# High-Normal $HbA_{1c}$ Is a Strong Predictor of Type 2 Diabetes in the General Population

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**OBJECTIVE**—Glycosylated hemoglobin ($HbA_{1c}$) recently has been recommended for the diagnosis of diabetes by the American Diabetes Association, but its value in the prediction of type 2 diabetes is poorly understood. In this study we evaluated how high-normal $HbA_{1c}$ levels predict type 2 diabetes.

**RESEARCH DESIGN AND METHODS**—We measured $HbA_{1c}$ in 919 Caucasian subjects, aged 40–79 years, and recorded new cases of type 2 diabetes in the following 15 years. Diabetes was diagnosed with $HbA_{1c}$.

**RESULTS**—Subjects were stratified according to baseline $HbA_{1c}$ (<5.0, 5.00–5.49 [reference], 5.50–5.99, and 6.00–6.49%). Sex- and age-adjusted hazard ratios (95% CI) for type 2 diabetes were 1.11 (0.30–4.41), 1.00, 3.79 (1.79–8.06), and 12.50 (5.51–28.34), respectively. Results did not change after adjusting for several putative confounding factors and were confirmed when models with updated variables were used.

**CONCLUSIONS**—$HbA_{1c}$ is an independent risk factor for type 2 diabetes. Subjects with high-normal levels of $HbA_{1c}$ deserve particular attention because they have a strong risk of developing diabetes.

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Glycosylated hemoglobin ($HbA_{1c}$) was proposed as a reliable tool for diagnosing diabetes and identifying subjects at increased risk of type 2 diabetes (1). In 2010, the American Diabetes Association (ADA) pointed out that prevention strategies should be particularly intensive in subjects with high-normal $HbA_{1c}$ because they have the greatest risk (2), but this recommendation was based more on common sense than literature data. In fact, only few studies (3,4) showed an elevated risk of type 2 diabetes in subjects with high-normal $HbA_{1c}$. Moreover, in these studies type 2 diabetes was self-reported during telephone interviews. To support ADA recommendations, we evaluated diabetes risk in the 6.00–6.49% category of $HbA_{1c}$, with a more robust approach based on laboratory measurement of glycemic parameters.

## RESEARCH DESIGN AND METHODS

The study was conducted within the framework of the Bruneck Study, a long-term, prospective population-based survey of atherosclerosis and its risk factors carried out in Bruneck (northeastern Italy), with a baseline evaluation in 1990 (5). Among 1,000 randomly sampled Caucasian men and women aged 40–79 years, 936 volunteered. After excluding the few individuals with incomplete data, those with diabetes at baseline, and the very few lost to follow-up, in the remaining 842 subjects new cases of type 2 diabetes were registered in the follow-up examinations of 1995, 2000, and 2005. The protocol was approved by the ethics committee of the University of Verona. All participants gave an informed consent.

### Clinical and biochemical measurements

Information about medical history, drug use, and lifestyle was collected by a questionnaire. Weight, height, waist and hip circumferences, and blood pressure were measured with standard techniques. At the baseline and follow-up examinations, venous blood was sampled in the morning after an overnight fast for laboratory measurements, including fasting plasma glucose (FPG) and $HbA_{1c}$ (Diabetes Control and Complications Trial–aligned assay; equipment and reagents from Bio-Rad, Milan, Italy, at both baseline and follow-up examinations). At both baseline and follow-up, diabetes was diagnosed when $HbA_{1c}$ was ≥6.5% or diabetes treatment was ongoing. In a parallel analysis, diabetes was diagnosed when FPG was ≥7.0 mmol/L or diabetes treatment was ongoing. Details on parameters examined and analytical procedures were previously reported (5,6).

### Statistical analysis

Subjects were stratified into four $HbA_{1c}$ categories (<5.0, 5.00–5.49 [reference], 5.50–5.99, and 6.00–6.49%). The $HbA_{1c}$ category 5.00–5.49% had the largest number of participants ($n$ = 345) and was used as the reference. Hazard ratios (HRs) for type 2 diabetes in the $HbA_{1c}$ categories were estimated with Cox proportional hazards models. Model 0 was unadjusted. Model 1 included age and sex. Model 2 also included LDL and HDL cholesterol, log-transformed triglycerides, BMI, waist-to-hip ratio, hypertension, family history of diabetes, education, alcohol, physical activity, and smoking. Model 3 included the variables in model 2 plus variables that are abnormal in conditions potentially affecting $HbA_{1c}$ (white blood cell count, hemoglobin, ferritin, and creatinine). Additional models were run with updated variables

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($HbA_{1c}$ and other variables were assessed every 5 years during follow-up). In these models, baseline $HbA_{1c}$ predicted diabetes in the first 5-year follow-up period, $HbA_{1c}$ at the 5-year follow-up predicted diabetes in the following 5-year follow-up, and so forth in multivariable equations overcoming the limitations of single measures. In parallel analyses, the same models were run with impaired fasting glucose (IFG) as a risk variable, and diabetes was diagnosed with FPG at baseline and follow-up. All reported *P* values are two-sided.

**RESULTS**—The table shows that incident cases of type 2 diabetes increased across categories of $HbA_{1c}$: approximately one of four subjects from the 6.00–6.49% category (high normal) developed diabetes over 15 years. In this category, type 2 diabetes risk was 13- to 16-fold increased (models 0 and 1). The risk was only slightly reduced after adjusting for several putative confounding factors (models 2 and 3) and was definitely greater when updated variables were included into the models (Table 1). Analyses including interaction terms between $HbA_{1c}$ categories and factors that might affect interpretation of $HbA_{1c}$ (i.e., white blood cell count, hemoglobin, ferritin, and creatinine) did not yield evidence of differential associations according to $HbA_{1c}$ level, supporting the lack of effect modification.

In parallel analyses in which diabetes was diagnosed at both baseline and follow-up with FPG, and in which subjects at risk were those in the IFG category, we found that the latter conferred an increased diabetes risk (HRs [95% CIs] in subjects with IFG vs. normal FPG [<5.55 mmol/L]: 8.20 [4.66–14.40], 7.72 [4.36–13.66], 5.83 [3.23–10.54], and 5.92 [3.24–10.80] in the four models, respectively). These models included the same variables as those focusing on $HbA_{1c}$. However, diabetes risk in subjects with IFG was substantially lower than in subjects with high-normal $HbA_{1c}$.

**CONCLUSIONS**—It is well known that $HbA_{1c}$ captures chronic hyperglycemia in the prior 2–3 months, is well correlated to chronic diabetes complications, and has less preanalytical problems and biological variability than plasma glucose, with a noninferior standardization (7). For such reasons, $HbA_{1c}$ was recommended for diabetes diagnosis and risk stratification (1,2).

The findings of the current study confirm a progressively increased risk of type 2 diabetes across categories of $HbA_{1c}$ and clearly document that subjects with high-normal $HbA_{1c}$ have a strong risk of developing type 2 diabetes, even after adjusting for several putative risk factors (e.g., BMI) and potentially confounding variables (e.g., anemia). Remarkably, diabetes risk in subjects with high-normal $HbA_{1c}$ is higher than in subjects with IFG.

Noteworthy, our study population was entirely Caucasian, and subjects were aged >40 years. Therefore, our findings cannot be necessarily extrapolated to other ethnicities and/or to younger subjects.

To the best of our knowledge, this study is the first to examine how baseline $HbA_{1c}$ predicts $HbA_{1c}$-diagnosed diabetes. Our findings, which are consistent with those of studies based on self-reported diagnosis of diabetes (3,4), more strongly support the ADA recommendations of using $HbA_{1c}$ for diabetes risk stratification

**Table 1—*HRs for 15-year incidence of type 2 diabetes according to $HbA_{1c}$***

| | $HbA_{1c}$ category | | | |
|---|---|---|---|---|
| | <5.00% | 5.00–5.49% | 5.50–5.99% | 6.00–6.49% |
| *n* | 112 | 345 | 315 | 70 |
| Cases of incident diabetes | 3 | 9 | 31 | 20 |
| Cases per 1,000 person-years | 1.9 | 1.9 | 7.8 | 25.8 |
| | HRs (95% CIs) in models with baseline variables* | | | |
| | Model 0 | Model 1 | Model 2 | Model 3 |
| $HbA_{1c}$ category | | | | |
| <5.00% | 1.00 (0.27–3.68) | 1.11 (0.30–4.14) | 1.18 (0.31–4.41) | 1.27 (0.34–4.79) |
| 5.00–5.49% (reference) | 1.00 | 1.00 | 1.00 | 1.00 |
| 5.50–5.99% | 4.30 (2.05–9.03) | 3.79 (1.79–8.06) | 3.24 (1.50–6.98) | 3.21 (1.49–6.92) |
| 6.00–6.49% | 15.67 (7.13–34.47) | 12.50 (5.51–28.34) | 9.74 (4.21–22.56) | 9.26 (4.01–21.40) |
| *P* value for trend | <0.001 | <0.001 | <0.001 | <0.001 |
| $HbA_{1c}$ (per 1% increase) | 11.00 (5.66–21.39) | 8.54 (4.21–17.31) | 6.08 (2.96–12.47) | 6.05 (2.90–12.60) |
| | HRs (95% CIs) in models with updated variables† | | | |
| | Model 0 | Model 1 | Model 2 | Model 3 |
| $HbA_{1c}$ category | | | | |
| <5.00% | 2.31 (0.39–13.92) | 2.55 (0.42–15.39) | 2.55 (0.42–15.58) | 2.43 (0.40–14.97) |
| 5.00–5.49% (reference) | 1.00 | 1.00 | 1.00 | 1.00 |
| 5.50–5.99 | 12.58 (3.83–41.30) | 11.62 (3.52–38.36) | 10.97 (3.30–36.47) | 11.43 (3.43–38.07) |
| 6.00–6.49% | 61.05 (18.23–204.4) | 52.82 (15.57–179.3) | 45.52 (13.1–158.0) | 46.72 (13.4–163.3) |
| *P* value for trend | <0.001 | <0.001 | <0.001 | <0.001 |
| $HbA_{1c}$ (per 1% increase) | 41.37 (18.79–91.07) | 36.82 (16.30–83.21) | 31.10 (13.31–72.7) | 32.24 (13.60–76.41) |

Model 0 was unadjusted. Model 1 included age and sex. Model 2 included the variables in model 1 plus LDL and HDL cholesterol levels, log-transformed triglyceride levels, BMI, waist-to-hip ratio, hypertension, family history of diabetes, education, alcohol use, physical activity score, and smoking status. Model 3 included all variables in model 2 plus white blood cell count, hemoglobin, ferritin, and creatinine. *Cox models in which $HbA_{1c}$ and other variables at baseline were used to predict diabetes in the 15-year follow-up. †Cox models in which updated $HbA_{1c}$ and other variables were used to predict diabetes in subsequent 5-year follow-up periods (see text for details).

and including subjects with high-normal levels in an effective prevention strategy. These subjects, indeed, have a high rate of progression to diabetes and deserve particular attention in order to prevent or delay the disease. Specific intervention trials, however, are needed to confirm such a conclusion because those conducted so far, based on lifestyle changes and/or drug use, recruited subjects at risk according to their plasma glucose levels and not $HbA_{1c}$.

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