Type 2 Diabetes Mellitus

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Key Points

- Both environmental and genetic factors contribute to the etiology of Type 2 diabetes mellitus (T2DM).
- A family history of T2DM indicates an increased risk for the disease.
- The most important preventive measure for an at-risk individual is a healthy lifestyle, including regular exercise, weight management, and a diet low in fats and concentrated sugars and high in fruits and vegetables.
- A small proportion of diabetes mellitus is due to highly penetrant autosomal dominant mutations that result in maturity-onset diabetes of the young (MODY), a form of diabetes mellitus that resembles T2DM.

Learning Objectives

Participants will be able to:

- Use family history to identify persons at increased risk of T2DM;
- Identify family history characteristics suggestive of MODY;
- Identify preventive measures that reduce the risk of developing T2DM.

Family History Issues

The lifetime risk of T2DM in the general population is about 5%. If a person has a biological relative with T2DM, the risk is increased. When a parent has T2DM, the lifetime risk for offspring is 10-15%. Risk is increased to a lesser degree if a only a second-degree relative, such as an aunt, uncle, or grandparent, is affected.

In rare families, a form of diabetes mellitus resembling T2DM is inherited as an autosomal dominant condition (maturity-onset diabetes mellitus, or MODY). In these families, the disease is seen in sequential generations, with about 50% of individuals affected in each generation, and onset usually occurs in early adulthood. MODY accounts for only 1% to 5% of diabetes mellitus.

Red Flags 

- Obesity, lack of exercise, and age are all associated with increased risk for T2DM.
- Prevalence of T2DM is higher in some racial and ethnic groups, including African Americans, Native Americans, Hispanic Americans, Asian Americans, and Pacific Islanders.
- Early signs of T2DM include increased thirst, frequent urination, sudden weight loss, blurred vision, and fatigue or irritability as a result of changes in blood sugar levels.

Case 20. Family History of Type 2 Diabetes Mellitus (T2DM)

A 35-year-old woman comes in for her annual physical examination. She notes that her mother just died of complications of T2DM and she is worried about her own risk for T2DM, because she has been told that it runs in families. Her mother developed T2DM at age 50 years and never achieved good blood sugar control; she developed heart disease at age 64 years and died at 68 years, of a heart attack. The patient describes her mother as "very overweight" and sedentary. There is no other family history of T2DM.

The patient's blood pressure is 128/82; height is 5"4" and weight is 147 (BMI= 25.2) (See BMI calculator at nhblisupport.com/bmi/). When questioned about her lifestyle, she says that she quit smoking a couple of years ago. Because she works full time and has two children, aged six and eight years, she has little time for exercise. She tries to serve her family a healthy diet, but tends to rely on fast food on busy days.

Clinical Care Issues

Lifestyle and genes. Type 2 diabetes mellitus (T2DM) is a hyperglycemic disorder characterized by insulin resistance and impaired insulin response to rising blood sugar levels. Although it can occur in early adulthood and even in childhood, it typically has onset in early middle age. Common secondary complications include coronary heart disease, peripheral vascular disease,

peripheral neuropathy, retinopathy, and renal failure.

T2DM is strongly associated with obesity and lifestyle factors such as lack of exercise and poor diet. As a result, lifestyle factors play a central role in modifying risk for T2DM. The Nurses' Health Study, a study that has followed a large cohort of women over time, estimated that 85% of T2DM could be prevented by healthy diet, daily moderate-to-vigorous exercise, and maintenance of body mass index below 25 [Hu et al 2001]. The reduction in risk associated with a healthy lifestyle was similar in women with and without a family history of diabetes mellitus.

Yet family and molecular studies provide evidence for important genetic contributors as well. Association studies and genome scanning have identified a potential association between T2DM and several genes [The Genetic Landscape of Diabetes, Chapter 3; Florez et al 2003] These include genes coding for insulin, the insulin receptor, enzymes involved in glucose metabolism, and related physiological functions. The genetic contribution to diabetes is assumed to be the result of the additive effects of small differences in these and other genes. T2DM is presumed to occur when a person with a predisposing genotype (potentially one of many different combinations of gene variants contributing to susceptibility) is exposed to one or more non-genetic precipitants. The relative contribution of genetic and non-genetic factors may vary considerably in different patients.

Implications for this patient. Because of her mother's history of T2DM, this patient has an increased risk of developing the disease herself. Her concern about risk is appropriate, and may provide the necessary motivation to make lifestyle changes that will reduce her risk.

Risk Assessment

The lifetime risk for T2DM in the general population is about 5%. Several studies have assessed risk in people with a family history of T2DM, by measuring the association between family history of T2DM and diagnosis of T2DM in unselected populations, case-control comparisons, and cohorts followed over time [Harrison et al 2003]. From these studies, it is estimated that people who have a parent or sibling with the disease have about a two- to threefold increased risk (~10-15% lifetime risk). If both parents have T2DM, risk is increased about fourfold.

In addition to family history, risk assessment needs to take into account other known risk factors for T2DM, [American Diabetes Association 2004a]

including:

- Age ≥45 years
- BMI ≥25 kg/m^2
- Habitual physical inactivity
- Member of a high-risk population (African Americans, Native Americans, Hispanic Americans, Asian Americans, and Pacific Islanders)
- Previously identified impaired fasting glucose (fasting glucose 100-126 mg/dL) or impaired glucose tolerance (2-h values of 140-200 mg/dL in the oral glucose tolerance test)
- History of gestational diabetes mellitus or delivery of a baby weighing >9 lbs
- Hypertension (≥140/90 mmHg)
- HDL cholesterol ≤35 mg/dL and/or triglyceride level ≥250 mg/dL
- Polycystic ovary syndrome
- History of vascular disease

Several of these risk factors contribute to the "**metabolic syndrome**," a constellation of risk factors of metabolic origin that is commonly seen in T2DM and is associated with increased risk of coronary heart disease (Table 1).

Table 1: Identifying the Metabolic Syndrome

Risk Factor	Diagnostic Measure	
	Men	Women
Abdominal obesity	>40 in	>35 in
HDL cholesterol	<40mg/dL	<50mg/dL
Triglycerides	≥150 mg/dL	
Fasting glucose	>110 mg/dL	
Blood pressure	≥130 / ≥85 mmHg	

NCEP

Screening

The American Diabetes Association (2004a) recommends screening for diabetes with a fasting blood glucose at three-year intervals starting at age

45, particularly for patients with BMI ≥25 kg/m^2 (see BMI Calculator).

The ADA guidelines also recommend consideration of screening at an earlier age or at more frequent intervals for patients with BMI ≥25 kg/m^2, if additional risk factors are identified.

What inherited syndromes might be considered?

A small subset of diabetes mellitus is due to a group of disorders termed maturity-onset diabetes mellitus of the young (MODY). These are six related genetic disorders (MODY Types I-VI), due to autosomal dominant mutations in the genes for glucokinase (a glycolytic enzyme) and five transcriptional factors [Fajans et al 2001; The Genetic Landscape of Diabetes, Chapter 4]. All of the genes are expressed in beta-cells, with mutations leading to beta-cell dysfunction and inadequate insulin secretion.

MODY differs from T2DM in certain features (Table 2):

Table 2: Identifying the Metabolic Syndrome

	MODY	T2DM
Inheritance	Autosomal dominant	Polygenic
Family history	Family history of early-onset diabetes mellitus in parent is usually present. Typically other affected relatives can be identified on the affected parent's side of the family, in a pattern consistent with autosomal dominant inheritance.	Family history of affected first-degree relative is often absent.
Genetic testing	Genetic testing available for MODY Types I,III, IV, V, and VI	No genetic testing available

Physiological basis for hyperglycemia	Indequate insulin secretion	Usually insulin resistance
Age of onset	Usually <25 years	Usually >40 years
Body weight	Non-obese	Usually obese
Metabolic syndrome	Absent	Usually present

Sources: The Genetic Landscape of Diabetes, Chapter 4; GeneTests: MODY

Implications for this patient

The patient has two risk factors: a positive family history and a BMI >25. If she were African American, Native American, Hispanic, Asian, or a Pacific Islander, she would be considered to have a third risk factor. These risk factors identify her as a potential candidate for further evaluation, e.g., to determine fasting blood sugar and assess for other components of the metabolic syndrome.

Her family history is not consistent with MODY because her mother developed diabetes mellitus after age 40 and was obese.

Even if screening does not identify an elevated blood sugar, she would benefit from measures to improve her exercise pattern, diet, and body weight.

Genetic Counseling and Testing

The patient's family history suggests an increased risk for T2DM, rather than MODY. No genetic counseling is needed, nor are there genetic tests to evaluate risk for T2DM (Table 2).

However, it is appropriate to counsel this patient about the risk associated with a positive family history of T2DM, which is significant for both herself and her children. Both she and her children will benefit from lifestyle measures to reduce their risk.

Interventions

The most important challenge for this patient is to assist her to implement and maintain a healthy lifestyle. Randomized trials have shown that lifestyle modifications such as a healthy diet and increased physical activity can

significantly decrease the incidence of T2DM in populations at increased risk [American Diabetes Association 2002]. Further, physician intervention to discuss physical activity can take as little as three to five minutes during an office visit yet play a critical role in motivating patients [McInnis et al 2003].

This patient has already expressed concern about her risk, and therefore may be receptive to advice concerning both exercise and diet. Her physician can provide important assistance by confirming the health benefit provided by lifestyle changes and also by helping the patient to set realistic goals for incremental change [McInnis et al 2003].

Physical Activity and Health: A Report of the Surgeon General summarizes current findings and recommendations related to physical activity.

The National Cholesterol Education Project (NCEP) provides additional guidelines for a healthy diet.

Ethical/Legal/Social/Cultural Issues

Potential for genetic risk information to cause fatalism. In this case the patient is worried about her risks for T2DM because of her mother's history of the disease. She has already inferred a genetic risk. Her concern may provide her with motivation to make important lifestyle changes. However, genetic risk information may also lead to fatalism [Marteau & Lerman 2001]. In talking with the patient, it is important to help her maintain a balanced view of her risk, so that she understands that while she may have a genetic predisposition toward T2DM, there are many steps she can take to reduce her risk.

Resources

- **American Diabetes Association**
- **National Institute of Diabetes & Digestive and Kidney Diseases**
- **National Diabetes Education Program**
  Contains free downloadable patient education booklets

- **Division of Diabetes Treatment and Prevention**
  Site maintained by Indian Health Service; standards of care for patients with type 2 diabetes and culturally specific information on diabetes

- **Diabetesgenes.org**
  Contains information on the genetics of MODY

- **GeneTests Laboratory Directory**
  Search for information on genetic testing for MODY.

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