Undiagnosed diabetes: Does it matter?

T. Kue Young, Cameron A. Mustard

Abstract

Background: The 1998 Canadian clinical practice guidelines for the management of diabetes lowered the cutoff point for diagnosing diabetes mellitus from a fasting plasma glucose (FPG) level of 7.8 to 7.0 mmol/L. We studied the prevalence and clinical outcomes of undiagnosed and diagnosed diabetes within specific ranges of FPG among a cohort of subjects recruited in 1990.

Methods: In 1990 a representative sample of 2792 adult residents of Manitoba participated in the Manitoba Heart Health Survey, which included measurement of FPG and a question about each participant’s past history of diabetes. Individuals who would now be classified as having undiagnosed diabetes under the new criteria were not considered as such in 1990. Through data linkage with the provincial health care utilization database, the use of health care by these individuals was tracked and compared with that of individuals whose diabetes had been diagnosed and with that of normoglycemic individuals over an 8-year period subsequent to the survey.

Results: The prevalence of undiagnosed diabetes in the adult population of Manitoba was 2.2%. Undiagnosed cases accounted for about one-third of all diabetes cases. Individuals with undiagnosed diabetes had an unfavourable lipid profile and higher blood pressure and obesity indices than normoglycemic individuals. Individuals who satisfied the new criteria for diabetes but remained undiagnosed had an additional 1.35 physician visits per year (95% confidence interval [95% CI] 0.93–1.96) and were more likely to be admitted to hospital at least once (odds ratio 1.23, 95% CI 0.40–3.79), compared with normoglycemic individuals.

Interpretation: Undiagnosed cases represent the unseen but clinically important burden of diabetes, with significant concurrent metabolic derangements and a long-term impact on health care use.

An individual with undiagnosed diabetes is someone whose diabetes has not been diagnosed by a physician but whose plasma glucose levels satisfy established criteria for diabetes. The most recent estimate of the burden of undiagnosed diabetes in the total population of the United States is 2.7% among adults aged 20 years and above, compared with 5.1% for diagnosed diabetes. It has also been shown in cross-sectional studies that undiagnosed diabetes is associated with a higher prevalence of hypertension, obesity, an unfavourable lipid profile and evidence of retinopathy and nephropathy when compared with values for normoglycemic individuals.

Undiagnosed diabetes can only be detected in a survey or screening setting when individuals are tested for plasma glucose levels and are asked about a past history of physician-diagnosed diabetes. Under the 1985 World Health Organization (WHO) criteria, diabetes is defined by a fasting plasma glucose (FPG) level equal to or exceeding 7.8 mmol/L or a 2-hour post-challenge plasma glucose level equal to or exceeding 11.1 mmol/L, or both. In 1998 the Canadian clinical practice guidelines for the management of diabetes adopted the diagnostic criteria proposed by the American Diabetes Association (ADA) in 1997, which are based on the fasting value only, and lowered the cutoff point from 7.8 to 7.0 mmol/L. A new category of “impaired fasting glucose” (IFG) was created, encompassing individuals with FPG levels greater than or equal to 6.0 mmol/L but less than 7.0 mmol/L.

A major difficulty in determining the clinical significance of undiagnosed diabetes prospectively is that once diabetes is detected, an individual is no longer “un-
diagnosed.” The change in diagnostic criteria proposed by the ADA and the Canadian practice guidelines, however, creates an opportunity to study the outcome of undiagnosed diabetes unaffected by clinical interventions.

In 1990 a representative sample of 2792 adult residents of Manitoba participated in a health and examination survey that included the measurement of FPG levels. This study identified subjects who would be classified as having undiagnosed diabetes under the new criteria, although their FPG level was not considered to be within the diabetic range in 1990. They constitute a unique cohort of individuals with undiagnosed diabetes to whom no special clinical interventions were directed.

This study used data linkage to determine the clinical significance of undiagnosed diabetes and also the predictive validity of the ADA criteria in a defined population of Canadians over a 10-year period.

Methods

This study involved linkage of 2 existing health data sets: the Manitoba Heart Health Survey (MHHS) and the Manitoba Health Services Insurance Plan (MHSIP).

The MHHS was a population-based cross-sectional survey that was conducted between October 1989 and February 1990 as part of a national effort to estimate the prevalence of cardiovascular risk factors and assess the level of knowledge about cardiovascular disease. Detailed descriptions of the design and methods of both the national study and the Manitoba survey have been published. The target population of the MHHS included all non-institutionalized adult residents of the province aged 18–74 years. A stratified random sample was drawn from the registry of beneficiaries of the provincial health insurance plan. A total of 2792 individuals participated in the interviews, providing a response rate of 77%. Each participant was assigned a sampling weight, which was inversely proportional to the probability of selection.

In addition to a personal interview concerning past health history (including diabetes) and health behaviours (such as smoking, physical activity and alcohol use), participants underwent selected clinical measurements, including blood pressure and anthropometry, and laboratory tests to measure levels of FPG, glycosylated hemoglobin and lipids (total cholesterol, high-density lipoprotein [HDL], low-density lipoprotein and triglycerides). At the time of the survey, individuals with an FPG level that was greater than or equal to 7.8 mmol/L, considered as diabetes under the WHO criteria, were notified and advised to seek further evaluation and care.

Clinical and hospital files for these individuals were extracted for 2 years prior to the MHHS survey date and for 8 years following the survey (from November 1, 1987, to November 30, 1997). Methodological papers on the linkage procedure have been published previously.

Among the individuals included in the linked sample, 435 did not undergo any laboratory tests, and an additional 79 individuals had missing FPG values. Twenty-five individuals did not answer the question concerning their past history of diabetes. Two individuals were over 75 years old at the time of the survey, although they had not been at the time of selection. All these cases were deleted from the final data set, which comprised 2133 individuals, or 76% of the original sample of 2792 individuals. The proportion of interviewed subjects without measured FPG values is virtually identical (16%) among individuals who reported a past history of diabetes and those without past diabetes.

Two types of analyses were conducted: the first was cross-sectional, involving only the MHHS data set, and was designed to estimate the prevalence of diabetes and investigate the correlation of the various diabetes categories with selected metabolic indicators (plasma lipids, obesity and blood pressure), whereas the second was longitudinal, involving the linked MHHS–MHSIP data set, and was intended to compare health care use and other clinical outcomes for the various diabetes categories. Table 1 cross-tabulates past history of diabetes with current FPG levels to yield

<table>
<thead>
<tr>
<th>Current fasting plasma glucose, mmol/L</th>
<th>Past history of diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>&lt; 6.0</td>
<td>DxDM</td>
</tr>
<tr>
<td>6.0 – &lt; 7.0</td>
<td>DxDM</td>
</tr>
<tr>
<td>7.0 – &lt; 7.8</td>
<td>DxDM</td>
</tr>
<tr>
<td>≥ 7.8</td>
<td>DxDM</td>
</tr>
</tbody>
</table>

Table 1: Definition of diabetes status categories based on past history of diagnosed diabetes and current fasting plasma glucose values

Note: DxDM = diagnosed diabetes, IFG = impaired fasting glucose, UnDxDM(B) = undiagnosed diabetes, cutoff point based on 1997 ADA criteria. UnDxDM(A) = undiagnosed diabetes, cutoff point based on 1985 WHO criteria. DM-old = DxDM + UnDxDM(A), DM-new = DxDM + UnDxDM(A) + UnDxDM(B).
the various diabetes categories. The abbreviation DxDM refers to individuals with diagnosed diabetes. UnDxDM(A) refers to individuals with an FPG level that was greater than or equal to 7.8 mmol/L at the time of the survey. Although their diabetes was undiagnosed at the time, it ceased to remain so after the survey. The group referred to as UnDxDM(B) had an FPG level that was greater than or equal to 7.0 mmol/L but less than 7.8 mmol/L. Their condition remained undiagnosed after the survey. The abbreviation IFG refers to the group with impaired fasting glucose.

In order to compare the data from Manitoba with those obtained for the US population according to the National Health and Nutrition Examination Survey of 1988–1994 (NHANES III), we computed age-standardized prevalence estimates using the 1980 US census population as standard.1

To measure health care utilization, we used 2 indicators: the mean number of consultations or physician visits per person-year of observation and the proportion of subjects with at least one stay in hospital during the period of observation. To determine whether the mean number of physician visits differed among the various categories of diabetes status, we performed multiple linear regression analyses, controlling for age and sex. Because the distribution of mean number of physician visits was highly skewed, we used logarithm-transformed values in the regression model, although we report the results as the number of physician visits. We used multiple logistic regression to compare the odds of being admitted to hospital at least once for the diabetes categories, controlling for age and sex.

To investigate whether the new criteria that lowered the cutoff point from 7.8 to 7.0 mmol/L affected clinical outcomes, we divided study subjects into 2 groups: diabetic and nondiabetic. Under the old criteria, the diabetic group (DM-old) comprised all cases of diagnosed diabetes (DxDM) and UnDxDM(A) cases; all other individuals were considered to be nondiabetic (non-DM). Under the new criteria, the diabetic group (DM-new) consisted of all DxDM, UnDxDM(A) and UnDxDM(B) individuals (Table 1). Cox proportional hazards analysis was used to compare the survival of nondiabetic and diabetic individuals (under the old and the new criteria) after adjusting for age and sex.

Results

The MHHS yielded 64 cases of undiagnosed diabetes, which corresponded to 15,580 individuals out of a total provincial adult population of 695,078, when weighting was taken into account (2.2%). Fig. 1 shows the age- and sex-specific prevalence of diagnosed diabetes (DxDM) and undiagnosed diabetes (UnDxDM) and impaired fasting glucose (IFG) according to the 1997 ADA criteria. Among men aged 18–74 years, 2.2% (95% confidence interval [95% CI] 1.0%–3.3%) had undiagnosed diabetes, which was very similar to the prevalence of 2.3% among women (95% CI 1.0%–3.6%). Undiagnosed cases of diabetes accounted for 35% of all diabetes cases (DxDM and UnDxDM) among men, and 32% among women. Without the change in diagnostic criteria, 52% of the undiagnosed cases would not have been included in this category.

When the 1980 US population was used as the standard, the Manitoba age-standardized prevalence of undiagnosed diabetes was 2.3% in men and 2.5% in women, compared with 3.1% in men and 2.5% in women in NHANES III.

Table 2 compares several key metabolic indicators for the different diabetes status categories. Normoglycemic individuals and those with IFG had lower mean FPG values than those with diagnosed diabetes. Individuals in the UnDxDM(A) group had higher values than those in the UnDxDM(B) group. Mean FPG values among the UnDxDM(A) group were higher than those among individuals with diagnosed diabetes (the DxDM group); the latter category included patients whose diabetes was being treated.

In general, individuals with undiagnosed diabetes had lower HDL cholesterol but higher triglycerides, total–HDL cholesterol ratio, glycosylated hemoglobin, body mass index, waist–hip ratio, and systolic and diastolic blood pressure than normoglycemic individuals. Compared with diagnosed cases, undiagnosed cases either did not differ significantly or had a worse metabolic profile (in terms of lipids, obesity, blood pressure). Comparing UnDxDM(A) and UnDxDM(B), there was no significant difference in any of the lipid, obesity or blood pressure measures.

The mean number of physician visits per year of obser-

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**Fig. 1:** Prevalence of diabetes and impaired fasting glucose in the adult population of Manitoba, according to the 1997 ADA criteria. IFG = impaired fasting glucose, UnDxDM = undiagnosed diabetes, DxDM = diagnosed diabetes.
We found that diabetic individuals reported more physician visits than nondiabetic individuals. Using the new criteria, a diabetic individual with diabetes (DM-new) had an excess of 1.43 visits per year of observation (95% CI 1.16–1.76). With the old criteria, the excess was 1.42 visits (95% CI 1.18–1.71). Diabetic individuals were about twice as likely to have been admitted to hospital at least once. Comparing DM-new with nondiabetic individuals, the OR was 1.88 (95% CI 1.12–3.17); comparing DM-old with nondiabetic individuals, the OR was 1.76 (95% CI 1.09–2.33).

We also established the mortality rate of the entire cohort over the observation period. Fig. 2 compares the survival curves for DM-new, DM-old and nondiabetic individuals. Using Cox regression analysis, controlling for age and sex, we found that diabetic individuals were about twice as likely to die during the study period as nondiabetic individuals. Comparing DM-new with nondiabetic individuals, the hazard ratio was 1.93 (95% CI 1.38–2.70); comparing DM-old with nondiabetic individuals, the hazard ratio was also 1.93 (95% CI 1.35–2.75). Because of the small number of events, we did not compare specific causes of death.

**Interpretation**

Our data show that about 2% of the adult population (aged 18–74 years) of Manitoba have undiagnosed diabetes, based on the 1998 Canadian practice guidelines. Undiagnosed diabetes cases comprise about one-third of all diabetes cases.

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**Table 2: Comparison of mean values of selected metabolic indicators for individuals with diagnosed diabetes, undiagnosed diabetes, impaired fasting glucose and normoglycemia**

<table>
<thead>
<tr>
<th>Metabolic indicator</th>
<th>DxDM n = 157</th>
<th>UnDxDM (A) n = 31</th>
<th>UnDxDM (B) n = 33</th>
<th>IFG n = 167</th>
<th>Normoglycemia n = 1745</th>
</tr>
</thead>
<tbody>
<tr>
<td>HGB, %</td>
<td>8.55 (8.03–9.06)</td>
<td>9.30 (8.18–10.4)</td>
<td>6.81 (6.52–7.10)</td>
<td>6.11 (6.00–6.22)</td>
<td>5.58 (5.56–5.61)</td>
</tr>
<tr>
<td>TC, mmol/L</td>
<td>5.25 (5.01–5.49)</td>
<td>5.49 (5.17–5.80)</td>
<td>5.92 (5.54–6.29)</td>
<td>5.46 (5.16–5.75)</td>
<td>5.05 (4.99–5.12)</td>
</tr>
<tr>
<td>HDL, mmol/L</td>
<td>1.17 (1.08–1.25)</td>
<td>1.07 (0.96–1.17)</td>
<td>1.10 (1.01–1.19)</td>
<td>1.17 (1.10–1.25)</td>
<td>1.29 (1.27–1.31)</td>
</tr>
<tr>
<td>TG, mmol/L</td>
<td>1.87 (1.64–2.10)</td>
<td>2.58 (2.01–3.14)</td>
<td>2.88 (2.26–3.50)</td>
<td>2.02 (1.67–2.38)</td>
<td>1.44 (1.37–1.51)</td>
</tr>
<tr>
<td>TC:HDL ratio</td>
<td>4.88 (4.50–5.26)</td>
<td>5.48 (4.87–6.09)</td>
<td>5.50 (5.01–5.98)</td>
<td>5.02 (4.59–5.45)</td>
<td>4.19 (4.09–4.28)</td>
</tr>
<tr>
<td>BMI</td>
<td>28.43 (26.9–29.9)</td>
<td>29.97 (28.1–31.9)</td>
<td>30.42 (28.3–32.6)</td>
<td>27.99 (26.7–29.3)</td>
<td>25.45 (25.2–25.7)</td>
</tr>
<tr>
<td>WHR</td>
<td>0.897 (0.876–0.918)</td>
<td>0.950 (0.920–0.980)</td>
<td>0.932 (0.903–0.960)</td>
<td>0.910 (0.889–0.930)</td>
<td>0.853 (0.847–0.859)</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>132.86 (129.5–136.2)</td>
<td>144.49 (138.1–150.9)</td>
<td>151.29 (143.7–158.8)</td>
<td>134.28 (130.0–138.6)</td>
<td>121.01 (120.2–121.9)</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>80.18 (78.3–82.0)</td>
<td>85.12 (82.7–87.5)</td>
<td>84.69 (81.9–87.5)</td>
<td>81.44 (79.2–83.7)</td>
<td>76.03 (75.5–76.6)</td>
</tr>
</tbody>
</table>

Note: FG = fasting plasma glucose, HGB = glycosylated hemoglobin, TC = total cholesterol, HDL = high-density lipoprotein, LDL = low-density lipoprotein, TG = triglycerides, BMI = body mass index, WHR = waist-hip ratio, SBP = systolic blood pressure, DBP = diastolic blood pressure.
cases. These data are comparable with those reported from the United States. Undiagnosed diabetes represents the unseen burden of a disease that is increasingly recognized as an important public health problem in the developed world.

Should we be concerned about this unseen burden and should any efforts be expended to identify undiagnosed cases of diabetes? We are able to establish the clinical significance of undiagnosed diabetes by showing the unfavourable lipid profile and higher blood pressure levels and obesity indices present in individuals with this condition at the time of its discovery. We were not able to detect a significant difference in clinical outcome between individuals who remained undiagnosed and normoglycemic individuals, using the indicators of mean number of physician visits per year and the odds of being admitted to hospital at least once during the study period.

The Canadian clinical practice guidelines recommend screening for all adults aged 45 years and over, although the health benefits of screening have not been established by a randomized controlled trial, and the justification for screening has been challenged. The decision to screen requires information on the burden of undiagnosed diabetes, its association with metabolic risk factors and potential long-term morbidity, as well as the costs and adverse effects of screening itself.

There has been considerable discussion in the literature of the merits and pitfalls of the new ADA criteria. Our data indicate that the new criteria, by lowering the cutoff point of FPG, almost double the prevalence of undiagnosed diabetes. The new criteria, however, are as capable as the old of predicting increased morbidity and mortality among diabetic compared with non-diabetic individuals.

Because of the importance of glycosylation in the development of microvascular complications, it has been argued that individuals with an FPG level of 7.0–7.7 mmol/L without elevated levels of glycosylated hemoglobin should not be considered as having diabetes. Our data (Table 2) indicate that individuals with undiagnosed diabetes, even those with an FPG level of 7.0–7.7 mmol/L, have elevated glycosylated hemoglobin (6.81% [95% CI 6.52%–7.10%]) compared with normoglycemic individuals (5.58% [95% CI 5.56%–5.61%]) and thus are at risk for microvascular complications.

The use of data linkage to study the long-term clinical outcome of undiagnosed diabetes is less time-consuming and expensive than a true follow-up study requiring repeat examinations of survey cohort members. We were able to exploit the opportunity for a “natural experiment” created by the change in diagnostic criteria, allowing the pattern of health care use by individuals with undiagnosed diabetes to be monitored without their being subjected to increased clinical surveillance or interventions. It is anticipated that with a longer study period (and a larger number of person-years) of observation, we should be able to further explore clinical outcomes using more specific diagnostic categories beyond overall measures of health care use.

Competing interests: None declared.

Contributors: Both authors were responsible for the project design and data analysis. Dr. Young was primarily responsible for the writing of the manuscript with input from Dr. Mustard. Both authors contributed to revisions of the manuscript. Both authors will take public responsibility for the paper.

Acknowledgements: Dr. Young is a Medical Research Council of Canada Senior Scientist and Dr. Mustard is a Medical Research Council of Canada Scientist. This project was supported by a grant from the Canadian Diabetes Association in honour of Blanche Gunning.

References

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