# Use of $HbA_{1c}$ in Predicting Progression to Diabetes in French Men and Women

## Data from an Epidemiological Study on the Insulin Resistance Syndrome (DESIR)

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**OBJECTIVE** — Early identification of subjects at high risk for diabetes is essential, and random $HbA_{1c}$ (A1C) may be more practical than fasting plasma glucose (FPG). The predictive value of A1C, in comparison to FPG, is evaluated for 6-year incident diabetes.

**RESEARCH DESIGN AND METHODS** — From the French cohort study Data from an Epidemiological Study on the Insulin Resistance Syndrome (DESIR), 1,383 men and 1,437 women, aged 30–65 years, were volunteers for a routine health check-up. Incident diabetes was defined by FPG ≥7.0 mmol/l or treatment by antidiabetic drugs. Multivariate logistic regression models were used to predict diabetes at 6 years. Receiver operating characteristic curves compared the predictive values of A1C and FPG.

**RESULTS** — At 6 years, 30 women (2.1%) and 60 men (4.3%) had developed diabetes. Diabetes risk increased exponentially with A1C in both sexes ($P < 0.001$). After stratifying on FPG, A1C predicted diabetes only in subjects with impaired fasting glucose (IFG) (FPG ≥6.10 mmol/l): the odds ratio (95% CI) for a 1% increase in A1C was 7.20 (3.00–17.00). In these subjects, an A1C of 5.9% gave an optimal sensitivity of 64% and specificity of 77% to predict diabetes.

**CONCLUSIONS** — A1C predicted diabetes, even though the diagnosis of diabetes was based on FPG, but it was less sensitive and specific than FPG. It could be used as a test if fasting blood sampling was not available or in association with FPG. In subjects with IFG, A1C is better than glucose to evaluate diabetes risk, and it could be used to select subjects for intensive early intervention.

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The prevalence of type 2 diabetes is increasing worldwide, and it is projected that the number of adults with diabetes will double between 2000 and 2030 (1). This means a large burden for the health care system. Recent clinical trials have demonstrated that lifestyle (2–4) or pharmaceutical (4–6) interventions in individuals with impaired glucose tolerance (IGT) can delay or prevent diabetes; thus high-risk subjects should be identified for early intensive lifestyle counseling or even pharmaceutical treatment (7).

Fasting and 2-h plasma glucose after an oral glucose tolerance test (OGTT) are currently used to identify subjects at high risk of diabetes (8): those with impaired fasting glucose (IFG) and IGT. However, the OGTT is not common in clinical practice, because it is time consuming, costly, and less reproducible (9) than measurement of fasting plasma glucose (FPG).

$HbA_{1c}$ (A1C), an indirect measure of mean blood glucose over the previous 2–3 months, is correlated with FPG and 2-h plasma glucose (10–12). A1C is more reproducible than FPG (13) and within-subject coefficients of variation are 1.7 and 5.7%, respectively (14). Moreover, measurement of A1C does not require that the subject is fasting. The use of A1C could better integrate chronic hyperglycemia than FPG.

Few studies have investigated predicting diabetes using A1C and none in a Caucasian population. Moreover, previous investigations were in populations at high risk of diabetes. A study in Pima Indians (15) reported that A1C was an independent predictor for diabetes only in individuals with IGT, not in subjects with normal 2-h plasma glucose. The same relation was found in a Chinese study (16).

To determine whether A1C predicted incident diabetes after a 6-year follow-up in a Caucasian population, we analyzed data from the prospective French cohort study: Data from an Epidemiological Study on the Insulin Resistance Syndrome (DESIR).

## RESEARCH DESIGN AND METHODS

— The 3,854 subjects studied, aged 30–65 years, were included in 1994–1996 in the DESIR Study, a follow-up study on the development of the insulin resistance syndrome. They were volunteers for a routine health check-up in seven Health Examination Centers financed by the French Social Security in the center-west of France. All participants gave informed consent, and the study was approved by an ethics committee (Comité Consultatif de Protection

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**Abbreviations:** DESIR, Data from an Epidemiological Study on the Insulin Resistance Syndrome; FPG, fasting plasma glucose; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; OGTT, oral glucose tolerance test; ROC, receiver operating characteristic.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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**Table 1—*Comparison of baseline characteristics between men and women who developed or did not develop diabetes at 6 years****

| | Men | | | Women | | |
|---|---|---|---|---|---|---|
| | Nondiabetic | Diabetic | Age-adjusted *P* value | Nondiabetic | Diabetic | Age-adjusted *P* value |
| *n* | 1,323 | 60 | | 1,407 | 30 | |
| Age (years) | 46.9 ± 9.9 | 50.5 ± 9.6 | | 47.4 ± 9.9 | 53.2 ± 8.2 | |
| A1C (%) | 5.4 ± 0.4 | 5.8 ± 0.5 | <0.0001 | 5.3 ± 0.4 | 5.9 ± 0.6 | <0.0001 |
| Fasting plasma glucose (mmol/l) | 5.54 ± 0.48 | 6.17 ± 0.50 | <0.0001 | 5.17 ± 0.46 | 6.00 ± 0.61 | <0.0001 |
| Insulin (pmol/l) | 41.1 ×/÷ 1.7 | 57.9 ×/÷ 1.8 | <0.0001 | 39.2 ×/÷ 1.6 | 64.5 ×/÷ 1.8 | <0.0001 |
| BMI (kg/m$^2$) | 25.1 ± 2.9 | 27.6 ± 4.3 | <0.0001 | 23.6 ± 3.7 | 29.4 ± 6.0 | <0.0001 |
| Waist circumference (cm) | 89 ± 9 | 98 ± 11 | <0.0001 | 77 ± 10 | 91 ± 13 | <0.0001 |
| HDL cholesterol (mmol/l) | 1.51 ± 0.38 | 1.47 ± 0.44 | 0.3 | 1.82 ± 0.42 | 1.48 ± 0.38 | <0.0001 |
| Triglycerides (mmol/l) | 1.12 ×/÷ 1.7 | 1.67 ×/÷ 1.8 | <0.0001 | 0.84 ×/÷ 1.64 | 1.50 ×/÷ 1.57 | <0.0001 |
| Systolic blood pressure (mmHg) | 132 ± 14 | 139 ± 16 | 0.001 | 126 ± 14 | 138 ± 16 | 0.0005 |
| Diastolic blood pressure (mmHg) | 82 ± 10 | 84 ± 9 | 0.1 | 77 ± 9 | 83 ± 6 | 0.003 |
| Hypertension (%)† | 42 | 63 | 0.008 | 29 | 63 | 0.006 |
| Family history of diabetes (%) | 17 | 25 | 0.08 | 20 | 47 | 0.0006 |
| Sporting activity (%) | | | | | | |
| None | 46 | 53 | | 50 | 77 | |
| Moderate (<1 session per week) | 20 | 22 | 0.5 | 15 | 13 | 0.03 |
| Frequent (≥1 session per week) | 34 | 25 | | 35 | 10 | |
| Smoking (%) | 25 | 28 | 0.2 | 12 | 13 | 0.2 |
| Alcohol intake (%)‡ | | | | | | |
| None | 13 | 7 | | 36 | 27 | |
| Moderate | 73 | 65 | 0.02 | 41 | 50 | 0.5 |
| Elevated | 14 | 28 | | 23 | 23 | |
| Child with birth weight >4 kg | — | — | — | 15 | 31 | 0.03 |

Data are means ± SD, geometric mean ×/÷ SD, or column %. *Comparisons are adjusted on age. †Arterial hypertension was defined by a systolic blood pressure ≥140 mmHg and/or a diastolic blood pressure ≥90 mmHg and/or an antihypertensive treatment (30). ‡Alcohol intake coding: no consumption, moderate (1–20 g/day for women and 1–40 g/day for men), and elevated (>20 g/day for women and >40 g/day for men).

des Personnes pour la Recherche Biomédicale of Kremlin-Bicêtre).

Of the 3,854 subjects, we excluded 114 with known diabetes or FPG ≥7.0 mmol/l at baseline, 92 who had an unknown glucose status, and 21 without A1C, waist circumference, or BMI information. Among the 3,627 remaining, 2,924 (81%) were reexamined 6 years after inclusion and the 104 subjects with incomplete information to evaluate glucose status were excluded: 1,383 men and 1,437 women were studied.

Participants were examined at inclusion and at 6 years. A medical interview provided information about lifestyle, use of medication, and personal and familial history of diabetes. Weight and height were measured with subjects lightly clothed, and a tape measure was used around the waist at the smallest circumference between the lower ribs and the iliac crests. Blood pressure was measured by a doctor with a sphygmomanometer on the right arm, with subjects lying at rest for at least 5 minutes.

Blood was drawn after a 12-h fast. A1C was measured in a central laboratory by high-performance liquid chromatography, using a L9100 automated ion-exchange analyzer (Hitachi/Merck-VWR). This assay was standardized to the National Glycohemoglobin Standardization Program. Intra- and interassay coefficients of variation (CVs) for A1C were 1.5 and 1.8%. FPG was assayed by the glucose oxidase method on fluoro-oxalated plasma, using a Technicon RA 1000 analyzer (Bayer). Fasting insulin was measured by a microenzyme immunoassay and total cholesterol, HDL cholesterol, and triglycerides by enzymatic methods.

## Definitions

Diabetes was defined according to the 1997 American Diabetes Association criteria (17): FPG ≥7.00 mmol/l or treatment by oral antidiabetic drugs or insulin. At inclusion, subjects were classified into three FPG groups: <5.60, 5.60–6.09, and ≥6.10 mmol/l (IFG). A family history of diabetes was coded if there was at least one diabetic first-degree relative. Sporting activity was assessed according to the number of sessions per week, alcohol intake was assessed by grams of alcohol per day, and subjects were classified as smokers or nonsmokers at inclusion.

## Statistical analyses

The symmetry of the distributions of quantitative variables was assessed graphically: logarithms of insulin and triglycerides were used. Results are given as means ± SD or as geometric means ×/÷ SD, in the case of logarithmic transformation. Means were compared by Student's *t* tests or by ANCOVA, after age adjustment. For qualitative variables, results are expressed as percentages and compared by $\chi^2$ or Fisher's tests or by logistic regression after age adjustment. The relation between A1C and FPG was evaluated by a Pearson correlation coefficient.

The role of A1C in the risk of developing diabetes at 6 years was evaluated by logistic regression models adjusted for age. Analyses were by sex, and in a second phase, sexes were pooled. For each continuous risk factor, linearity was studied by plotting the middle of each quartile group against the β coefficient of each quartile, obtained from logistic regression

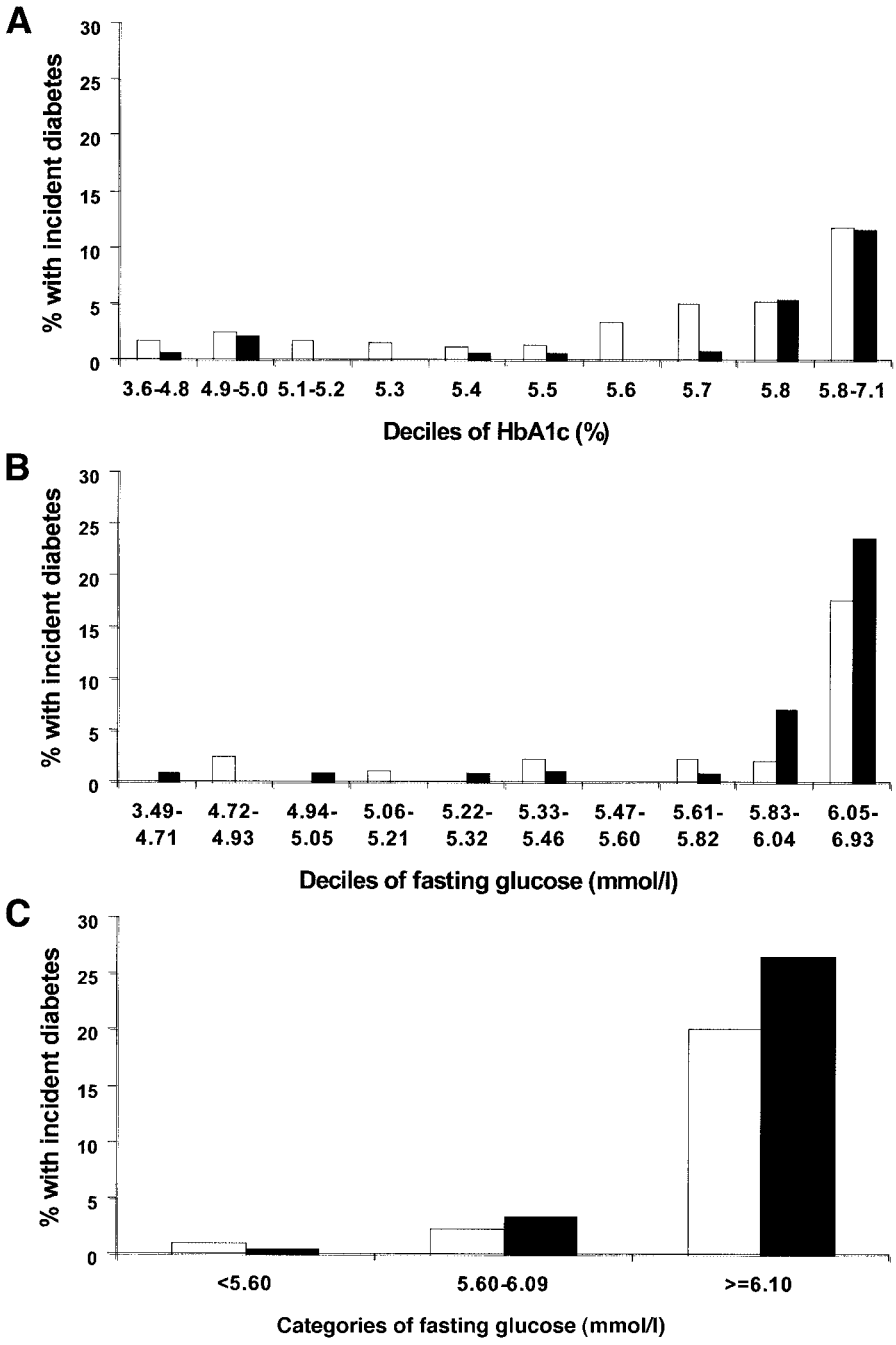


**Figure 1—** *Percentage of men and women with diabetes after 6 years of follow-up according to A1C deciles* (A)*, FPG deciles* (B)*, and fasting plasma glucose* (C) *categories.* □*, men;* ■*, women.*

(18). A linear trend was observed for BMI, waist circumference, triglycerides (log), HDL cholesterol, insulin (log), and systolic and diastolic pressure, and the continuous variable was chosen. A1C had a nonlinear relation, and its squared term was added to model this relation. Alcohol was coded in classes (Table 1). Diabetes risk according to A1C was modeled by logistic regression, adjusting on age and using those variables with a trend toward being significant ($P = 0.25$) in the age-adjusted comparison between diabetic and nondiabetic groups. For adjusting variables, in the case of highly correlated variables (e.g., BMI and waist circumference), only the variable most significantly related to diabetes was used. Variable selection was based on likelihood ratio tests. FPG was added to test whether A1C remained significantly predictive. Likelihood ratio tests were used to evaluate interaction terms between A1C and FPG. As this interaction was marginally significant, we stratified on FPG categories. All models fitted well according to the Hosmer-Lemeshow test (18).

We compared the predictive performances of A1C and FPG as continuous variables, using receiver operating characteristic (ROC) curves, plotting sensitivity against (1 − specificity) at all possible thresholds. STATA software was used to calculate the ROC curves and to estimate areas (95% CIs) under these curves and the statistical significance of differences between these areas (19). The optimal threshold corresponds to the value where sensibility plus specificity is maximized.

All other analyses used the SAS software (SAS Institute, Cary, NC). A $P$ value $< 0.05$ was regarded as statistically significant for a two-sided test.

## RESULTS

### Incidence of diabetes at 6 years and baseline characteristic of subjects according to development or not of diabetes

Ninety subjects developed diabetes over the 6 years: 30 women and 60 men, 2.1 and 4.3%, respectively. The incidence of diabetes at 6 years increased in a nonlinear manner with the deciles of A1C and FPG and with the three categories of FPG at inclusion (Fig. 1). Subjects excluded and included were comparable at baseline for all variables except age (44.1 ± 9.9 vs. 47.3 ± 9.9 years) and smoking (32 vs. 18%).

Mean A1C at inclusion was 5.3 ± 0.4% for the 1,913 subjects with FPG <5.60 mmol/l, 5.5 ± 0.4% for the 635 subjects with FPG between 5.60 and 6.09 mmol/l, and 5.7 ± 0.5% for the 272 individuals with FPG ≥6.10 mmol/l, ($P <$ 0.0001). The Pearson correlation coefficient between A1C and FPG at inclusion was 0.38($P < 0.0001$).

In both sexes, subjects who developed diabetes were older than those who did not ($P = 0.0005$) (Table 1). After age adjustment, mean A1C, FPG, insulin, triglycerides, BMI, waist circumference, and systolic blood pressure were higher in those who developed diabetes, compared with those who did not, whereas HDL cholesterol was significantly lower only in women. A family history of diabetes was more frequent in the diabetic group, significantly in women. In men, alcohol intake was higher in the subjects with incident cases of diabetes and the absence of sporting activity and having a child

**Table 2—*Predictive value of A1C for diabetes at 6 years, according to successive multiple logistic regression models**

| Variables included in model | β Coefficient of A1C | β Coefficient of $A1C^2$ | *P* value of A1C | *P* value of $A1C^2$ | −2 log likelihood |
|---|---|---|---|---|---|
| Age + sex | | | | | 768.81 |
| Age + sex + A1C | | | | | 674.70† |
| Age + sex + A1C + $A1C^2$ | −13.10 | 1.39 | 0.0001 | <0.0001 | 660.69† |
| Age + sex + A1C + $A1C^2$ + waist circumference | −13.09 | 1.35 | <0.0001 | <0.0001 | 604.72† |
| Age + sex + A1C + $A1C^2$ + waist circumference + triglycerides (log) | −13.10 | 1.35 | <0.0001 | <0.0001 | 589.30† |
| Age + sex + A1C + $A1C^2$ + waist circumference + triglycerides (log) + familial history of diabetes | −12.84 | 1.33 | <0.0001 | <0.0001 | 582.99†‡ |

Data are β coefficients (= ln OR) of A1C and $A1C^2$; $n$ = 2,820. *Variables were added successively. †Likelihood ratio test between this model and the preceding nested model was significant at $P < 0.05$. ‡Likelihood ratio test between this model and a model with an interaction term between A1C and sex was not significant. The interaction between A1C and sex was tested only in this final model.

with a birth weight >4 kg were more common in the future diabetic women.

### A1C and diabetes prediction

After adjustment for age, A1C predicted incident diabetes in both sexes (data not shown). Addition of insulin, systolic and diastolic pressure, smoking, and sporting activity did not improve the prediction of diabetes significantly in either sex; neither did alcohol in men nor having a child with a birth weight >4 kg in women. As variables included in the models and β coefficients were similar in men and women and as there was no significant interaction between sex and A1C, sexes were pooled (Table 2). A1C predicted diabetes at 6 years, independently of other variables. Diabetes risk increased exponentially with A1C at inclusion: odds ratio (OR) for an A1C increase from 4.5 (mean − 2 SD) to 5.0% was 0.90 (95% CI 0.50–1.50), from 4.5 to 5.5% was 1.50 (0.70–3.40), from 4.5 to 6.0% was 5.0 (2.00–12.80), and from 4.5 to 6.5% was 32.70 (11.50–92.60).

FPG was then included in this model, and as there was a marginally significant interaction between A1C and FPG ($P$ = 0.07), models were stratified on FPG categories, adjusted on the same variables as the last model in Table 2. The addition of a squared A1C term did not improve the models, and there was no interaction between A1C and sex. A1C was only a significant risk factor for diabetes at 6 years in subjects with FPG ≥6.10 mmol/l: OR for a 1% A1C increase was 0.78 (95% CI 0.20–3.07) ($P$ = 0.7) for FPG <5.60 mmol/l, 1.47 (0.36–5.80) ($P$ = 0.6) for FPG 5.60–6.09 mmol/l, and 7.20 (3.00–17.00) ($P$ < 0.0001) for FPG ≥6.10 mmol/l (IFG).

For FPG ≥6.10 mmol/l, FPG as a continuous variable was not predictive of diabetes, whether A1C was included in the model (OR for 1 mmol/l increase 1.0 [95% CI 0.2–4.8], $P$ = 0.9) or not (2.4 [0.6–9.4], $P$ = 0.2). In contrast, A1C was predictive of diabetes in these subjects (7.22 [2.95–17.80], $P$ < 0.001, for a 1% A1C increase), independently of whether or not FPG was in the model.

### ROC curves

In the entire study population of 2,820 subjects (Fig. 2), the area under the curve for FPG to predict incident diabetes at 6 years of follow-up was significantly greater than that for A1C: 0.85 (95% CI 0.80–0.90) versus 0.78 (0.72–0.83) ($P$ = 0.005). The optimal value for FPG was 5.9 mmol/l, with sensitivity and specificity of 76 and 86%, respectively. For A1C, the optimal value was 5.7% with corresponding sensitivity and specificity of 66 and 88%.

In contrast, in subjects with IFG (FPG ≥6.10 mmol/l) (Fig. 2*B*), the area under the curve for A1C was significantly greater than that for FPG: 0.75 (95% CI 0.69–0.82) versus 0.60 (0.52–0.68) ($P$ = 0.001). The optimal cutoff for A1C was 5.9%, with sensitivity and specificity of 64 and 77% and a positive predictive value of 44%.

If the test is based on both glucose and A1C, the optimal cutoffs were 5.9 mmol/l and 5.0%, respectively, with sensitivity of 73% and specificity of 87%. Alternatively, for either glucose or A1C, the corresponding optimal cutoffs were 5.9 mmol/l and 6.3%, with corresponding sensitivity and specificity of 77 and 86%, respectively.

**CONCLUSIONS** — A1C predicted diabetes in this Caucasian population and the risk increased exponentially in both sexes. As for FPG, Fig. 1 provides evidence that there is an A1C threshold below which the incidence of diabetes is very low and above which the incidence is considerably higher. However, A1C is less sensitive and specific than FPG for diabetes in the entire population (Fig. 2*A*).

For screening in a nonfasting state, A1C could be used in a general population. At the present time, this use is limited because FPG is still needed for the diagnosis of diabetes. However the diagnosis of diabetes by A1C has been debated for many years. In a study using an external gold standard, diabetic microvascular complications, McCance et al. (20) showed that A1C was as predictive as FPG and 2-h glucose. Moreover, several authors have recommended the use of A1C, in combination with FPG or random plasma glucose, to diagnose diabetes (13,21–23): a FPG ≥7.00 mmol/l or a random plasma glucose ≥11.10 mmol/l associated with an A1C exceeding the mean + 2 SD would better determine the diagnosis of treatment-requiring diabetes.

After stratifying on FPG classes, A1C was predictive only in subjects with IFG (FPG ≥6.1 mmol/l), with an OR of 7.2 (95% CI 3.00–17.00); thus subjects with IFG and high A1C could be identified for preventive care. Moreover within this IFG category, FPG did not predict diabetes risk, in contrast with A1C: subjects with A1C >5.9% had a 50% risk of progressing to diabetes within 6 years. This optimal threshold of 5.9% remains to be confirmed in other populations.

It is important to note that the diagnostic criteria for diabetes in this study were based on FPG, giving it an advantage over A1C to predict diabetes. The best

way to compare the two parameters would be with an external diagnostic criterion, such as diabetic retinopathy.

This study was in volunteers presenting for a health check-up, which may constitute a healthier population than the general population, at low risk for type 2 diabetes. Diabetes prevalence in this cohort was 2.7% (24), slightly lower than national data from the French Health Care study of 3.4% (25) in the same age-group. Even if the population studied is not representative of the general French population, it probably represents the population, and, in particular, subjects with IFG, who would accept screening for diabetes and then preventive measures.

One limitation of our study is the small number of incident cases of diabetes and the resulting lack of power, especially in stratified analyses. A1C may also be significantly predictive of diabetes in subjects with the newer definition of IFG: FPG 5.60–6.09 mmol/l with a larger sample, but it would carry a lower OR than IFG (FPG ≥6.10 mmol/l).

Our results apply to diabetes diagnosed by FPG and could be different if the 2-h glucose measurement following an OGGT was also available, as a large percentage of subjects diagnosed as diabetic by a 2-h glucose value have normal FPG (26). We cannot exclude the possibility that some individuals, particularly subjects with IFG, were already diabetic at inclusion, which might overestimate the relation between A1C and diabetes. However, the OGTT is seldom used in clinical practice in France (27), and the American Diabetes Association encourages the use of FPG for screening (17). Therefore, this study reflects daily practice.

In participants with IFG, a small difference in FPG did not predict diabetes, in contrast to A1C. This suggests that A1C integrates blood glucose variations during the day, reflecting postload glucose abnormalities not shown by FPG (28). A prospective study, comparing 2-h glucose versus FPG and their association with A1C in predicting diabetes diagnosed by specific diabetic microvascular complications, is needed.

Our results are similar to those of Little et al. (15), except that we studied fasting and not 2-h postload plasma glucose. In 381 Pima Indians, A1C predicted diabetes diagnosed by 2-h glucose concentrations at 3.3 years follow-up only in subjects with IGT, with an OR for 1% increase in A1C of 6.76 (95% CI 1.77–25.8).

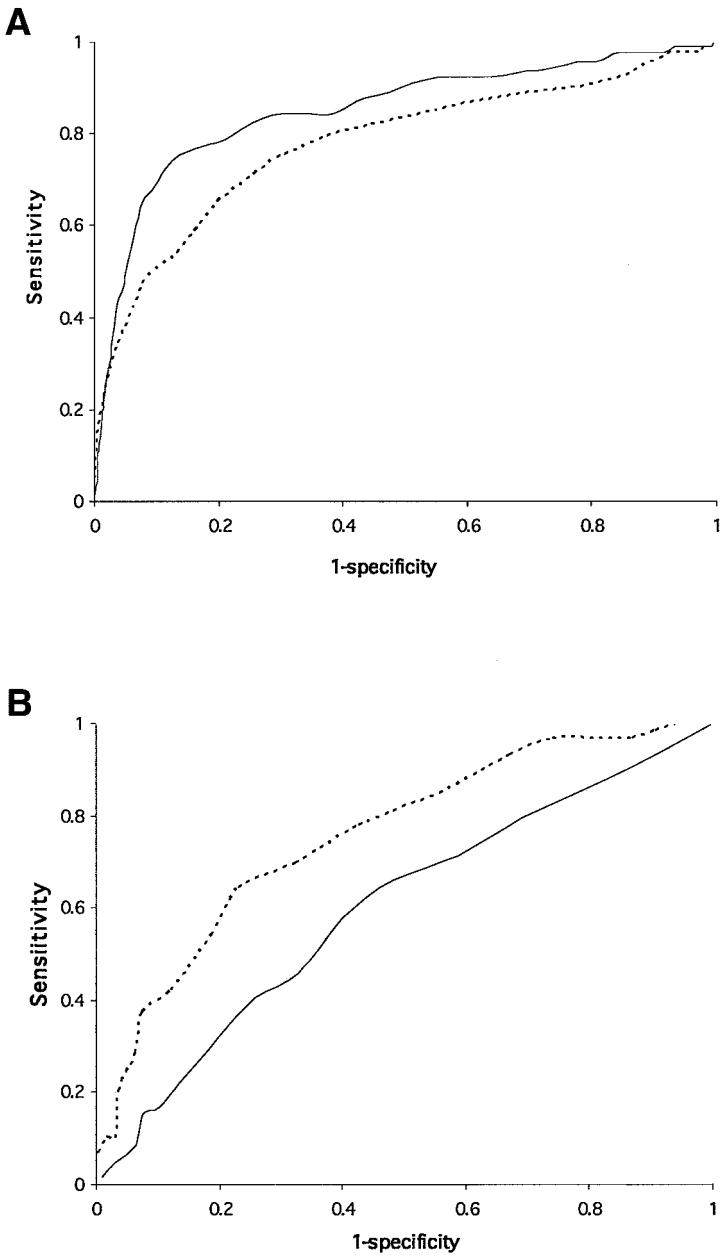


**Figure 2**—*ROC curves for incident diabetes after 6 years of follow up: A1C (dashed line) and fasting plasma glucose (solid line) in the entire study population* (A) *and in subjects with IFG* (B).

In another study, 208 Chinese subjects at high risk of diabetes, with FPG <7.0 mmol/l and 2-h glucose <11.1 mmol/l, were followed for 1.6 years (16). In subjects with IFG subjects, the progression to diabetes, diagnosed by 2-h glucose, was 44.1% for A1C >6.1% versus 17.4% for A1C <6.1%. In subjects with normal FPG, the conversion rate to diabetes was 13.7 versus 8.1%.

Until 10 years ago, using A1C as a screening tool was limited by poor comparability between measures and between laboratories. Most routine A1C assays are now standardized against one of the local standardization schemes, such as the National Glycohemoglobin Standardization Program. A new more specific reference measure was developed in 2003 (29). This prompted the reevaluation of A1C as a predictive test for diabetes.

In summary, in the absence of FPG, for example, in the middle of the day, A1C could be used to screen for diabetes in a general population. It could also be used in association with FPG, as in subjects with IFG, A1C better screened those at risk of diabetes, subjects who could be targeted for intensive prevention intervention. Moreover, it could help them to

become aware of their metabolic abnormalities and motivate asymptomatic subjects to modify their lifestyle.

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## APPENDIX

### Members of the DESIR Study Group

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