Fasting glucose and glycated haemoglobin (HbA1c) levels may both be useful to predict diabetes, according to the results of population-based analyses reported online September 20 in Diabetes Care.

"Although HbA1c is now recommended to diagnose diabetes, its test performance for diagnosis and prognosis is uncertain," writes Elizabeth Selvin, from the Johns Hopkins Bloomberg School of Public Health in Baltimore, and colleagues. "Our objective was to assess the test performance of HbA1c against single and repeat glucose measurements for diagnosis of prevalent diabetes and for prediction of incident diabetes."

The study sample consisted of 12,485 participants enrolled in the Atherosclerosis Risk in Communities (ARIC) Study and a subpopulation of 691 participants in the Third National Health and Nutrition Examination Survey (NHANES III) who had repeated glucose test results available.

For detection of prevalent diabetes against a single FBG of 7 mmol/l or more, the sensitivity of an HbA1c level of at least 6.5 % was 47 %, and the specificity was 98 % (AUC, 0.892). Against fasting glucose measurements of 7 mmol/l or more repeated at an interval of 3 years, the sensitivity of an HbA1c level of at least 6.5 % improved to 67 %, whereas the specificity was still high at 97 % (AUC, 0.936).

In NHANES III, findings were similar with use of FBG repeated 2 weeks apart. For groups based on age, body mass index, and race, HbA1c had consistent accuracy. The 10-year risk for diagnosed diabetes was 88 % for persons with a FBG of at least 7 mmol/l and an HbA1c level of at least 6.5 % at baseline vs. 55 % for those with a FBG of at least 7 mmol/l and an HbA1c level of 5.7 % to less than 6.5 %.

HbA1c performs well as a diagnostic tool when diabetes definitions that most closely resemble those used in clinical practice are used as the gold standard. The high risk of diabetes among initially undiagnosed persons with both elevated FBG and HbA1c suggests a dual role for fasting glucose and HbA1c for prediction of diabetes.

Limitations of this study include lack of head-to-head comparison of the accuracy of glucose vs. HbA1c; small number of cases of diabetes in the NHANES III subsample, resulting in imprecise estimates and preventing further subgroup analyses; and lack of 2-hour glucose data at the time of HbA1c measurement in the ARIC Study.

In conclusion, HbA1c performs best when more stringent glucose criteria are used to define diabetes (i.e., FBG ≥ 7 mmol/l on two separate occasions), similar to clinical practice. The data support current (US) recommendations for use of HbA1c in the diagnosis of diabetes and demonstrate that an HbA1c cut-off of 6.5 % is highly specific and may be reasonably sensitive in the context of evidence linking HbA1c to risk of long-term microvascular and macrovascular outcomes in non-diabetic adults. HbA1c and FBG both strongly predict subsequent risk of diagnosed diabetes but the very high risk observed for persons with both elevated FBG and HbA1c suggests a dual role for fasting glucose and HbA1c for prediction of diabetes.

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Stenting versus Endarterectomy for Treatment of Carotid Artery Stenosis

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**Background** Carotid-artery stenting and carotid endarterectomy are both options for treating carotid-artery stenosis, an important cause of stroke.

**Methods** Patients with symptomatic or asymptomatic carotid stenosis were randomly assigned to undergo carotid-artery stenting or carotid endarterectomy. The primary composite end point was stroke, myocardial infarction, or death from any cause during the peri-procedural period or any ipsilateral stroke within 4 years after randomisation.

**Results** For 2502 patients over a median follow-up period of 2.5 years, there was no significant difference in the estimated 4-year rates of the primary end point between the stenting group and the endarterectomy group (7.2% and 6.8%, respectively; hazard ratio with stenting, 1.11; 95% confidence interval, 0.81 to 1.51; P=0.51). There was no differential treatment effect with regard to the primary end point according to symptomatic status (P=0.84) or sex (P=0.34). The 4-year rate of stroke or death was 6.4% with stenting and 4.7% with endarterectomy (hazard ratio, 1.50; P=0.03); the rates among symptomatic patients were 8.0% and 6.4% (hazard ratio, 1.37; P=0.14), and the rates among asymptomatic patients were 4.5% and 2.7% (hazard ratio, 1.86; P=0.07), respectively. Peri-procedural rates of individual components of the end points differed between the stenting group and the endarterectomy group: for death (0.7% vs. 0.3%, P=0.18), for stroke (4.1% vs. 2.3%, P=0.01), and for myocardial infarction (1.1% vs. 2.3%, P=0.03). After this period, the incidences of ipsilateral stroke with stenting and with endarterectomy were similarly low (2.0% and 2.4%, respectively; P=0.85).

**Conclusions** Among patients with symptomatic or asymptomatic carotid stenosis, the risk of the composite primary outcome of stroke, myocardial infarction, or death did not differ significantly in the group undergoing carotid-artery stenting and the group undergoing carotid endarterectomy. During the peri-procedural period, there was a higher risk of stroke with stenting and a higher risk of myocardial infarction with endarterectomy. (ClinicalTrials.gov number, NCT00004732 [ClinicalTrials.gov]).

**B12 Deficiencies Increase with Longer Metformin Treatment**

Chronic metformin use increases the risk of developing vitamin B12 deficiency, and is likely to worsen over time if not monitored for and corrected. Though shorter studies have shown that metformin induces Vit B12 malabsorption, little is known about the effect in the long term. Vit B12 deficiencies can cause anaemia, mental changes and neuropathy, among other effects; they can cause elevated homocysteine levels, an independent risk factor for CVD.

The new findings suggest that metformin’s deleterious effect on vit B12 levels can continue with the duration of metformin therapy to clinical deficiency (<150 pmol/L). Jolien de Jager, et al randomised 390 patients already on insulin to placebo or metformin 850 mg tds for 4.3 years, with B12, Folate and homocysteine levels measured at baseline, 4 months, and yearly to 52 months (BMJ 2010;340:c2181[doi:10.1136/bmj.c2181]). 196 patients were assigned to the metformin (mean age 64) and 194 to placebo (mean age 59). Of those, 131 patients on metformin and 146 on placebo completed the study and were included in the final analysis.

The metformin group had a mean decrease in B12 concentrations of 19% from baselines, compared with subjects on insulin and placebo. The number of metformin patients with B12 deficiencies increased over the course of the study, from 3 at baseline to 19 at 52 months, compared with a much smaller increase (from 4 patients to 5) in the placebo group.

Absolute risk of B12 deficiency was 7.2% higher in the metformin group; risk of developing low B12 (150-220 pmol/L), was 11.2% higher in the metformin group. This decrease is not a transitory phenomenon, but persists and grows over time. The folate concentrations decreased by 5% from baseline in the metformin group, compared with placebo, and a 5% increase in homocysteine levels. However, the placebo group had a higher proportion of smokers and higher BMI, and no statistically significant differences in folate concentration was found after adjusting for those factors. Nor did they find differences in folate concentration over time. Homocysteine levels increased the most in subjects whose B12 levels had decreased. One limitation of the study was that all study subjects received frequent nutrition counselling, the likelihood of vitamin deficiency may have been decreased in the study population, compared with that in the population at large. There is a strong case for routine assessment of B-12 levels during long term treatment with metformin.

It is recommended that regular measurement of vitamin B-12 concentrations during long-term metformin treatment should be considered. The study also raised questions about how and how often to monitor for B12 deficiency, and how to treat it. It is not clear what form the intervention should take, as options could include dietary changes, supplements, and intramuscular injections.
Effects of Intensive Glucose Control on Cardiovascular Events

Trials have shown that intensive glucose control (IGC) in type 2 diabetes (T2DM) reduces progression of microvascular disease, but effect on macrovascular complications remains uncertain. In epidemiological studies the association between glucose control and CVD has been inconsistent. Two studies reported no significant decrease in cardiovascular events (CVE) with IGC. The ACCORD trial ended its IGC early, after 3.5 years, because of significant increase in deaths in the IGC group. The primary goal of the VADT was to compare the effects of IGC and standard glucose control (SGC) on cardiovascular events.

Commentary

Duckworth et al. recently reported the results of a large, multicentre, randomized, controlled trial, which studied the effects of IGC on CVE in long-standing T2DM. In this study, 1,791 veterans (mean age, 60.4 years), who had a suboptimal response to therapy for T2DM, were randomly assigned to receive either IGC or SGC. The goal in the IGC group was an absolute reduction in the HbA1c of 1.5 %, as compared with the SGC group. The primary outcome was the time from randomization to the first occurrence of a major CVE. The median follow-up was 5.6 years. No differences in microvascular complications, and major CVE and death were observed between the groups.

Many large studies published during 2008 investigated the effects of IGC on CVE. The ACCORD study (N Engl J Med 2008;358:2545-59) showed increased mortality among IGC treated T2DM, while the ADVANCE study (N Engl J Med 2008;358:2560-72) showed a reduction in microvascular complications. The present VADT study demonstrated no effect in the study population. Previous studies, including the UKPDS (BMJ 2000;321:405-12) of T2DM patients and the DCCT (N Engl J Med 1993;329:977-86) in patients with type 1 diabetes, have shown that IGC reduces the incidence of microvascular complications linked to diabetes in the short term, and the incidence of both microvascular and macrovascular complications in the long term.


Summary

The effects of IGC on CVE in patients with long-standing type 2 diabetes (T2DM) remain uncertain. A total of 1,791 military veterans (mean age 60.4 years), who had a suboptimal response to therapy for T2DM, were randomly assigned to receive either IGC or SGC. Other cardiovascular risk factors were treated uniformly. The mean time since the diagnosis of diabetes was 11.5 years. 40 % of patients had already had a CVE. The goal in the IGC group was an absolute reduction of 1.5 % in the HbA1c, as compared with the SGC group. The primary outcome was the time from randomization to the first occurrence of a major CVE, a composite of myocardial infarction, stroke, death from CV causes, congestive heart failure, surgery for vascular disease, inoperable coronary disease and amputation for ischaemic gangrene. The median follow-up was 5.6 years. Median HbA1c levels were 8.4 % in the SGC group and 6.9 % in the IGC group. The primary outcome occurred in 264 patients in the SGC group and 235 patients in the IGC group (hazard ratio [HR] in the IGC group 0.88; 95% confidence interval [CI], 0.74-1.05; p = 0.14). There was no significant difference between the 2 groups in any component of the primary outcome or in the rate of death from any cause (HR 1.07; 95 % CI 0.81-1.42; p = 0.62). No differences in microvascular complications were observed between the 2 groups. The rates of adverse events, predominantly hypoglycaemia, were 17.6 % in the SGC group and 24.1 % in the IGC group.

The authors concluded that intensive glucose control in patients with poorly controlled T2DM had no significant effect on the rates of major cardiovascular events, death, or microvascular complications.

References


The Obesity Paradox

Two-thirds of Americans are obese or overweight. The Centers for Disease Control has declared that obesity is at epidemic proportions in the United States. Obesity is a risk factor for many diseases, such as diabetes mellitus, hypertension, stroke, and heart and renal disease. Despite this relationship, obese people with these diseases live longer than their normal-weight counterparts. This conundrum has been called the "obesity paradox." But let's examine the data.

The Obesity Paradox is best studied in congestive heart failure, showing that obese patients have a better prognosis than leaner ones. Of note, none of the congestive heart failure trials have found obesity to worsen the prognosis.

The obesity paradox has also been described for other diseases, including coronary artery disease, hypertension, stroke and in dialysis patients. Cachexia from advanced disease was at first thought to be the explanation. These findings, however, show a continuous dose-response reduction in mortality across a gradation of body mass index values. And in many of these studies, the lowest body mass index was calculated to have a healthy percentage of body fat and not at levels consistent with a malnourished state.

How do we explain the obesity paradox? In short, the answer is unknown, but there are several possibilities. First, obese patients may present earlier with less disease burden. Second, obese patients may be more aggressively treated. Third, adipose tissue may secrete protective cytokines and other hormonal products. Finally, these findings are associative, but do not prove a cause-and-effect relationship.

So can we have our cake and eat it too? Based on the data at hand, it is likely that the obesity paradox is a real association, but what it means for the recommendations and treatment of our patients is food for thought.

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Autoimmune Diabetes: a Spectrum of Disease

Numerous screening procedures are proposed in diabetes. However, such proposals should be approached with care as they are likely to result in expensive diabetes programmes. The paper by Leslie et al. discusses latent autoimmune diabetes in adults (LADA) in relation to type 1 diabetes and the spectrum of diseases related to it [2]. A careful scientific review is provided of the spectrum of LADA versus type 1 diabetes. However, the review's relevance for the practising diabetologist must be questioned until the clinical trials discussed in the paper have been completed, and they are set to last several years. The paper is of theoretical interest and of interesting scientific value, but I am sceptical regarding its value in terms of medicine in daily practice. The paper does not provide any significant justification for the suggestion that one should screen for LADA. Obviously, it could be of interest to ascertain whether a patient has type 1 diabetes or LADA. The finding of glutamic acid decarboxylase (GAD) antibodies can reveal that a patient may be mimicking T2DM when, in actual fact, the correct diagnosis is type 1 DM. Such antibodies cannot be documented in patients with type 2 diabetes, or in patients with diabetes secondary to chronic pancreatitis, for example. Positive GAD antibodies can therefore provide a correct diabetes classification. The question is, what does this mean in clinical practice?

We do not screen for GAD antibodies, because the results would not influence our clinical practice. Whether patients with GAD antibodies actually need a different treatment is open to question. Obviously, they may need treatment with insulin earlier than the typical T2DM. However, there is a huge overlap and many patients with T2DM in fact need insulin. Obviously, the situation may change if we have new treatment strategies for patients classified as LADA, but this is really not the case at present. Ongoing studies, as organised by the authors of the paper, include a prevention trial with Diapep 277. This is a running double-blind placebo-controlled trial in patients with LADA, probably including approximately 350 patients throughout Europe. In my mind, we have to await the results of this trial before we can start to screen for LADA in general practice. Obviously, in selecting patients (who may be lean and with a high level of HbA1c), it may be interesting to perform a screening, but I cannot see that this would change our daily practice.

The prevalence of LADA clearly varies between regions and patient populations. However, it may be quite low, and there are no clear-cut data available clarifying the situation in different countries. Generally speaking, in autoimmune type 1 diabetes and possibly LADA, radical treatment has so far been unsuccessful. Therefore, it would be premature to start screening for LADA, unless your clinic is blessed with unlimited laboratory resources.


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