Laboratory reporting of HbA₁c should be standardised world-wide using two sets of units, according to a joint consensus statement from five professional societies.

The statement calls for HbA₁c results to be reported by labs in Système International (SI) units (mmol/mol – no decimals), and derived National Glycohaemoglobin Standardisation Program (NGSP) units (% – one decimal). The HbA₁c value will be derived using a master equation to convert it to the familiar currently used units (i.e. 6.0%, 7.0%).

HbA₁c test results should be standardised world-wide, and HbA₁c conversion tables including both SI and NGSP units should be easily accessible. The statement is endorsed by the ADA, the EASD, the IDF, the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC), and the International Society for Paediatric and Adolescent Diabetes.

Editors of journals are strongly recommended to require that submitted manuscripts report HbA₁c in both sets of units. This issue arose several years ago, when the IFCC adopted a new standardised reference measurement system for HbA₁c with higher specificity than the previous one. Rather than causing confusion by switching to the new, lower values for HbA₁c, it was decided to use the SI values (mmol/mol), along with the converted HbA₁c values.

There is also discussion about using an “estimated average glucose” value which would be reported in the familiar glucose units mg/dl or mmol/l, but not all populations have been evaluated adequately in order to do that. The consensus recommendations apply through 2011, when they will be discussed again at the next consensus meeting at the IDF meeting in Dubai December 2011.

The consensus statement is available on line at www.easd.org.

Because the International Expert Committee continued to define diabetes as the point at which retinopathy becomes prevalent, recommending the use of the A1c assay to diagnose diabetes is not a substantial departure from previous recommendations.

It would have been enlightening for the Committee to consider other outcomes, such as CVD or nephropathy, but the ongoing use of retinopathy makes sense because, unlike other diseases, it is almost uniquely a diabetic condition. A1c assays are standardised now, and a laboratory measure, such as A1c, that captures long-term glycaemic exposure is bound to be a better marker than single measures of glucose. There will be some issues to iron out. For example, the A1c and FPG may identify different individuals. Does this mean that a patient with an FPG of 7.1 mmol/l but an A1c of 6.2% no longer has diabetes? Also, the glucose component of the metabolic syndrome is based on FPG levels. Will the definition of the metabolic syndrome also be revised? The enormity of the changes contained in this report goes beyond the A1c recommendation.

Aside from identifying which test (s) to use, previous recommendations focused on where the cut-point for diagnosis should occur. Although the new report provides an A1c cut-point, it also clearly emphasises that diabetes risk is continuous, and that intervention should occur when dictated not just by glucose measures, but by other risk factors as well. Thus, the new report now reflects what most clinicians have been doing all along -- examining the whole patient.

The International Expert Committee


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A low degree of beta-cell sensitivity per degree of insulin sensitivity may be the defining quality of type 2 diabetes, according to a retrospective study of severely obese patients who experienced remission of type 2 diabetes after undergoing gastric bypass surgery.

The classic explanation that has been used to describe the transition from obesity to type 2 diabetes holds that obesity leads to insulin resistance, followed by a compensatory increase in beta-cell sensitivity, which allows for normal glycaemic control for a period of time, and then the eventual development of irreversible beta-cell exhaustion and poor glycaemic control.

But the results of a study of 219 consecutive gastric bypass patients with and without type 2 diabetes suggest that patients with diabetes have a reversible down-regulation of insulin secretion rather than beta-cell exhaustion.

Richard A. Perugini and his co-investigators in the department of surgery at the University of Massachusetts, measured fasting glucose and insulin levels in patients undergoing laparoscopic Roux-en-Y gastric bypass (LRYGB). They estimated insulin resistance and beta-cell sensitivity prior to and at regular times up to 1 year after surgery. Each LRYGB procedure formed a 30- to 45-ml gastric pouch and a Roux limb of about 100 cm. Both groups had a mean BMI greater than 40 kg/m².

Beta-cell sensitivity was defined as the ability of the beta cells to produce insulin in response to glucose, whereas insulin sensitivity is the ability of peripheral tissues to store glucose or fat in response to insulin. Insulin resistance is the inverse of insulin sensitivity. The investigators estimated insulin resistance, insulin sensitivity, and beta-cell sensitivity with the homeostatic model assessments for insulin resistance (HOMA-IR) and beta cells (HOMA-B).

Levels of insulin resistance ranged broadly among 47 patients with type 2 diabetes and 172 non-diabetic patients who had undergone LRYGB at the institution, including “plenty of patients with type 2 diabetes who had fairly good insulin sensitivity,” Perugini said at the annual meeting of the American Society for Metabolic and Bariatric Surgery.

Prior to surgery, the investigators discovered a hyperbolic relationship between insulin sensitivity and beta-cell sensitivity in both groups. The presence of type 2 diabetes shifted the relationship between the two factors so that the patients with diabetes were producing less insulin for each degree of insulin sensitivity than were non-diabetic patients. “We can’t look at these two parameters independently when we’re talking about type 2 diabetes,” Perugini said.

Among patients with lower levels of insulin resistance (HOMA-IR less than 2.3), beta-cell sensitivity followed a similar trajectory of improvement among 20 diabetic and 107 non-diabetic patients at a point in time between the measurements taken at 40 and 180 days after surgery.

The investigators also analysed the patients who had both high insulin resistance and poor insulin sensitivity (HOMA-IR of 2.3 or more) prior to surgery. At baseline, estimates of beta-cell sensitivity were lower among the 27 patients with diabetes than in the 65 non-diabetic patients in this category. By 40 days after surgery, beta-cell sensitivity had improved to match the level of non-diabetic patients.

At the end of 1 year, patients with diabetes had higher fasting blood glucose levels than did non-diabetic patients. Although patients with diabetes (with lower or higher insulin resistance) had mean body weight, body mass index, and excess body weight similar to those of non-diabetic patients at baseline, diabetic patients at 1 year ended up with lower overall levels of each measure than did non-diabetic patients.
Erectile dysfunction (ED) is a predictor of major cardiac events in men with type 2 diabetes who have asymptomatic coronary artery disease (CAD), according to a study published in the Journal of the American College of Cardiology. Researchers also found that statins provided significant protection in this population, and phosphodiesterase type 5 (PDE-5) inhibitors appear promising as well.

Because only case-control studies have demonstrated an association between ED and CAD in people with diabetes, a prospective trial was launched. A total of 291 men with complete follow-up data were assessed from an initial cohort of 317 consecutive type 2 diabetes patients with type 1 silent coronary CAD. The investigators screened for presence and extent of ED using the International Index of ED-5 Questionnaire. A total of 118 patients (41%) met the criteria. CAD was documented with angiography, and treated on the basis of angiographic severity. A total of 176 participants had coronary bypass; 48 had coronary angioplasty; and 67 were treated solely with pharmacologic therapy.

During a mean follow-up of 4 years, 49 patients experienced a major adverse cardiac event (MACE) (J. Am. Coll. Cardiol. 2008;51:2040-4).

In participants with ED, the MACE incidence was 25% (30 events), significantly greater than the 11% rate (19 events) in participants without ED. Major events included CAD death, sudden death, heart failure, unstable angina, a need for repeat revascularisation other than for re-stenosis, stroke or transient ischaemic attack, and symptomatic peripheral artery disease documented by angiography.

“The finding that ED is a powerful predictor of MACE is of clinical interest,” the authors wrote. “Our study suggests that, although all patients with diabetes are at high CV risk, those with ED might be at particularly very high risk.” In an accompanying editorial comment, Robert Kloner wrote that the finding of ED as a predictor suggests that “physicians seeing patients with diabetes should ask about ED and aggressively treat CV risk factors including dyslipidaemia and hypertension.” (J. Am. Coll. Cardiol. 2008;51:2051-2).

Gazzaruso et al also assessed the potential impact of different types of medication on the incidence of MACE. They found no effect from ACE inhibitors, angiotensin-receptor blockers, beta-blockers, and many other agents. However, they discovered that use of statins could protect against the occurrence of MACE in people with diabetes and ED. “This observation is not unexpected,” wrote Kloner, from the University of Southern California, Los Angeles. “The surprising and somewhat hopeful new finding in the Gazzaruso et al. study was the observation that there was a trend for phosphodiesterase type 5 [PDE5] inhibitor use to be associated with a lower rate of major adverse cardiac events.”

Although the finding fell short of clinical significance, Kloner wrote, “With evidence that PDE5 inhibitors improve endothelial function, slightly reduce blood pressure, and might have a primary cardio protective effect, the time has come to study these agents systematically as potential therapies for the prevention of adverse cardiac events in patients with vascular risk factors.”

Gazzaruso and his associates proposed a few mechanisms for beneficial effects of PDE5 inhibitors in this population. The agents were first developed as antianginal drugs. Also, they improve endothelial dysfunction and have several cardio protective effects (Am. J. Physiol. Heart Circ. Physiol. 2002;283:1263-9; J. Mol. Cell Cardiol. 2006;40:405-11).

The current investigators said that if their findings are confirmed in specific intervention studies, it would suggest that PDE5 inhibitors could play a major role in the prevention of cardiovascular events.
Background
It is controversial whether maternal hyperglycaemia less severe than that in diabetes mellitus is associated with increased risks of adverse pregnancy outcomes.

Methods
25,505 pregnant women at 15 centres in nine countries underwent a 75 g OGTT at 24 to 32 weeks of gestation. Data remained blinded if the FPG was 5.8 mmol/l or less and the 2-hour plasma glucose 11.1 mmol/l or less. Primary outcomes were birth weight above the 90th percentile for gestational age, primary caesarean delivery, clinically diagnosed neonatal hypoglycaemia, and cord-blood serum C-peptide level above the 90th percentile. Secondary outcomes were delivery before 37 weeks of gestation, shoulder dystocia or birth injury, need for intensive neonatal care, hyperbilirubinaemia, and preeclampsia.

Results
For the 23,316 participants with blinded data, we calculated adjusted odds ratios for adverse pregnancy outcomes associated with an increase in the fasting plasma glucose level of 1 SD (0.4 mmol/l), an increase in the 1-hour plasma glucose level of 1 SD (1.7 mmol/l), and an increase in the 2-hour plasma glucose level of 1 SD (1.3 mmol/l). For birth weight above the 90th percentile, the odds ratios were 1.38 (95% confidence interval [CI], 1.32 to 1.44), 1.46 (1.39 to 1.53), and 1.38 (1.32 to 1.44), respectively; for cord-blood serum C-peptide level above the 90th percentile, 1.55 (95% CI, 1.47 to 1.64), 1.46 (1.38 to 1.54), and 1.37 (1.30 to 1.44); for primary caesarean delivery, 1.11 (95% CI, 1.06 to 1.15), 1.10 (1.06 to 1.15), and 1.08 (1.03 to 1.12); and for neonatal hypoglycaemia, 1.08 (95% CI, 0.98 to 1.19), 1.13 (1.03 to 1.26), and 1.10 (1.00 to 1.12). There were no obvious thresholds at which risks increased. Significant associations were also observed for secondary outcomes, although these tended to be weaker.

Conclusions
Our results indicate strong, continuous associations of maternal glucose levels below those diagnostic of diabetes with increased birth weight and increased cord-blood serum C-peptide levels.

Adding Renin Inhibitor to Optimal Therapy Enhances Renoprotection

The renin inhibitor aliskiren enhanced renoprotection in patients with type 2 diabetes, hypertension, and proteinuria who were already receiving the maximal recommended renoprotective treatment with losartan and optimal antihypertensive therapy.

Aliskiren’s renoprotective effect was independent of its ability to lower blood pressure in this trial involving 150 medical centres in 15 countries, according to Hans-Henrik Parving and his associates.

The 599 study subjects were randomly assigned to receive either daily aliskiren (301 patients) or placebo (298 patients) for 6 months, in addition to maximal losartan therapy and antihypertensive treatment. By the end of the study, aliskiren had reduced the mean urinary A:Cr ratio by 20%, compared with placebo.

Nearly one-fourth of the study subjects given aliskiren showed a reduction of 50% or more in albuminuria, compared with 12% of those given placebo. (N. Engl. J. Med. 2008;358:2433-46). The drug also reduced BP by a mean of 2 mmHg systolic and 1 mmHg diastolic. However, its renoprotective effects were largely independent of this antihypertensive effect.

There were no differences between the active treatment and placebo in the overall incidence of adverse events (67% in both groups), the rate of serious adverse events (9% in both groups), or the proportion of patients who withdrew from the study because of adverse events (approximately 6% in both groups).

In an editorial comment accompanying this report, Julie R. Ingelfinger noted that “until longer-term studies are carried out, it is not known whether aliskiren plus an angiotensin–receptor blocker will constitute well-tolerated durable therapy.”

There are concerns that dual-agent blockade of the renin-angiotensin-aldosterone system may increase the incidence of hyperkalaemia and decrease the glomerular filtration rate. “Although adverse events were not marked” in this study, subjects were chosen carefully, and patients with low glomerular filtration or high potassium levels were excluded (N. Engl. J. Med. 2008;358:2503-5).