Journal of Diabetes Science and Technology
Volume 3, Issue 4, July 2009

SYMPOSIUM

Detecting Undiagnosed Type 2 Diabetes: Family History as a Risk Factor and Screening Tool

Rodolfo Valdez, Ph.D.

Abstract

A family history of diabetes is a major risk factor for the disease. As such, it is often included in a variety of tools designed to detect either people at risk of diabetes or people with undiagnosed diabetes. One of the reasons to screen for diabetes is that it has a prolonged asymptomatic phase, which includes impaired fasting glucose, impaired glucose tolerance, and the early stages of diabetes. In terms of prevalence, diabetes is a major public health problem. Evidence shows that the detection of impaired glucose metabolism in its early stages (prediabetes) could lead to the delay or prevention of the disease and its complications. However, the issue of using family history to screen for diabetes must be discussed within the context of screening for diabetes in general. Screening for a disease among asymptomatic people must meet a series of stringent requirements to ensure the best possible outcomes. Screening for diabetes meets most of these requirements but the ones it does not meet are still important. Therefore, based on systematically collected evidence or simply by consensus among scientists, influential organizations recommend screening only among high-risk individuals. As a result, researchers have developed a variety of simple tools to identify high-risk individuals for diabetes in populations. Family history is included as a key variable in the vast majority of them. This article is a brief overview of the reasons to screen for diabetes in general, the tools available for conducting this screening, and the role of family history in these tools.

J Diabetes Sci Technol 2009;3(4):722-726

Background

Overt type 2 diabetes mellitus (T2DM) is preceded by two major asymptomatic indicators of imbalance in the metabolism of glucose: impaired glucose tolerance (IGT) and impaired fasting glucose (IFG).[1] These two indicators, collectively labeled as prediabetes, are correlated but they may also appear separately. (**Table 1** contains the different categories used for determining normal and impaired glucose metabolism.) Similar to IFG and IGT, the early stages of T2DM are asymptomatic; consequently, people with the disease may go undiagnosed for prolonged periods. In the continuum of plasma glucose distributions (fasting or 2 hour), the escalation from prediabetes to T2DM is marked by a sharp increase in the risk of complications, which, in the long run, can

Author Affiliation: Office of Public Health Genomics, Coordinating Center for Health Promotion, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia

Abbreviations: (ADA) American Diabetes Association, (AUC ROC) area under the receiver operating characteristic curve, (BMI) body mass index, (IFG) impaired fasting glucose, (IGT) impaired glucose tolerance, (T2DM) type 2 diabetes mellitus, (WHO) World Health Organization, (USPSTF) U.S. Preventive Services Task Force

Keywords: family history, glucose intolerance, prediabetes, screening, type 2 diabetes

Corresponding Author: Rodolfo Valdez, Ph.D., CDC\Office of Public Health Genomics, 1600 Clifton Rd, NE, Mailstop E61, Atlanta, GA 30333; email address *rvaldez@cdc.gov*

seriously affect a variety of organs and tissues, such as eyes, kidneys, nerves, and blood vessels (large and small).[1] Therefore, prediabetes and undiagnosed T2DM are conditions for which screening can be helpful in preventing major health problems in a sizable portion of the population. This article examines the conditions under which such screening can take place and emphasizes the use of a family history of diabetes as a screening tool.

Table 1.
Current Categories for Normal and Impaired Glucose Metabolism[a]

Category	Fasting glucose[b] (mg/dl)	2-hour glucose[c] (mg/dl)
Normal	<100	<140
Impaired glucose tolerance	—	≥140 and <200
Impaired fasting glucose	≥100 and <126	—
Diabetes	≥126	≥200

[a] From American Diabetes Association.[1]
[b] After an overnight fasting of at least 8 hours.
[c] After ingesting a standard solution with 75 grams of glucose.

The Population

Recent estimates among U.S. adults aged 20 years or older indicate that approximately 13% have T2DM (diagnosed or undiagnosed) and an additional 30% have prediabetes.[2] Results vary by race or ethnicity. The number of people affected by these conditions in the United States was calculated by applying recent prevalence estimates to population estimates from the 2007 U.S. census. **Table 2** shows results of this calculation for the three major U.S. racial or ethnic groups, according to their glycemic status. In total, about 56.8 million people have prediabetes, about 25.6 million have diabetes, and 10.7 million of them remain undiagnosed.

Is Screening for Diabetes Justifiable?

The variety and severity of the health consequences of diabetes and the large number of people that are or can be affected by the disease leave no doubt that diabetes is a major public health problem.[3] A critical step toward the solution of this problem is to screen the population in search of individuals at high risk, particularly those at the early stages of impaired glucose metabolism. The World Health Organization (WHO) has set stringent conditions for any screening program that would assign a health risk to a potentially large number of asymptomatic individuals.[4,5] First, the condition should be an important

Table 2.
Estimated Number of U.S. Adults (Age ≥20 years) in Several Categories of Impaired Glucose Metabolism for 2007[a]

	Total population	Prediabetes (IFG/IGT)	Diabetes	
			Undiagnosed (FG/OGTT)[b]	Diagnosed (self-report)
Non-Hispanic White	151,789,928	44,474,449	8,500,236	10,018,135
Non-Hispanic Black	26,051,718	6,538,981	1,068,120	3,334,620
Mexican American	18,338,148	5,813,193	1,155,303	1,540,404
Total	196,179,794	56,826,623	10,723,659	14,893,159

[a] Portions taken from Cowie and colleagues[2] and applied to census data from the 2007 U.S. population (www.census.gov).
[b] According to fasting glucose or the oral glucose tolerance test.

health problem, amenable to primary prevention, and its epidemiology and natural history should be adequately understood. Second, the screening test should be simple, safe, precise, and validated; the distribution of the values generated by the test and its risk thresholds should be known in the target population; the test should be acceptable to the population; and there should be a clear policy on the management of individuals with a positive test result. Third, there should be an effective intervention with better outcomes for those treated early rather than late as well as a clear policy to deliver such intervention; the clinical management of the condition and the health outcomes should be optimized by the health care providers before they join the screening program. Fourth, there should be strong evidence that the screening program is effective in reducing mortality or morbidity and that the entire program is clinically, socially, and ethically acceptable to health professionals and the public; the benefits of the program should clearly outweigh the harms; the cost of the screening program should be reasonable in relation to expenditure on medical care as a whole; the screening program should be adequately staffed and managed from the start; potential participants should be well informed of the consequences of testing and available treatment; and there must be flexibility for widening the eligibility criteria, reducing the screening interval, and improving the test if such changes are supported by scientific evidence.

Does screening for diabetes meet the conditions just stated? Diabetes and its associated conditions meet most of the requirements for a screening program,[5] but no major national organization recommends universal

screening for diabetes. The reason is that screening for diabetes does not meet some important requirements set by the WHO;[5] namely, there is no evidence that a screening program would eventually reduce mortality and morbidity, no country has the infrastructure in place to handle large-scale screening and treatment programs for diabetes, and the clinical management of the disease may not be optimal throughout entire health care systems.[5] The WHO, then, considers that the best approaches to screen for undiagnosed diabetes or prediabetes are (1) selective (among groups known to have risk factors for diabetes) and (2) opportunistic (among potentially high-risk individuals at the time they visit their health care providers).[6] It is important to note here that recent evidence-based screening recommendations, issued by the U.S. Preventive Services Task Force (USPSTF), do not favor universal screening for diabetes either.[7,8] The main reason is that the USPSTF found, with moderate certainty, that even though screening for diabetes in adults with hypertension would lead to a substantial benefit, the evidence was insufficient to determine the benefit of screening in other populations.[7] On the positive side, a diagnosis of hypertension offers the opportunity for health care providers to offer a diabetes test to their patients.

Who Is at Risk of Diabetes?

The current recommendations on who should be screened for diabetes range from considering just one risk factor to a complete list of common risk factors. For example, as a result of a systematic review of the evidence, the USPSTF recommends screening for type 2 diabetes only in asymptomatic adults with sustained blood pressure (treated or untreated) greater than 135/80 mm Hg.[7,8] However, based on a long-standing consensus among its national and international members and partners, the American Diabetes Association (ADA) recommends screening for type 2 diabetes in all overweight adults [body mass index (BMI) ≥25 kg/m^2] who have one or more of the following risk factors: physical inactivity; a first-degree relative with diabetes; members of a high-risk ethnic population; women who developed gestational diabetes or had a baby weighing 9 pounds or more; hypertension; low concentrations of high-density lipoprotein cholesterol or high concentrations of triglyceride in blood; polycystic ovarian syndrome; IGT or IFG on a previous test; other clinical conditions associated with insulin resistance; and a medical history of cardiovascular disease. In the absence of these risk factors, the ADA recommends that testing for diabetes should begin at age 45 years. If results are normal, the test should be repeated after 3 years or sooner, depending on risk status.[1]

Given the public health importance of diabetes and the extensive knowledge of its many risk factors, researchers have developed a number of algorithms (risk tools) that, short of measuring glucose in blood, can be used to detect people with either prediabetes or undiagnosed diabetes in the general population. These risk tools have been the subject of a recent review.[9] **Table 3** provides a few examples extracted from this review of some of these risk tools along with the variables they include and the percentage area under the receiver operating characteristic curve (AUC ROC, a standard measure of the ability of a screening test to distinguish cases from no cases). Percentage areas under the curve in these examples, which range from almost 70 to 80%, show a reasonable ability of these simple tools to discriminate between people with and without undiagnosed diabetes.[9]

Of the risk factors commonly associated with increasing the risk of T2DM, the ones consistently displaying the strongest associations are old age, high BMI, high blood pressure, dyslipidemia, one or more first-degree relatives with the disease, and belonging to some racial or ethnic groups. In the U.S. population, these risk factors have been found to increase the risk of having T2DM independently of each other.[10]

Table 3.
Examples of Simple Tools Used to Screen for Type 2 Diabetes Mellitus (DM) in Populations, Variables Included, and Performance According to a Receiving Operating Characteristic Curve[a]

Name	Variables included	%AUC[b]
Cambridge risk score	Age, antihypertensive medication, BMI, family history of DM, sex, smoking, steroid use	80.0
Danish diabetes risk score	Age, BMI, family history of DM, hypertension, physical activity, sex	80.3
Indian diabetes risk score	Abdominal obesity, family history of DM, physical activity	69.8

[a] Extracted from Schwarz and colleagues.[9]
[b] Percentage area under the receiving operating characteristic curve.

Genetic and Environmental Risk Factors for Diabetes

Evidence of the influence of genes on the development of T2DM has emerged from multiple sources: high recurrence among relatives (family history), twin concordance studies, adoption studies, the existence of monogenic and mitochondrial cases of diabetes, and the growing number of genetic markers found associated with the disease.[11] However, there is also a clear influence of environmental risk factors on the development of T2DM, particularly risk factors conducive to obesity.[12] Much has been argued about the relative contribution of genes and environment to the development of chronic diseases, mostly because determining the predominance of one factor over the other has major implications for prevention. In the case of diabetes, where both influences have been clearly established, the argument of interest should be less about the predominance of one factor over the other and more about how both factors, genes and environment, come together to produce the disease.

Family History as a Risk Factor for Diabetes

Probabilistically, a disease such as diabetes with a demonstrated genetic component is expected to cluster among relatives. Family history is a reflection of this fact with the added value that it also reflects the environment, cultural practices, and behaviors shared to some extent by close relatives. It has been amply documented that having one or more first-degree relatives with T2DM increases the odds of having the disease compared with someone without such relatives. The estimations vary, but the odds usually range from two to six times more likely.[13] Also, a long-term study reported that the cumulative prevalence of T2DM at age 80 years is about 3.5 times higher (38% vs 11%) for people with a first-degree relative with T2DM compared to people without any affected relative.[14]

The strength, independence, and consistency of the association between family history of diabetes and presence of the disease justify the inclusion of family history in any simple tool designed to identify potential cases of prediabetes and undiagnosed diabetes in a population. Indeed, most diabetes screening tools include a family history of diabetes among their key variables, and these tools display an acceptable degree of discrimination judging from their AUC ROC values (examples given in **Table 3**).[9] The only caveat is that these tools include family history as a dichotomous (positive/negative) variable. A more useful approach used to assess a familial risk of diabetes has been proposed and corroborated in several studies: this risk can be divided into several strata and a sizable group of individuals at a relatively higher familial risk can be identified.[15–17] The stratification has been detailed elsewhere. Essentially, a high familial risk is having at least two first-degree relatives or one first-degree and two second-degree relatives with diabetes; a moderate familial risk is having just one first-degree relative or at least two second-degree relatives with diabetes; and others are at average risk. **Table 4** shows results of this stratification in three racial/ethnic groups of the U.S. population. Data for **Table 4** are from a previous publication.[18] Overall, about 1 in every 4 adults has a moderate familial risk and 1 in every 13 adults has a high familial risk of diabetes. Compared with individuals of average familial risk, and independently of other important variables, individuals at moderate and high familial risk are about 2.3 and 5.5 times more likely to have diabetes, respectively.

Table 4.
Percentage Distribution of Familial Risk of Diabetes in Adults (Age ≥18 Years) from Three Racial/Ethnic Groups of U.S. Population and Overall Odds of Having Diabetes According to Risk Stratum (National Health and Nutrition Examination Survey 1999–2004)[a]

	Familial risk of diabetes		
	Average	Moderate	High
Non-Hispanic White	71.6	22.1	6.3
Non-Hispanic Black	63.1	25.4	11.5
Mexican American	64.0	25.7	10.3
Total	69.8	22.7	7.5
Odds of having diabetes (95% CI[b])	Referent	2.3[c] (1.8–2.9)	5.5[c] (4.4–6.8)

[a] Data obtained from Valdez and colleagues.[18]
[b] Confidence interval.
[c] Controlling for sex, race or ethnicity, age, BMI, hypertension, and household income.

Conclusion

The USPSTF, the WHO, and the ADA do not recommend universal screening for diabetes. Based on a systematic review of the literature, the USPSTF recommends screening for diabetes only among individuals with high blood pressure. Based on a list of consistent risk factors developed by consensus, the WHO and the ADA recommend screening only among high-risk, asymptomatic individuals. Given these recommendations, many researchers have

proposed and tested risk tools composed of simple variables to detect individuals at high risk for diabetes. A review of the literature found many of them capable of such detection.[9] Consistently, a family history of diabetes is one of the variables included in these tools as an independent contributor to risk. Recent studies have shown that people at moderate or high familial risk of diabetes are relatively common in the U.S. population.[16,17,18] Therefore, since genetic tests are not currently available for the most common forms of diabetes, the use of tools that include a family history of diabetes is potentially applicable to the U.S. general population. The use of such tools in widespread screening programs, however, must not be evaluated less rigorously than the way other genetic tests are evaluated.[19]

Disclosure:

The findings and conclusions in this article are those of the author and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

References:

1. American Diabetes Association. Standards of medical care in diabetes--2009. Diabetes Care. 2009; 32 Suppl 1:S13-61.
2. Cowie CC, Rust KF, Ford ES, Eberhardt MS, Byrd-Holt DD, Li C, Williams DE, Gregg EW, Bainbridge KE, Saydah SH, Geiss LS. Full accounting of diabetes and pre-diabetes in the U.S. population in 1988-1994 and 2005-2006. Diabetes Care. 2009;32(2):287- 94.
3. Vinicor F. Is diabetes a public-health disorder? Diabetes Care. 1994; 17 Suppl 1:s22-7.
4. National Screening Committee. UK NSC criteria for evaluating screening programmes. Available from: *http://www.nsc.nhs.uk/pdfs/criteria.pdf*.
5. Waugh N, Scotland G, McNamee P, Gillett M, Brennan A, Goyder E, Williams R, John A. Screening for type 2 diabetes: literature review and economic modelling. Health Technol Assess. 2007;11(17):iii-iv, ix-xi, 1-125.
6. World Health Organization. Guidelines for the prevention, management and care of diabetes mellitus. Khatib OM, editor. EMRO Technical Publications Series 2006; 32.
7. U.S. Preventive Services Task Force. Screening for type 2 diabetes in adults: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2008;148(11): 846-54.
8. Norris SL, Kansagara D, Bougatsos C, Fu R; U.S. Preventive Services Task Force. Screening adults for type 2 diabetes: a review of the evidence for the U.S. Preventive Services Task Force. Ann Intern Med. 148(11):855-68.
9. Schwarz PE, Li J, Lindstrom J, Tuomilehto J. Tools for predicting the risk of type 2 diabetes in daily practice. Horm Metab Res. 2009;41(2): 86-97.
10. Dallo FJ, Weller SC. Effectiveness of diabetes mellitus screening recommendations. Proc Natl Acad Sci U S A. 2003;100(18):10574-9.
11. Florez JC, Hirschhorn J, Altshuler D. The inherited basis of diabetes mellitus: implications for the genetic analysis of complex traits. Ann Rev Genomics Hum Genet. 2003;4:257-91.
12. Van Dam RM. The epidemiology of lifestyle and risk for type 2 diabetes. Eur J Epidemiol. 2003;18(12):1115-25.
13. Harrison TA, Hindorff LA, Kim H, Wines RC, Bowen DJ, McGrath BB, Edwards KL. Family history of diabetes as a potential public health tool. Am J Prev Med. 2003;24(2):152-59.
14. Köbberling J, Tillil H. Empirical risk figures for first degree relatives of non-insulin dependent diabetics. In: Kobberling J, Tattersall RB, editors. The genetics of diabetes mellitus. London: Academic Press; 1982. p 201-9.
15. Scheuner MT, Wang SJ, Raffel LJ, Larabell SK, Rotter JI. Family history: a comprehensive genetic risk assessment method for the chronic conditions of adulthood. Am J Med Genet. 1997;71(3):315-24.
16. Hariri S, Yoon PW, Qureshi N, Valdez R, Scheuner MT, Khoury MJ. Family history of diabetes: a population-based screening tool for prevention. Gene Med. 2006; 8(2):102-8.
17. Annis AM, Caulder MS, Cook ML, Duquette D. Family history, diabetes, and other demographic and risk factors among participants of the National Health and Nutrition Examination Survey 1999-2002. Prev Chronic Dis. 2005;2(2):A19.
18. Valdez R, Yoon PW, Liu T, Khoury M. Family history and prevalence of diabetes in the U.S. population: the 6-year results from the National Health and Nutrition Examination Survey (1999-2004). Diabetes Care. 2007;30(10):2517-22.
19. Yoon PW, Scheuner MT, Peterson-Oehlke KL, Gwinn M, Faucett A, Khoury MJ. Can family history be used as a tool for public health and preventive medicine? Gene Med. 2002;4(4):304-10.