EDITORIAL (SEE HEIKES ET AL., P. 1040)

Screening for Diabetes

The U.K. National Screening Committee provides criteria against which screening programs can be evaluated (http://www.nsc.nhs.uk/pdfs/criteria.pdf). Using these criteria, screening for diabetes in the general population was deemed not to be warranted in 2001 (1) because *1*) the benefits of early diagnosis and treatment had not been proved, *2*) screening for diabetes to reduce cardiovascular disease had not been shown to be effective, *3*) disadvantages of screening were not quantified, and *4*) the clinical management of those with diabetes should be optimized before instituting a screening program.

A more recent 2007 report from the U.K. on screening for type 2 diabetes concluded that the case for screening was somewhat stronger given the possible "options for reduction of cardiovascular disease" (mainly with statins) and "because of the rising prevalence of obesity and hence diabetes" (2). Further, since the 2001 evaluation, some of the possible disadvantages of screening have been quantified and found not to be of great harm (3–5).

In this issue of *Diabetes Care*, the Diabetes Risk Calculator that aims to detect both undiagnosed diabetes as well as prediabetes is proposed (6). A number of other screening tools have already been developed in various populations and are reviewed in the U.K. report (2). In particular, for the U.S., Herman et al. (7) developed a simple questionnaire based on National Health and Nutrition Examination Survey (NHANES) II data using a classification tree approach. The questionnaire included age, weight for height, exercise, diabetes in the family, and delivery of a large baby. It is currently proposed by the American Diabetes Association as a "Diabetes Risk Test" (available at http://www.diabetes.org/risk-test.jsp).

The Diabetes Risk Calculator (6) was developed and validated using American data from NHANES III (1988–94) and studied 7,000 men and women aged ≥20 years. Diabetes and pre-diabetes were defined by fasting plasma glucose, and in about half of the participants aged 40–75 years, 2-h glucose concentrations following an oral glucose tolerance test were also used. Thus, the glucose phenotype identified by the tool is not homogeneous. A total of 18 potential explanatory variables were reviewed, all of which would be known to an individual. Two methods were compared for the development of a calculator: logistic regression and classification and regression tree (CART) analysis. Details are presented in a technical report prepared for GlaxoSmithKline available in the online appendix of the article in this issue (6).

For logistic regression, two methods of variable selection were used to detect "diabetes + pre-diabetes": the best model with *k* variables and forward stepwise selection. Pragmatically, the same equation was also used for predicting undiagnosed diabetes alone, even though there appear to be differences in the variables that would be chosen to predict the two entities (sex is included for one but not the other). Threshold values were determined to achieve sensitivities of 80%, a better criterion than the usual optimum threshold, which corresponds to maximizing (sensitivity + specificity). The corresponding positive predictive values are not given. Ethnicity was not included for technical reasons because SAS is not able to cope with a four-class variable in best model logistic regressions, but the stepwise technique could still have been used. This important variable has been included in the CART classification and found to be a discriminator. The final logistic regression model included eight variables: age, sex, weight, height, waist-to-hip ratio, BMI, high blood pressure, and familial diabetes. Although all of these variables were statistically significant, it is probable that some of the highly correlated anthropometric variables could be deleted without loss to the capacity of the model to predict undiagnosed diabetes. Indeed, in the formulation of the CART model, neither BMI nor waist-to-hip ratio was included as a possible variable to enter into the model.

The final CART model required 10 variables: age, sex, weight, height, waist, high blood pressure, familial diabetes, exercise, ethnicity, and gestational diabetes mellitus. The areas under the receiver operating characteristic curves for the two techniques were similar, as seen in Fig. 7 of the technical report.

The logistic model is quickly dismissed because CART is said to be of "equivalent accuracy but greater ease of use." The two methods have not been compared on equal grounds because different variables were used in developing the two techniques. Further, the two methods were essentially compared by the areas under the receiver operating characteristic curves, which were very similar. Other characteristics for the CART method are difficult to compare with those of the logistic regression because the thresholds have been set to have a sensitivity of 80%. As for the ease of use, the results from both techniques need to be written as an additive score to provide a simple prescreening score.

As a clinical tool, I am not sure whether a busy physician would take the time to go through a chart to calculate the probability of a patient having diabetes or pre-diabetes. It needs to be put into a more useable format, as has been done for the Diabetes Risk Test (7). A diabetes risk calculator could be developed in an electronic format or as a Web-based facility to prescreen for undiagnosed diabetes or pre-diabetes. It might be a useful tool for patients who would like to estimate their risk of diabetes.

One of the unmet criteria for screening given above is hard evidence that screening for diabetes reduces cardiovascular risk. One trial, the Anglo-Danish-Dutch Study of Intensive Treatment in People with Screen Detected Diabetes in Primary Care, or ADDITION, Study, a randomized clinical trial that aims to study whether systematic screening and subsequent cardiovascular risk reduction have benefits on morbidity and mortality (8), is underway. Over 3,000 primary care patients were recruited in the U.K., Denmark, and the Netherlands, and we now await the results from this 5-year trial.

Diabetic individuals with an isolated 2-h hyperglycemia following an oral charge of glucose are not detected by a fasting hyperglycemia and deserve special attention. They tend to be older and slimmer, and more are women (9). Although (obviously) the prevalence of diabetes is increased when these individuals are included, the current article does not provide information on this group, and we are told that "the lack of oral glucose tolerance data for some participants did not materially affect the stability of the results." It would be very useful to have a

prescreening tool only for this group because they are not routinely picked up. From Table 3 in the technical report, in the individuals aged 40–74 years with both fasting and 2-h glucose values available, 3.2% had diabetes screened on the basis of an isolated 2-h hyperglycemia; almost one-third of the people screened as diabetic. A similar remark can be made for the diabetes + pre-diabetes group, where 7% of the population would be missed; one-seventh of the 49% of the NHANES population is in the group. These percentages are not trivial.

Adiposity plays a large part in the presence of hyperglycemia, and it is still a primary, simple criterion for entry into any diabetes screening process. Further, the choice of the marker of adiposity is not important because BMI, waist circumference, and waist-to-hip ratio have similar discriminating capabilities (10).

BEVERLEY BALKAU, PHD

From INSERM U780, Epidemiological and Statistical Research, Villejuif, France; and Université Paris-Sud, Orsay, France.

Corresponding author: Beverley Balkau, INSERM U780, 16 Avenue Paul Vaillant Couturier, 94807 Villejuif Cedex, France. E-mail: balkau@vjf.inserm.fr.

Abbreviations: CART, classification and regression tree; NHANES, National Health and Nutrition Examination Survey.

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References

1. Wareham NJ, Griffin SJ: Should we screen for type 2 diabetes? Evaluation against National Screening Committee criteria. *BMJ* 322:986–988, 2001
2. Waugh N, Soctland G, McNamee P, Gillett M, Brennan A, Goyder E, Williams, R John A: Screening for type 2 diabetes: literature review and economic modeling. *Health Technol Assess* 11:1–125, 2007
3. Adriaanse MC, Snoek FJ, Dekker JM van der Ploeg HM, Heine RJ: Screening for type 2 diabetes: an exploration of subjects' perceptions regarding diagnosis and procedure. *Diabet Med* 19:406–411, 2002
4. Edelman D, Olsen MK, Dudley TK, Harris AC, Oddone EZ: Impact of diabetes screening on quality of life. *Diabetes Care* 25:1022–1026, 2002
5. Eborall HC, Griffin SJ, Prevost AT, Kinmonth AL, French DP, Sutton S: Psychological impact of screening for type 2 diabetes: controlled trial and comparative study embedded in the ADDITION (Cambridge) randomised controlled trial. *BMJ* 335:486, 2007
6. Heikes KE, Eddy DM, Arondekar B, Schlessinger L: Diabetes Risk Calculator: a simple tool for detecting undiagnosed diabetes and pre-diabetes. *Diabetes Care* 31: 1040–1045, 2008
7. Herman WH, Smith PJ, Thompson TJ, Engelgau MM, Aubert RE: A new and simple questionnaire to identify people at increased risk for undiagnosed diabetes. *Diabetes Care* 18:382–387, 1995
8. Lauritzen T, Griffin S, Borch-Johnsen K, Wareham NJ, Wolffenbuttel BH, Rutten G, Anglo-Danish-Dutch Study of Intensive Treatment in People with Screen Detected Diabetes in Primary Care: The ADDITION study: proposed trial of the cost-effectiveness of an intensive multifactorial intervention on morbidity and mortality among people with type 2 diabetes detected by screening. *Int J Obes Relat Metab Disord* 24 (Suppl. 3):6–11, 2000
9. DECODE Study Group: Age- and sex-specific prevalences of diabetes and impaired glucose regulation in 13 European cohorts. *Diabetes Care* 26:61–69, 2003
10. Balkau B, Sapinho D, Petrella A, Mhamdi L, Cailleau M, Arondel D, Charles MA, D.E.S.I.R. Study Group: Prescreening tools for diabetes and obesity-associated dyslipidaemia: comparing BMI, waist and waist hip ratio. The D.E.S.I.R. Study. *Eur J Clin Nutr* 60:295–304, 2006