoimmunity present - Presymptomatic - Multiple islet autoantibodies	Normal	5-year risk of approximately 44%
Stage 2	- Autoimmunity present - Dysglycemia - Multiple islet autoantibodies - Presymptomatic	HbA1c 5.7 to 6.4% FPG 100-125 mg/dL	2-year risk of approximately 60% and 5-years risk of approximately 75%
Stage 3	- Autoimmune diabetes - Overt hyperglycemia - Usually symptomatic - Autoantibodies may become absent	HbA1c ≥ 6.5% Meets standard diagnostic criteria for diabetes	Diagnosis of T1D that requires prompt treatment

Abbreviations: DM – diabetes; FPG – fasting plasma glucose; HbA1c – hemoglobin A1c; T1D – type 1 diabetes

In Stage 1 there is autoimmunity against beta-cells but no changes in glucose levels.[2] Progression to Stage 3 is dependent upon age, number of autoantibodies, type of autoantibodies, titer and genetic factors.[2] In Stage 2, islet autoimmunity is present with abnormal glucose regulation, as reflected in higher than normal blood glucose values. In Stage 3, clinical and laboratory presentation meets criteria for standard diagnosis of T1D.[2] Individuals in Stage 3 may have clinical symptoms such as polyuria, polydipsia, weight loss, blurred vision and diabetic ketoacidosis (DKA).

Individuals with a family history of T1D or elevated genetic risk should be offered autoantibody-based screening.[2] Those with multiple autoantibodies without overt diabetes should be

referred to a specialist for education and consideration of preventative treatments.

Treatment Recommendations for Initial Management

For individuals with prediabetes there is evidence that lifestyle interventions, such as weight loss and exercise can play an important role in preventing progression to T2D.[3] While healthy lifestyle choices are important in individuals at high risk for T1D they do not prevent progression in the autoimmune process of pancreatic beta-cell destruction.

In individuals with prediabetes, pharmacotherapy may be an appropriate option. Metformin can be considered for those individuals at high risk of developing T2D, especially in those with a BMI $\geq$ 35 kg/m^2, fasting blood glucose of $\geq$ 110 mg/dL, HbA1c of $\geq$ 6.0% or history of gestational diabetes.[3]

For patients diagnosed with T2D, lifestyle management plus pharmacotherapy is recommended.[4] There are many treatment options and patient characteristics that need to be considered before initiating therapy for T2D. Discussion of all aspects of T2D treatment is beyond the scope of this newsletter; however, initial medication options will be presented.

Metformin is still considered a first-line option in patients with T2D without significant comorbidities.[4] A sodium -glucose cotransporter 2 (SGLT2) inhibitor or a glucagon-like peptide 1 receptor agonist (GLP-1 RA) should be considered in patients with T2D and atherosclerotic cardiovascular disease (ASCVD), high ASCVD risk, and/or chronic kidney disease (CKD).[4] For patients presenting with T2D and heart failure an SGLT2 inhibitor is recommended. If a patient has obesity or overweight starting a GLP-1 RA, such as semaglutide or tirzepatide, may be appropriate.[4]

For Stage 1 T1D there is no pharmacotherapy that has been FDA approved to modify the disease process.[3] Individuals identified as having Stage 1 should be educated on sign and symptoms of hyperglycemia, including DKA, and receive metabolic monitoring. For Stage 2, recommendations for Stage 1 should be applied and the addition of teplizumab may be appropriate.[5] Teplizumab is an intravenous (IV) CD-3 directed antibody that has been approved for use in adult and pediatric patients, 1 year of age and older, with Stage 2 T1D to delay the onset of stage 3 T1D.[5] Teplizumab may also be considered for the use to delay the decline in endogenous insulin production in pediatric patients, ages 8 to 17 years, that have been recently diagnosed with Stage 3 T1D.[5] There is insufficient evidence for teplizumab use in adults 45 years and older with Stage 2 T1D. Teplizumab is not indicated for patients with T2D.

Conclusion

Identifying and diagnosing individuals at risk for diabetes is crucial to slowing disease progression, reducing risk of complications and optimizing treatment strategies. Additional evidence on underlying pathophysiology to determine the diagnostic category of diabetes is a key component to patient management.

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