Hemoglobin A_{1c} levels were associated with increased cardiovascular disease and all-cause mortality in persons with and without diabetes

Khaw KT, Wareham N, Bingham S, et al. **Association of hemoglobin A_{1c} with cardiovascular disease and mortality in adults: the European Prospective Investigation into Cancer in Norfolk.** Ann Intern Med. 2004;141:413-20.

QUESTION

What is the relation between hemoglobin (Hb) A_{1c} levels and coronary heart disease (CHD) events, cardiovascular disease (CVD) events, and all-cause mortality?

METHODS

Design: Cohort study (European Prospective Investigation into Cancer in Norfolk [EPIC-Norfolk]) with a mean follow-up of 6 years.

Setting: Norfolk, England, United Kingdom.

Patients: 10 232 patients 45 to 79 years of age (54% women, 2.4% with diabetes) who were recruited from general practice registers and had baseline data on a health and lifestyle questionnaire and HbA_{1c} levels.

Risk factors: HbA_{1c} levels, known diabetes, age, body mass index, waist-to-hip ratio, systolic blood pressure, cholesterol levels, triglyceride levels, cigarette smoking, and history of heart attack or stroke.

Outcomes: CHD events (hospital admission or death from CHD), CVD events (hospital admission or death from CHD, stroke, or other vascular causes), and all-cause mortality.

MAIN RESULTS

Persons with known or undiagnosed diabetes had a greater risk for all-cause mortality and CVD or CHD events than did those without diabetes. A gradient of increasing rates of all-cause mortality, CHD, and CVD was found for the entire distribution of HbA_{1c} levels in men and women ($P < 0.001$ for linear trend).

Regression analyses adjusted for age and other risk factors (except for HbA_{1c} level) showed that compared with persons without diabetes, men with diabetes had a higher risk for CHD events, CVD events, and all-cause mortality, and women with diabetes had an increased risk for CHD events and CVD events (Table). In a regression analysis that did not adjust for diabetes, HbA_{1c} levels predicted an increased risk for CHD, CVD, and all-cause mortality in both men and women. A 1% increase in HbA_{1c} level was associated with a 20% to 30% increase in event rates. When the regression model included both diabetes and HbA_{1c} levels, similar relative risks for an increase in HBA_{1c} were noted, but diabetes was no longer a significant risk factor.

CONCLUSIONS

A 1% increase in hemoglobin A_{1c} levels was associated with a 20% to 30% increase in cardiovascular events and all-cause mortality in men and women 45 to 79 years of age. This relation was independent of diabetes status.

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Adjusted relative risk (RR) for coronary heart disease events, cardiovascular disease events, and all-cause mortality by hemoglobin (Hb) A_{1c} levels and history of diabetes*

Outcomes at mean 6 y	Adjusted RR (95% CI) per 1% increase in HbA_{1c} level		Adjusted RR (CI) for diabetes history (yes vs no)	
	Men	Women	Men	Women
Coronary heart disease	1.25 (1.16 to 1.34)	1.20 (1.07 to 1.34)	1.87 (1.30 to 2.71)	2.71 (1.48 to 4.98)
Cardiovascular disease	1.21 (1.13 to 1.29)	1.21 (1.11 to 1.31)	1.81 (1.31 to 2.49)	1.89 (1.09 to 3.23)
All-cause mortality	1.24 (1.14 to 1.34)	1.28 (1.06 to 1.32)	1.94 (1.31 to 2.87)	0.71 (0.26 to 1.93)†

*Adjusted for age and cardiovascular risk factors (systolic blood pressure, serum cholesterol level, body mass index, waist-to-hip ratio, cigarette smoking, and history of myocardial infarction or stroke).

†Not significant.

COMMENTARY

Diabetes mellitus is a major risk factor for CVD, and unlike hypertension, smoking, and dyslipidemia, it is becoming more common over time.

The diagnostic criteria for diabetes include fasting plasma glucose levels ≥ 7.0 mmol/L or 2-hour postload plasma glucose levels ≥ 11.1 mmol/L, values above which the risk for *microvascular* complications of diabetes, such as retinopathy, neuropathy, and nephropathy, increases. These values correspond approximately to an HbA_{1c} level of 7%. However, there is considerable epidemiologic evidence that the risk for CVD begins to increase at lower glycemic levels than would be considered "abnormal"—levels that would not be associated with increased microvascular disease risk (1). The study by Khaw and colleagues adds to this evidence because of its large study population and particularly large number of female participants.

In this study, 72% of the excess CVD risk that was attributable to higher HbA_{1c} levels occurred in patients with HbA_{1c} levels of 5.0% to 6.9%. In light of this evidence, perhaps the cutpoint for a "normal" HbA_{1c} level should be revised downward, as has been done for cholesterol and blood pressure. It would also be desirable to develop and validate cardiovascular risk calculators that include HbA_{1c} level as a predictor variable, as has been done for patients with type 2 diabetes in the UKPDS Risk Engine (2). In the meantime, HbA_{1c} levels provide an additional measure of an individual patient's CVD risk.

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References

1. **Selvin E, Marinopoulos S, Berkenblit G, et al.** Meta-analysis: glycosylated hemoglobin and cardiovascular disease in diabetes mellitus. Ann Intern Med. 2004;141:421-31.
2. **Stevens RJ, Kothari V, Adler AI, Stratton IM.** The UKPDS risk engine: a model for the risk of coronary heart disease in Type II diabetes (UKPDS 56). Clin Sci (Lond). 2001;101:671-9.