Metabolic syndrome and its components as predictors of incident type 2 diabetes mellitus in an Aboriginal community

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ABSTRACT

Background: Risk factors for type 2 diabetes remain poorly characterized among Aboriginal Canadians. We aimed to determine the incidence of type 2 diabetes in an Aboriginal community and to evaluate prospective associations with metabolic syndrome and its components.

Methods: Of 606 participants in the Sandy Lake Health and Diabetes Project from 1993 to 1995 who were free of diabetes at baseline, 540 (89.1%) participated in 10-year follow-up assessments. Baseline anthropometry, blood pressure, fasting insulin and serum lipid levels were measured. Fasting and 2-hour postload glucose levels were obtained at follow-up to determine incident cases of type 2 diabetes.

Results: The 10-year cumulative incidence of diabetes was 17.5%. High adiposity, dyslipidemia, hyperglycemia, hyperinsulinemia and hypertension at baseline were associated with an increased risk of diabetes after adjustment for age and sex (all \( p \leq 0.03 \)). Metabolic syndrome had high specificity (75%–88%) and high negative predictive value (85%–87%) to correctly detect diabetes-free individuals at follow-up. It had low sensitivity (26%–48%) and low positive predictive value (29%–32%) to detect future diabetes. Metabolic syndrome at baseline was associated with incident diabetes after adjustment for age and sex, regardless of whether the syndrome was defined using the National Cholesterol Education Program criteria (odds ratio [OR] 2.03, 95% confidence interval [CI] 1.10–3.75) or the International Diabetes Federation criteria (OR 2.14, 95% CI 1.29–3.55). The association was to the same degree as that for impaired glucose tolerance assessed using the oral glucose tolerance test (OR 2.87, 95% CI 1.52–5.40; \( p > 0.05 \) for comparison of C statistics).

Interpretation: Metabolic syndrome and its components can be identified with readily available clinical measures. As such, the syndrome may be useful for identifying individuals at risk of type 2 diabetes in remote Aboriginal communities.

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would offer a practical alternative. Metabolic syndrome has been identified to offer this potential in other populations.\textsuperscript{8–10} However, its role has not been assessed in Aboriginal Canadians, who have experienced a rapid epidemiologic transition in conjunction with a unique genetic susceptibility to diabetes.\textsuperscript{1,16}

We conducted this study to determine the incidence of type 2 diabetes in an Aboriginal community and to evaluate prospective associations between readily available clinical variables and diabetes.

**Methods**

**Study design**

The Sandy Lake Health and Diabetes Project is a population-based cohort study designed to determine the incidence of diabetes and its associated risk factors in an Aboriginal Canadian population. The project has been described in detail previously.\textsuperscript{11,17} Between 1993 and 1995, baseline data were obtained from 728 (71.5%) of 1018 eligible residents of Sandy Lake First Nation aged 10–79 years. Informed consent was obtained from all participants. The study was approved by the Sandy Lake First Nation Band Council and the University of Toronto Ethics Review Committee.

Between 2003 and 2005, 540 (89.1%) of 606 participants who were free of diabetes at baseline participated in 10-year follow-up assessments. They were slightly older than the 66 who did not return for follow-up but otherwise were similar in terms of sex and body mass index. During follow-up, 27 (5.0%) of the 540 participants died because of cancer (\(n = 6\)), pneumonia (\(n = 5\)), cirrhosis of the liver (\(n = 3\)), cardiovascular disease (\(n = 2\)), brain tumour or aneurysm (\(n = 2\)), suicide (\(n = 2\)) and other causes (\(n = 7\)). In the present analysis, we excluded participants who died during follow-up, who had missing results of baseline fasting and 2-hour postload glucose tests, or who had diabetes at baseline as defined by the revised diagnostic criteria of the World Health Organization.\textsuperscript{18} This left 492 men and women for inclusion in our study (Figure 1).

**Baseline data collection and laboratory procedures**

At baseline, blood samples were collected after an 8- to 12-hour overnight fast to determine each participant’s glucose, insulin and lipid profile. A 75-g oral glucose tolerance test was administered, after which a second blood sample was drawn for glucose measurement.

Details of the baseline biochemical analyses have been described previously.\textsuperscript{11} In brief, the glucose level was determined by means of the glucose oxidase method. The fasting plasma insulin level was analyzed by means of a radioimmunoassay (Pharmacia, Piscataway, USA). Levels of triglycerides, high-density lipoprotein (HDL) cholesterol and low-density lipoprotein (LDL) cholesterol were determined using standard methods described in the Lipid Research Clinics manual of operations.\textsuperscript{19}

Each anthropometric measurement and blood pressure reading was taken twice; we used the average in the analyses.\textsuperscript{11} Height was measured with an Accustat wall-mounted stadiometer (Genentech Inc., San Francisco, USA) and weight with a hospital beam scale (Health-o-Meter Inc., Bridgeview, USA). Waist circumference was measured at the iliac crest using an inelastic tape. Percent body fat was estimated by means of bioelectrical impedance analysis (Tanita TBF-201 Body Fat Analyzer, Tanita Corp., Tokyo, Japan). Blood pressure was recorded with the participant seated.

The participants’ medical history and their family history of diabetes were obtained by means of an interviewer-administered questionnaire. Participants were considered to have a family history of diabetes if one or both biological parents had diabetes.\textsuperscript{17}

**Definition of incident type 2 diabetes**

Incident diabetes was defined as the presence of any of the following at follow-up assessments: (a) a fasting plasma glucose level of 7.0 mmol/L or greater, or a 2-hour postload plasma glucose level of 11.1 mmol/L or greater on an oral glucose tolerance test; (b) current use of insulin or oral hypoglycemic agents; or (c) a positive response to the question Have you ever been diagnosed with diabetes by a nurse (practitioner) or a doctor? Among the 492 participants, follow-up blood samples were collected from 383 (77.8%). The diabetes status of the remaining 109 (22.2%) participants was ascertained on the basis of a self-reported clinical diagnosis of diabetes through a phone interview.

**Definitions of metabolic syndrome**

We determined whether participants had metabolic syndrome according to 2 definitions of the syndrome: that of the Na-
tional Cholesterol Education Program and that of the International Diabetes Federation.

According to the National Cholesterol Education Program definition, we considered participants to have metabolic syndrome if they met 3 or more of the following criteria: abdominal obesity (waist circumference > 102 cm in men and > 88 cm in women); high triglyceride level (≥ 1.7 mmol/L); low HDL cholesterol level (< 1.03 mmol/L in men and < 1.29 mmol/L in women); hypertension (systolic pressure ≥ 130 mm Hg, diastolic pressure ≥ 85 mm Hg, or use of antihypertensive drug therapy); or high fasting plasma glucose level (≥ 6.1 mmol/L).

The International Diabetes Federation defines metabolic syndrome using age-specific criteria. According to this definition, participants aged 16 years or more were considered to have metabolic syndrome if they had central obesity (waist circumference ≥ 94 cm in men and ≥ 80 cm in women [we used European cut-off points given the absence of cut-off points for Aboriginal populations]) in addition to any 2 of the following criteria: high triglyceride level (≥ 1.7 mmol/L); low HDL cholesterol level (< 1.03 mmol/L in men and < 1.29 mmol/L in women); hypertension (systolic blood pressure ≥ 130 mm Hg, diastolic blood pressure ≥ 85 mm Hg or use of antihypertensive drug therapy); or high fasting plasma glucose level (≥ 5.6 mmol/L). For participants aged 10–15 years, the International Diabetes Federation criteria are the same as those for adults, except that central obesity is defined as a waist circumference in the 90th percentile or higher (as assessed by the Third National Health and Nutrition Examination Survey [NHANES III] waist circumference percentile regression for European-American children) and the cut-off for HDL cholesterol is 1.03 mmol/L for both boys and girls.

**Statistical analysis**

We assessed distributions of continuous variables for normality; we used natural log-transformations of skewed variables in descriptive statistical analyses. Descriptive statistics for continuous variables are summarized as means and standard deviations, or as medians and interquartile ranges for variables with a skewed distribution. Categorical variables are summarized as proportions. We com-

| Characteristic | No | Yes | p value |
|---------------|----|-----|--------|
| Age, yr, mean (SD) | 25.4 (13.0) | 31.5 (12.4) | < 0.001 |
| Sex, no. (%) | 0.60 | | |
| Male | 173 (42.6) | 34 (39.5) | |
| Female | 233 (57.4) | 52 (60.5) | |
| Diabetes family history, no. (%) | 153 (38.7) | 40 (47.1) | 0.16 |
| Current smoker, no. (%) | 258 (63.9) | 54 (62.8) | 0.85 |
| Anthropometry, mean (SD) | | | |
| Body mass index | 25.4 (5.5) | 29.4 (5.3) | < 0.001 |
| % body fat | 33.0 (13.2) | 40.1 (10.3) | < 0.001 |
| Waist circumference, cm | 94.4 (14.1) | 104.7 (12.1) | < 0.001 |
| Waist-to-height ratio | 0.57 (0.08) | 0.63 (0.08) | < 0.001 |
| Blood pressure | | | |
| Systolic, mm Hg, median (IQR) | 113.0 (103.5–120.0) | 118.0 (110.0–130.0) | < 0.001 |
| Diastolic, mm Hg, mean (SD) | 64.0 (11.5) | 69.9 (12.3) | < 0.001 |
| Hypertension, no. (%) | 54 (13.3) | 29 (33.7) | < 0.001 |
| Lipid profile, mmol/L | | | |
| HDL cholesterol, mean (SD) | 1.26 (0.28) | 1.19 (0.25) | 0.020 |
| LDL cholesterol, mean (SD) | 2.42 (0.74) | 2.74 (0.66) | < 0.001 |
| Triglyceride, median (IQR) | 1.10 (0.81–1.53) | 1.48 (1.16–1.82) | < 0.001 |
| Glucose homeostasis | | | |
| Fasting glucose, mmol/L, mean (SD) | 5.3 (0.46) | 5.6 (0.58) | < 0.001 |
| 2-hour postload glucose, mmol/L, mean (SD) | 5.4 (1.62) | 6.5 (2.08) | < 0.001 |
| Fasting insulin, pmol/L, median (IQR) | 94 (66–131) | 123 (91–187) | < 0.001 |
| Impaired glucose tolerance, no. (%) | 36 (8.9) | 23 (26.7) | |
| Impaired fasting glucose, no. (%) | 22 (5.4) | 10 (11.6) | < 0.001 |
| Normal fasting glucose, no. (%) | 348 (85.7) | 53 (61.6) | |
| Metabolic syndrome, no. (%) | | | |
| As per NCEP definition | 47 (11.6) | 22 (25.6) | < 0.001 |
| As per IDF definition | 102 (25.3) | 41 (47.7) | < 0.001 |

Note: HDL = high-density lipoprotein, IDF = International Diabetes Federation, IQR = interquartile range, LDL = low-density lipoprotein, NCEP = National Cholesterol Education Program, SD = standard deviation.

*The number of participants for each category varies slightly owing to occasional missing values.

1 Defined as systolic blood pressure ≥ 130 mm Hg or diastolic blood pressure ≥ 85 mm Hg or use of antihypertensive drug therapy.

2 Defined as fasting plasma glucose level < 7.0 mmol/L, and 2-hour postload glucose level ≥ 7.8 mmol/L and < 11.1 mmol/L.

3 Defined as fasting plasma glucose level 6.1–6.9 mmol/L and 2-hour postload glucose level < 7.8 mmol/L.
to evaluate the association of clinical variables with incident diabetes. The clinical variables were body mass index, percent body fat, waist circumference, waist-to-height ratio, systolic and diastolic blood pressures, hypertension, HDL cholesterol, LDL cholesterol and triglyceride levels, fasting plasma glucose and 2-hour postload glucose levels, fasting insulin level and current smoking status. Each clinical variable was individually assessed in 2 models: model 1 adjusted for age and sex, and model 2 adjusted for model 1 variables in addition to individual components of metabolic syndrome (i.e., International Diabetes Federation criteria for waist circumference, triglycerides, HDL cholesterol, blood pressure and fasting plasma glucose, excluding the main effect). We calculated odds ratios (ORs) and 95% confidence intervals (CIs). We assessed sex interactions with independent variables by adding an interaction term into a model adjusted for model 2 variables in addition to the main effect.

We calculated the sensitivity, specificity, positive predictive value and negative predictive value to assess the ability of baseline impaired glucose tolerance status to detect incident diabetes after adjustment for age and sex. We performed the same diagnostic tests to assess the ability of metabolic syndrome and its components, using each definition. We used age- and sex-adjusted logistic regression analysis to evaluate the association between metabolic syndrome (each definition) and incident diabetes, and between impaired glucose tolerance and incident diabetes. To compare different logistic models in their capability to discriminate participants with and without incident diabetes, we calculated C statistics, which are analogous to the area under the receiver-operating-characteristic curve; we determined significance using the DeLong algorithm.21

**Results**

The baseline characteristics of the participants with and without incident diabetes at 10-year follow-up are presented in Table 1. Of the 492 participants included in our analysis, 86 (17.5%) were found to have diabetes at follow-up. Diabetes was ascertained on the basis of fasting or 2-hour postload glucose levels, or both, in 72 (18.8%) of 383 participants. For 14 (12.8%) of 109 participants without follow-up blood samples, diabetes was ascertained on the basis of self-reported clinical diagnosis only. Compared with participants who had follow-up blood samples, those without samples were younger (p = 0.009) but were not different in terms of sex or body mass index (each p ≥ 0.05). When only self-report was considered for ascertainment of incident diabetes among participants with follow-up blood samples, 53 (13.8%) of 383 had diabetes.

The incidence of diabetes increased with age (p < 0.001). It was 10.5% among participants aged 10–19 years, 15.1% among those aged 20–29 years, 27.3% among those 30–39 years, 43.3% among those 40–49 years and 18.9% among those aged 50 and older.

Compared with individuals who did not have diabetes at the 10-year follow-up, those who did have incident diabetes had a higher body mass index, percent body fat, waist circumference and waist-to-height ratio at baseline (each p < 0.001). They also had a lower baseline HDL cholesterol level (p = 0.02) and higher baseline LDL cholesterol, triglyceride, fasting plasma glucose, 2-hour postload glucose and fasting insulin levels, and higher baseline systolic and diastolic blood pressures (each p < 0.001). Participants with incident diabetes were also more likely than those without diabetes to have had hypertension, impaired glucose tolerance and metabolic syndrome at baseline (each p ≤ 0.001) (Table 1).

| Variable                      | Odds ratio (95% CI) |
|-------------------------------|---------------------|
| Body mass index (per 1 kg/m²) | 1.13 (1.08-1.18)    |
| Percent body fat (per 2%)     | 1.16 (1.09-1.24)    |
| Waist circumference (per 2.5 cm) | 1.13 (1.08-1.19) |
| Waist-to-height ratio (per 0.02) | 1.18 (1.10-1.26)  |
| Systolic blood pressure (per 10 mm Hg) | 1.24 (1.04-1.47) |
| Diastolic blood pressure (per 10 mm Hg) | 1.41 (1.14-1.74) |
| Hypertension (yes/no)         | 2.59 (1.43-4.70)    |
| HDL cholesterol (per 1 mmol/L) | 0.31 (0.12-0.79)    |
| LDL cholesterol (per 1 mmol/L) | 1.49 (1.05-2.12)    |
| Triglycerides (per mmol/L)    | 2.07 (1.46-2.93)    |
| Fasting glucose (per mmol/L)  | 2.30 (1.40-3.77)    |
| 2-hour postload glucose (per mmol/L) | 1.36 (1.18-1.58) |
| Fasting insulin (per 20 pmol/L) | 1.10 (1.04-1.16) |
| Active smoker (yes/no)        | 0.93 (0.57-1.52)    |

**Figure 2:** Age- and sex-adjusted risk of type 2 diabetes associated with readily accessible clinical measurements.
In the multiple logistic regression analysis, we found that the following clinical variables at baseline were significantly associated with an increased risk of incident diabetes in the age- and sex-adjusted models: high body mass index, percent body fat, waist circumference, waist-to-height ratio; high fasting plasma glucose, 2-hour postload glucose and fasting insulin levels; high systolic and diastolic blood pressures; high LDL cholesterol and triglyceride levels; a low HDL cholesterol level; and hypertension (each $p \leq 0.03$) (Figure 2).

When we adjusted the models further for individual components of metabolic syndrome, excluding the main effect, we found that the direction of the associations of clinical variables with incident diabetes remained the same (data not shown), except for certain variables that were no longer significantly associated with incident diabetes after adjustment for components of metabolic syndrome, excluding the main effect, waist circumference as defined by the International Diabetes Federation (OR 1.03, 95% CI 0.98–1.08), high triacylglycerol (OR 1.24, 95% CI 0.84–1.84) and fasting insulin level (OR 0.51, 95% CI 0.18–1.44), LDL cholesterol and triglyceride levels; a low HDL cholesterol level; and hypertension (each $p \leq 0.03$) (Figure 2).

When we adjusted the models further for individual components of metabolic syndrome, excluding the main effect, we found that it had high specificity (91%) and high negative predictive value (85%), yet low sensitivity and low positive predictive value (Table 2). We found similar performance results for metabolic syndrome regardless of which set of defining criteria were used; however, we observed a slightly lower specificity and higher sensitivity for the syndrome as defined by the International Diabetes Federation criteria (Table 2). For the individual components of metabolic syndrome, we found that, in general, the specificity and negative predictive values were within a moderate to high range, and the sensitivity and positive predictive values were low (Table 2). As an exception, waist circumference as defined by the International Diabetes Federation had a high sensitivity and negative predictive value but a low specificity and positive predictive value (Table 2).

We found that metabolic syndrome at baseline was associated with incident diabetes after adjustment for age and sex regardless of whether we used the National Cholesterol Education Program definition (OR 2.03, 95% CI 1.10–3.75) or the International Diabetes Federation definition (OR 2.14, 95% CI 1.29–3.55) (Figure 3). There was no significant difference between the 2 definitions in their ability to discriminate participants with incident diabetes from those who did not have diabetes ($p \geq 0.05$ for comparison of C statistics).

When we lowered the fasting plasma glucose cut-off to 5.6 mmol/L or greater in the National Cholesterol Education Program criteria, we found that the modified definition of metabolic syndrome was significantly associated with incident diabetes to the same degree as the original definition ($p = 0.54$ for comparison of C statistics) and as the International Diabetes Federation criteria.

**Table 2:** Diagnostic performance of baseline impaired glucose tolerance, metabolic syndrome and individual components of metabolic syndrome in predicting incident type 2 diabetes at 10-year follow-up

| Variable                                                      | Sensitivity, % | Specificity, % | Positive predictive value, % | Negative predictive value, % |
|---------------------------------------------------------------|----------------|----------------|-------------------------------|------------------------------|
| Impaired glucose tolerance*                                   | 27             | 91             | 39                            | 85                           |
| Metabolic syndrome defined by NCEP criteria†                  | 26             | 88             | 32                            | 85                           |
| High waist circumference                                      | 53             | 61             | 22                            | 86                           |
| High triglyceride level                                       | 31             | 82             | 27                            | 85                           |
| Low HDL cholesterol level                                     | 53             | 58             | 21                            | 85                           |
| High blood pressure                                           | 34             | 87             | 36                            | 86                           |
| High fasting plasma glucose level                             | 21             | 94             | 41                            | 85                           |
| Metabolic syndrome defined by IDF criteria†                   | 48             | 75             | 29                            | 87                           |
| High waist circumference†                                      | 91             | 30             | 22                            | 94                           |
| High triglyceride level                                       | 31             | 82             | 27                            | 85                           |
| Low HDL cholesterol level†                                    | 49             | 64             | 22                            | 85                           |
| High blood pressure                                           | 34             | 87             | 36                            | 86                           |
| High fasting plasma glucose level                             | 53             | 70             | 27                            | 88                           |

Note: HDL = high-density lipoprotein, IDF = International Diabetes Federation, NCEP = National Cholesterol Education Program.

*Defined as fasting plasma glucose level < 7.0 mmol/L, and 2-hour postload glucose level ≥ 7.8 mmol/L and < 11.1 mmol/L.
†Age-specific cut-offs used.
Interpretation

In this prospective study, we documented that the 10-year cumulative incidence of type 2 diabetes was 17.5% in the Aboriginal study population. We also noted that the incidence increased with age, from 10.5% among participants 10–19 years old, to 43.3% among those 40–49 years. High adiposity, dyslipidemia, hyperglycemia and hypertension at baseline were associated with increased risk of diabetes after adjustment for age and sex. Although metabolic syndrome at baseline had low sensitivity and low positive predictive value for detecting future diabetes, it had high specificity and high negative predictive value for correctly identifying disease-free individuals at follow-up. In addition, metabolic syndrome at baseline was associated with incident diabetes to the same degree that impaired glucose tolerance was.

Similar observations were reported in the Strong Heart Study, a cohort study that followed Aboriginal North Americans aged 45–74 years with a high prevalence of diabetes and metabolic syndrome. In that study, the incidence of diabetes over a follow-up period of about 8 years was 17.0%. The risk of diabetes was higher among those with metabolic syndrome than among those without the syndrome.

Our results confirmed that traditional risk factors documented in non-Aboriginal populations, including obesity, dyslipidemia, hyperglycemia and hypertension, were associated with increased risk of diabetes in this Aboriginal population with unique genetic susceptibility to diabetes. There were no significant sex interactions with these traditional risk factors in predicting diabetes, except for fasting plasma glucose level at baseline. When we stratified data by sex, we found a significant association between fasting plasma glucose level and incident diabetes among males, but not among females. This difference may have been influenced by sex differences in other baseline characteristics: a higher number of females in the study population had obesity at baseline, which has a greater impact on 2-hour postload glucose levels and impaired glucose tolerance than on fasting plasma glucose levels.

Randomized controlled trials have previously shown that lifestyle interventions, including physical activity and dietary modification, reduce the incidence of diabetes among participants with impaired glucose tolerance at baseline. However, impaired glucose tolerance is determined by means of a 2-hour oral glucose tolerance test, which often is not accessible or easy to perform in community settings. Stern and colleagues demonstrated that a multivariable model including routinely obtained clinical variables (i.e., age, sex, ethnicity, fasting plasma glucose level, systolic blood pressure, HDL cholesterol level, body mass index and family history of diabetes) was better than the oral glucose tolerance test alone in identifying individuals at high risk of diabetes.
risk of diabetes ($p < 0.001$). They also found that a multivariable model including lipid levels, blood pressure, body mass index, smoking history and family history of cardiovascular disease was better than the oral glucose tolerance test alone in detecting individuals at high risk of cardiovascular disease.10

A number of studies have shown an association between metabolic syndrome, defined using common clinical measurements, and increased risk of diabetes4–10 and cardiovascular disease.9,9 Our findings are consistent with this literature and offer the potential to use metabolic syndrome in identifying individuals at increased risk of diabetes and possibly cardiovascular disease in remote community settings. This potential is of particular interest to Aboriginal communities with a high prevalence of diabetes11,12 and evidence of increasing rates of hospital admission because of cardiovascular disease.12,31

The Diabetes Prevention Program randomized trial showed that intensive lifestyle intervention and metformin therapy can reduce the incidence of metabolic syndrome and also the prevalence of metabolic syndrome at follow-up.32 Other randomized controlled trials have confirmed that lifestyle intervention can reduce the prevalence of metabolic syndrome.33,34 Therefore, implementing intervention strategies for individuals with the syndrome may be a practical solution to prevent, or at least to delay, the onset of diabetes in Aboriginal communities.

Limitations
Limitations of our study include challenges of conducting investigations in a remote community. Specifically, we were unable to collect interim data to analyze the time to onset of diabetes. Also, we were unable to obtain follow-up blood samples from all of the participants: for 109 (22.2%), the assessments of diabetes outcomes were by self-reported clinical diagnosis only. This may have caused underreporting of incident diabetes. Nevertheless, we were able to retain a high 10-year follow-up rate of 89.1% (540/606).

Conclusion
The presence of metabolic syndrome at baseline was associated with incident diabetes to the same degree that impaired glucose tolerance was, although not all individuals with the syndrome had incident diabetes. The absence of the syndrome at baseline was, although not all individuals with the syndrome may be a practical solution to prevent, or at least to delay, the onset of diabetes in Aboriginal communities.

lifestyle interventions to reduce long-term risk. They may also assist in reducing the incidence of diabetes in Aboriginal populations by influencing future public health initiatives.

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REFERENCES

1. Young TK, Reading J, Elias B, et al. Type 2 diabetes mellitus in Canada’s First Nations: status of an epidemic in progress. CMAJ 2000;163:561-6.

2. Stumvoll M, Goldstein BJ, van Haeften TW. Type 2 diabetes: principles of pathogenesis and therapy. Lancet 2005;365:1333-46.

3. National Cholesterol Education Program. Executive summary of the third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). JAMA 2001;285:2456-64.

4. International Diabetes Federation. The IDF consensus worldwide definition of the metabolic syndrome. Brussels (Belgium): International Diabetes Federation; 2005.

5. International Diabetes Federation. The IDF consensus definition of the metabolic syndrome in children and adolescents. Brussels (Belgium): International Diabetes Federation; 2007.

6. Gale EAM. Should we dump the metabolic syndrome? Yes. BMJ 2008;336:640.

7. Alberti KGMM, Zimmet PZ. Should we dump the metabolic syndrome? No. BMJ 2008;336:641.

8. Lorenzo C, Williams K, Hunt KJ, et al. The National Cholesterol Education Program-Adult Treatment Panel III, International Diabetes Federation, and World Health Organization definitions of the metabolic syndrome as predictors of incident cardiovascular disease and diabetes. Diabetes Care 2007;30:8-13.

9. Wilson PWF, D’Agostino RB, Parise H, et al. Metabolic syndrome as a precursor of cardiovascular disease and type 2 diabetes mellitus. Circulation 2005;112:3066-72.

10. Resnick HE, Jones K, Ruotolo G, et al. Insulin resistance, the metabolic syndrome, and risk of incident cardiovascular disease in nondiabetic American Indians: the Strong Heart Study. Diabetes Care 2003;26:861-7.

11. Harris SB, Gittelsohn J, Hanley A, et al. The prevalence of NIDDM and associated risk factors in Native Canadians. Diabetes Care 1997;20:185-7.

12. Harris SB, Zinman B, Hanley A, et al. The impact of diabetes on cardiovascular risk factors and outcomes in a Native Canadian population. Diabetes Res Clin Pract 2002;55:165-73.

13. Liu J, Young TK, Zinman B, et al. Lifestyle variables, non-traditional cardiovascular risk factors, and the metabolic syndrome in an Aboriginal Canadian population. Obesity (Silver Spring) 2006;14:900-7.

14. Green C, Blanchard JF, Young TK, et al. The epidemiology of diabetes in the Manitoba-registered First Nation population: current patterns and comparative trends. Diabetes Care 2003;26:1993-8.

15. Horn OK, Jacobs-Whyte H, Ing A, et al. Incidence and prevalence of type 2 diabetes in the First Nation community of Kawakwage, Quebec, Canada, 1986–2003. Can J Public Health 2007;98:438-43.

16. Hegele RA, Zinman B, Hanley AG, et al. Genes, environment and Oji-Cree type 2 diabetes. Clin Biochem 2003;36:163-70.

17. Hanley AJ, Harris SB, Barrie A, et al. The Sandy Lake Health and Diabetes Project: design, methods and lessons learned. Chronic Dis Can 1995;16:149-56.
18. World Health Organization. Definition, diagnosis, and classification of diabetes mellitus and its complications: report of a WHO consultation. Geneva (Switzerland): World Health Organization; 1999.

19. Lipid Research Clinics Program. Manual of laboratory operations. Washington (DC): US Government Printing Office; 1984. p. 1-81. NIH publ. no. 75-6282.

20. Fzewadez JR, Redden DT, Pietrobelli A, et al. Waist circumference percentiles in nationally representative samples of African-American, European-American, and Mexican-American children and adolescents. J Pediatr 2004;145:439-44.

21. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. Biometrics 1988;44:837-45.

22. Lee ET, Howard BV, Savage PJ, et al. Diabetes and impaired glucose tolerance in three American Indian populations aged 45–74 years. The Strong Heart Study. Diabetes Care 1995;18:599-610.

23. Resnick HE. Metabolic syndrome in American Indians. Diabetes Care 2002;25:1246-7.

24. Russell M, de Simone G, Resnick HE, et al. The metabolic syndrome in American Indians: the Strong Heart Study. J Cardiometab Syndr 2007;2:283-7.

25. Festa A, D’Agostino R Jr, Hanley AJ, et al. Differences in insulin resistance in nondiabetic subjects with isolated impaired glucose tolerance or isolated impaired fasting glucose. Diabetes 2004;53:1549-55.

26. Tuomilehto J, Lindstrom J, Eriksson JG, et al. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. N Engl J Med 2001;344:1344-50.

27. Knowler WC, Barrett-Connor E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 2002;346:193-403.

28. Diabetes Prevention Program Research Group. The Diabetes Prevention Program (DPP): description of lifestyle intervention. Diabetes Care 2002;25:2165-71.

29. Stern MP, Williams K, Haffner SM. Identification of persons at high risk for type 2 diabetes mellitus: Do we need the oral glucose tolerance test? Ann Intern Med 2002;136:575-81.

30. Stern MP, Fatehi P, Williams K, et al. Predicting future cardiovascular disease: Do we need the oral glucose tolerance test? Diabetes Care 2002;25:1851-6.

31. Shih AB, Hux JE, Zarnan B. Increasing rates of ischemic heart disease in the Native population of Ontario, Canada. Arch Intern Med 2000;160:1862-6.

32. Orchard TJ, Temprosa M, Goldberg R, et al. The effect of metformin and intensive lifestyle intervention on the metabolic syndrome: the Diabetes Prevention Program randomized trial. Ann Intern Med 2005;142:699-701.

33. Bo S, Ciccone G, Balbi C, et al. Effectiveness of a lifestyle intervention on metabolic syndrome. A randomized controlled trial. J Gen Intern Med 2007;22:1695-703.

34. Ilanne-Parikka P, Eriksson JG, Lindstrom J, et al. Effect of lifestyle intervention on the occurrence of metabolic syndrome and its components in the Finnish Diabetes Prevention Study. Diabetes Care 2008;31:805-7.

35. Young HC, Chane C. The Indian experience in the Central Subarctic. Toronto (ON): University of Toronto Press; 1988.