Now, results from a total of three randomised studies that have tested metformin in patients without diabetes (MetCAB[1], CAMERA[7], and GIPS-III[8]) have not shown an effect of metformin on cardiovascular outcomes. In CAMERA,[7] metformin (850 mg twice per day) given to 173 patients without diabetes did not result in a significant reduction in the primary outcome measure of carotid intima-media thickness after 18 months. In GIPS-III,[8] metformin (500 mg twice per day) given to 380 patients without diabetes was not associated with a significant effect on left ventricular ejection fraction compared with placebo after 4 months. In our opinion, the results from these studies show how far standard care for cardiovascular patients without diabetes has advanced; as a consequence, the potential benefit of any additional intervention is small. In all three trials the mortality rate was very low—in MetCAB,[1] all patients were alive 30 days after surgery; in CAMERA, only one cardiovascular death occurred over an 18-month follow-up period;[7] and in GIPS-III, all patients were alive 4 months after acute myocardial infarction.[8] Moreover, peak troponin I concentrations in all patients in the MetCAB trial were only 50% of those in the historical cohort that was the basis of the investigators' power calculation.[1] According to the power calculation, to show any effect, metformin needed to lower postoperative troponin I concentrations by an additional 50%. Thus, the expected effect of metformin in patients without diabetes treated to current standards might have been too high.

Taking together the results of all studies on metformin in patients without diabetes so far, no proof exists for a beneficial effect of metformin on cardiovascular outcomes. Much larger trials—ie, with thousands of high-risk patients—might identify protective effects of metformin in such patients; however, undertaking such large investigator-driven studies is extraordinarily challenging. Nevertheless, metformin reduces hyperglycaemia in patients with or without diabetes, and glucose reduction, or the absence of hyperglycaemia, is pivotal for a potential beneficial effect of metformin on cardiovascular outcomes.

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Which biochemical assay is best for measuring diabetes prevalence?

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Accurate assessments of diabetes prevalence are needed to allocate resources for treating patients and monitoring treatment coverage. Researchers need methods of making population-wide assessments of diabetes that are cost effective, precise, and reliable.

Because up to half of all diabetes cases might be undiagnosed,[1] one of three biochemical tests are used to estimate diabetes prevalence. Fasting plasma glucose (FPG) is a measure of glucose concentrations after the person has refrained from eating or drinking anything other than water for 12 h. The oral glucose tolerance test (OGTT) measures the changes in blood glucose after a fixed amount of glucose has been administered. HbA_{1c} does not directly measure blood glucose, but represents the average amount of glucose in the blood in the past 2–3 months.[2] The degree to which these different measures correlate in diverse geographical and ethnic populations has largely been unanswered.

The question of whether these measures give comparable results is particularly important when comparing data from resource-poor countries. Diabetes affects an estimated 8·3% of adults (aged 20–79 years) worldwide, and varies with geographical region, from 5·1% in sub-Saharan Africa to 11·4% in North America and the Caribbean.[1] At present, high quality diabetes surveys are available for only 57% of 221 countries and territories worldwide, and only 19% of countries have OGTT-based results.[1] Instead, many countries with limited resources use the simple and standardised WHO STEPwise approach to Surveillance (STEPS) protocol for risk factor surveillance, published in 2005. The STEPS core risk factors include demographic information, health behaviours, BMI, waist circumference, and blood pressure. WHO recommends that well-resourced countries also analyse FPG, with an optional module for OGTT.[3]

When it was first correlated to FPG in the late 1970s, HbA_{1c} was unstandardised.[4] However, by 2009, technology had improved to such a degree that an international expert committee appointed by the American Diabetes Association, the European Association for the Study of Diabetes, and the International Diabetes Federation recommended that a standardised HbA_{1c} test done in a laboratory could be used to diagnose type 2 diabetes.[5] An HbA_{1c} of 6·5% (48 mmol/mol) or higher is diagnostic for diabetes, although a value below this threshold does not exclude diabetes.

In *The Lancet Diabetes & Endocrinology*, the NCD Risk Factor Collaboration has done a global meta-analysis of various methods of assessing national and subnational prevalence of diabetes.[6] They concluded that prevalence estimates based on FPG only and those based on FPG or 2hOGTT had a very strong correlation (r=0·98), and HbA_{1c}-based definitions had a lower (although still strong) correlation (r=0·91) with FPG-based definitions. Prevalence based on HbA_{1c} was lower than prevalence based on FPG in 42·8% of cases and higher in 41·5%. HbA_{1c} was less sensitive than FPG only and than FPG or 2hOGTT for detecting undiagnosed diabetes. The identification of previously undiagnosed diabetes based on HbA_{1c} had a pooled specificity (true negative rate) of 99·7% and a pooled sensitivity (true positive rate) of 52·8% compared with FPG, and a sensitivity of 30·5% compared with FPG or 2hOGTT.[6]

These results will affect the design of epidemiological studies. Researchers should consider resources and population characteristics when deciding whether to use FPG, OGTT, or HbA_{1c} tests. Testing FPG is faster than testing OGTT, and needs less equipment and staff training. However, it does require the person to have fasted, which cannot be guaranteed. An HbA_{1c} test can be done at any time, requires no fasting or glucose consumption, and the sample is relatively stable at room temperature. However, the HbA_{1c} test must be standardised and done in a certified laboratory, and cannot be used in a population with a condition that changes red blood cell turnover, such as chronic malaria.[5] Furthermore, the NCD Risk Factor Collaboration reported that the relation between glucose-based and HbA_{1c}-based prevalences varied with national income, year of study, and BMI.[6] This finding, together with the reduced sensitivity in detecting undiagnosed diabetes, suggests that, under existing diagnostic criteria, an HbA_{1c} test should be supplemented with a glucose-based test in assessments of population-level prevalence.

Nevertheless, the high degree of correlation reported by the NCD Risk Factor Collaboration suggests some flexibility might be possible in using different measurement strategies in different contexts, increasing the ease of producing a worldwide estimate of present and future epidemiological patterns for diabetes.

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