Impaired fasting glucose and impaired glucose tolerance, as well as known diabetes, increased risk for death within 5 years

Barr EL, Zimmet PZ, Welborn TA, et al. **Risk of cardiovascular and all-cause mortality in individuals with diabetes mellitus, impaired fasting glucose, and impaired glucose tolerance. The Australian Diabetes, Obesity, and Lifestyle Study (AusDiab).** Circulation. 2007;116:151-7.

Clinical impact ratings: GIM/FP/GP ★★★★★☆☆ Cardiology ★★★★★☆☆ Endocrinology ★★★★★☆☆

QUESTION

What is the contribution of different categories of abnormal glucose metabolism to risk for all-cause and cardiovascular disease (CVD) mortality?

METHODS

Design: Prospective cohort study with median 5.2 years follow-up.

Setting: Population-based study in 42 randomly selected districts across Australia.

Participants: 10 428 noninstitutionalized persons ≥ 25 years of age (mean age 51 y, 55% women) who attended a biomedical examination after completing a household interview.

Risk factors: Based on baseline fasting plasma glucose (FPG) level and 2-hour plasma glucose (PG) level after a 75-g oral glucose tolerance test, participants were categorized as having known diabetes (4%) (reported physician-diagnosed diabetes and were taking hypoglycemic medication or had FPG ≥ 7.0 mmol/L or 2-h PG ≥ 11.1 mmol/L), newly diagnosed diabetes (4%) (did not report having diabetes but had FPG ≥ 7.0 mmol/L or 2-h PG ≥ 11.1 mmol/L), impaired glucose tolerance (12%) (FPG < 7.0 mmol/L and 2-h PG 7.8 to 11.0 mmol/L), impaired fasting glucose (6%) (FPG 6.1 to 6.9 mmol/L and 2-h PG < 7.8 mmol/L), or normal glucose tolerance (73%) (FPG < 6.1 mmol/L and 2-h PG < 7.8 mmol/L).

Outcomes: All-cause and CVD mortality (determined by linkage with the Australian National Death Index).

MAIN RESULTS

After other risk factors were adjusted for, risk for all-cause mortality was increased in persons with impaired fasting glucose, impaired glucose tolerance, and known diabetes compared with persons with normal glucose tolerance (Table). Risk for CVD mortality was increased in persons with impaired fasting glucose and known diabetes (Table). The pattern was similar for men and women.

CONCLUSIONS

Persons ≥ 25 years of age with impaired fasting glucose and impaired glucose tolerance, as well as known diabetes, had increased risk for death within 5 years compared with those with normal glucose levels. After other risk factors were adjusted for, the increase in risk for death from cardiovascular causes was similar in persons with impaired fasting glucose and those with known diabetes.

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Different categories of abnormal glucose metabolism as risk factors for all-cause and cardiovascular disease (CVD) mortality at median 5.2 years*

Risk category	Unadjusted mortality rate	Adjusted hazard ratios (95% CI)	
		All-cause mortality	CVD mortality
Normal glucose tolerance	1.7%	1.0 (reference)	1.0 (reference)
Impaired fasting glucose	3.9%	1.6 (1.0 to 2.4)	2.5 (1.2 to 5.1)
Impaired glucose tolerance	5.2%	1.5 (1.1 to 2.0)	1.2 (0.7 to 2.2)
Newly diagnosed diabetes	6.2%	1.3 (0.9 to 2.0)	1.8 (0.9 to 3.6)
Known diabetes	11.8%	2.3 (1.6 to 3.2)	2.6 (1.4 to 4.7)

*CI defined in Glossary. Hazard ratios adjusted for other risk factors, such as age, sex, history of CVD, smoking, blood pressure, waist circumference, and dyslipidemia.

COMMENTARY

The AusDiab investigators reported a graded relation between glycemia (categorized according to World Health Organization criteria) and all-cause and CVD mortality. Similar results have been reported with hemoglobin (Hb) A_{1c}: Every 1% increase in HbA_{1c} is associated with a 22% to 28% increase in mortality (1). Absence of HbA_{1c} is an important study limitation.

The conclusions of this study are clear-cut and consistent with those of many other studies—dysglycemia is a risk marker for mortality. However, we have no evidence from randomized trials that improving dysglycemia reduces mortality. Indeed, a jaded observer might say that the nearly 2-fold difference in mortality between "undiagnosed (= untreated)" and "diagnosed (= treated)" diabetes reported by Barr and colleagues occurred because our current therapeutic armamentarium lowers blood sugar but increases such adverse events as weight gain and non-CVD mortality. Like Barr and colleagues, other researchers have reported increased cancer-related mortality among persons with dysglycemia; 1 study even reported that sulfonylureas and insulin, but not metformin, increased risk for cancer-related mortality (2).

Across dysglycemia categories, Barr and colleagues observed progressive increases in mean age (49 to 64 y), body mass index (26 to 30 kg/m^2), waist circumference (88 to 102 cm), systolic blood pressure (126 to 144 mm Hg), and related variables. The ability of traditional multivariable techniques to adjust for these differences aside, dysglycemia seems to be a marker for some underlying genetic or behaviorally determined cluster of risks. It would be more useful to demonstrate how many patients with dysglycemia would be "reclassified" as having sufficient additional 10-year risk to warrant guideline-concordant treatments for hypertension and dyslipidemia—I suspect few.

We do not know if labeling patients as "prediabetic" is motivating or harmful; we have few safe and clinically effective pharmacologic means to lower blood sugar (even for persons with diabetes). So for now, this study only adds to a burgeoning dysglycemia literature that demands evidence from randomized trials before any changes are made to clinical practice.

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