Diabetes 2010

From the 46th Annual Meeting of the European Association for the Study of Diabetes • Stockholm, Sweden

Sponsored by Yale University School of Medicine, Department of Internal Medicine, Section of Endocrinology

Volume 22 • September 22, 2010 • Issue 2

Diagnosing GDM: The Shifting Sands

The diagnosis of gestational diabetes mellitus (GDM) has evolved steadily since 1964 when Dr. John O’Sullivan and Claire Mahan published the first diagnostic criteria based on a statistical assessment of glycemic normality in pregnancy (O’Sullivan, Diabetes). Drs. Carpenter and Coustan later modified the criteria in 1982 based on accumulating data on neonatal and maternal outcomes in association with maternal hyperglycemia (Table 1). Over the last 3 decades, these standards have taken various forms from different professional organizations because there was no unifying data to inform a single criteria set. To say the least, it was confusing to have different cut-offs for ‘abnormal’ glycemia, determined from a single or combination of a 50, 75, or 100 grams of oral glucose over 2 or 3 hours.

While there remain dissenters regarding the clinical importance of identifying hyperglycemia in pregnancy, women with GDM are clearly at risk for many complications, including pre-term delivery, pre-eclampsia, and higher C-section rates. Also, their babies tend to be larger, with hyperinsulinemia and greater adiposity, leaving them at increased risk for shoulder distocia and neonatal hypoglycemia. Recent investigations have also raised the possibility that these offspring are at greater risk for childhood obesity and Type 2 diabetes. This increased risk may result from a metabolically abnormal intrauterine environment and/or epigenetic phenomena, as well as post-natal environmental factors.

The standard therapeutic approach in women with GDM is to normalize blood glucose concentrations, focusing especially on postprandial readings, first with lifestyle change. Insulin is used if dietary interventions are not successful. In some centers, oral agents, such as glyburide and even metformin, have been incorporated into treatment regimens. Modest decreases in pregnancy and fetal/neonatal complications have generally been demonstrated in clinical trials. Thankfully, most women with GDM will experience a reprieve post-partum, when their severe insulin resistance, which was heightened by circulating placental factors, abates. They do, however, remain at considerable risk of future GDM and even frank Type 2 diabetes.

The landmark Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) Study has shifted the paradigm over the past 2 years. HAPO further distinguished GDM from ordinary Type 2 diabetes by confirming a linear relationship between maternal blood glucose levels and the risk for neonatal and maternal complications (HAPO Study Cooperative Research Group, NEJM, 2008; Figure 1). This important observation has led to a challenging reconsideration of diagnostic cut-points for GDM. Six months ago the International Association of Diabetes in Pregnancy Study Groups (IADPSG) published recommendations for the diagnosis of GDM, based directly on the HAPO data (Table 2). The proposed criteria require just one abnormal glucose level during a 75-g OGTT as well as lowering the threshold for fasting glucose from 95 to 92 mg/dl and the 2-hour glucose from 155 to 153 mg/dl, as compared to current American Diabetes Association (ADA) guidelines (Table 1). The latter were based on the criteria of 1997 4th International Workshop Conference of GDM, which endorsed a 2-step process and the Carpenter-Coustan thresholds (see above). This consists of a 1-hour 50-g glucose challenge test (GCT) at 24-28 weeks,

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<th>Glucose Measure</th>
<th>Glucose Threshold*(mg/dl)</th>
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<td>Fasting plasma glucose</td>
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<td>100-g OGTT</td>
<td>1-hour plasma glucose</td>
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<td>2-hour plasma glucose</td>
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<td>3-hour plasma glucose</td>
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*≥2 must be ≥ threshold

Table 1. Current ADA Criteria for Diagnosis of Gestational Diabetes (Carpenter-Coustan criteria)
Diagnosing GDM …

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with those women whose plasma glucose exceed 140 mg/dl proceeding to a 3-hour 100-g OGTT, the diagnosis of GDM is made if 2 or more of the glycemic thresholds are reached, either fasting or at hours 1, 2, or 3. The term “overt diabetes” is additionally applied to women meeting traditional criteria for diabetes, and is meant to describe likely pre-gestational diabetes and a higher risk profile for both adverse neonatal and maternal outcomes.

The implications of these more stringent—and quite controversial—criteria were presented during an opening-day symposium, and may provide evidence in support of the IADPSG criteria. We note that the recommendations are currently being considered, but have not yet been endorsed by international groups who set clinical policies, such as the ADA, the World Health Organization (WHO), and the American College of Obstetrics and Gynecology (ACOG).

David Hadden, MD from Ireland, the first speaker, reported the frequency of GDM within the HAPO study using the new IADPSG criteria. The overall frequency of GDM was 17.8%, including 1.7% overt diabetes, but the frequency varied substantially among sites, ranging from 8.7% in Israel to 23.7% in Cleveland, Ohio. Of note, all the U.S. sites were among the highest for GDM. This variation between sites persisted even when body mass index (BMI) was taken into account as a potential confounder. Dr. Hadden concluded that the variation was most likely a result of ethnic differences, and more detailed analyses are currently in progress.

Dr. Annunziata Lapolla also applied the new IADPSG criteria to a retrospective analysis of 3,953 pregnancies in Italy, finding that the more stringent criteria incorporated 112 (2.8%) more women into the GDM group, previously classified as having normal glucose tolerance (NGT). Interestingly, 85% of these women met the new criteria because of elevated fasting glucose levels. The newly GDM/previous NGT (GDM-NGT) women were younger (32.4±4.5 vs. 33.4±4.4 years, p=0.0039) and had a lower pre-pregnancy BMI (23.7±4.3 vs. 24.7±5.1 kg/m², p=0.005) than their traditional GDM counterparts. In comparison to women who remained NGT with the new criteria, GDM-NGT women had more C-sections (43.6% vs. 31.1%, p=0.008). However, there were no differences in gestational age at delivery or birthweight between the groups. Dr. Lapolla concluded that the women newly included into the GDM category showed similar metabolic characteristics and certain adverse pregnancy outcomes to those women currently being identified as GDM.

In a similar study re-analysis, Dr. Alexander Kautzky-Willer from Austria presented their longitudinal data of 1,466 pregnant women, comparing the impact of using the IADPSG versus older criteria on neonatal complications and maternal postpartum glucose tolerance. Invoking the new cutpoints increased the prevalence of GDM by 3%; women newly identified were older and had greater parity and higher blood pressures than women previously defined. IADPSG-diagnosed women proved to have 6.1% more large-for-gestational-age (LGA) neonates (p=0.0047), with 4.5% more babies >4,000 gram birth weight (p=0.0047), and 3.3% more C-sections (p=0.0001) than if the current criteria were used. However, no difference in impaired postpartum glucose tolerance was detected between the two groups. Based on these findings, the speaker also supported the use of the IADPSG definition of GDM, and reported that Austria has actually been using it over the past year.

The new IADPSG criteria, if adopted, will obviously create an immediate increase by at least 3% in the overall prevalence of GDM, in some societies perhaps doubling the risk to the 15-16% range. In addition, an increase in GDM is anticipated as obesity rates continue to increase in women of reproductive age. What are the societal implications of doing so? Will resources be made available to address this new large group of patients? Yet, the studies from Italy and Austria, as well as from other centers, indicate that the inclusion of women with milder glucose intolerance does identify pregnancies at greater risk for adverse outcomes. Moreover, two studies suggest some benefit by treating these more mildly hyperglycemic mothers through lifestyle changes. Also, given concerns for epigenetic influences on future obesity and diabetes risk in offspring, the hope is that identification and treatment of GDM may play a downstream role in obesity and diabetes prevention.

Additional data will, of course, be required to understand how more aggressive glycemic control in pregnancy will affect long-term outcomes, especially weighed against the cost of resources required to supply the necessary medical care. Unfortunately, there is no randomized clinical trial that has yet been designed to specifically test diagnosis and treatment approaches based on the IADPSG criteria. Whether professional societies will eventually adopt the proposed criteria is unknown, but decisions should be made within...
Cardiovascular disease (CVD) remains the leading cause of morbidity and mortality in patients with diabetes. How to detect it early and its connection to glucose control was the subject of multiple presentations this week.

Bouchi and colleagues from Japan examined the effect of HbA1c fluctuations on incident CVD in 689 Japanese Type 2 diabetes patients (abstract 79). Patients were included if they had at least 3 HbA1c measures per year and at least 12 months of follow-up. Fluctuations were defined as the intra-individual standard deviation (SD) of serially measured HbA1c values during follow-up. Patients had an average of 26 ± 14 HbA1c values during a mean follow-up period of 3.3 years. 61 patients met the primary endpoint, which included all incident CVD events (i.e., stroke, myocardial infarction, or angina requiring revascularization).

Patients in higher quartiles of SD had a higher incidence of CVD (5-year cumulative incidence was 4.9, 8.7, 17.1, and 26.2% in the first to fourth SD quartiles, respectively; p < 0.001). As expected, cumulative incidence of events was also higher in patients with higher mean HbA1c; indeed, the HbA1c SD and the mean HbA1c were significantly correlated (r = 0.54, p < 0.001). In multivariate Cox analysis (adjusting for traditional CVD risk factors, including mean HbA1c and the number of HbA1c measures), the fourth (i.e., highest) quartile of SD HbA1c was associated with significantly higher incidence of CVD (HR 3.4, 95% CI 1.1-10.6) compared to the first quartile. Additionally, in multivariate Cox analyses stratified by mean HbA1c (above and below 7.7%) and SD of HbA1c (above and below 0.54, see Figure 2), patients with both higher mean HbA1c and higher HbA1c SD category were at the greatest risk for CVD events (HR 3.6). The investigators concluded that visit-to-visit variability in HbA1c in Japanese patients with Type 2 diabetes may be a potent predictor of incident CVD. This is the first we’ve seen ‘macro-variability’ addressed in a scientific report, whereas the alleged deleterious effects of ‘micro-variability’ (glucose fluctuations within a day) have been extensively studied. Certainly, these results warrant further investigation as well as careful assessment of other confounders (such as insulin therapy), which may modify this relationship. It would also be important to ensure that HbA1c variability is not just a marker of poor compliance, which may also extend to their other cardioprotective therapies.

Gansch and colleagues from Austria and Liechtenstein, in a provocatively titled presentation: “Type 2 Diabetes is Not a Coronary Heart Disease Equivalent”, reported on data from 750 consecutive patients undergoing coronary angiography for established or suspected coronary artery disease (CAD) (abstract 84). Based upon the results of angiography, presence of significant CAD was defined as coronary stenoses ≥ 50%. Patients were prospectively followed for 8 years and vascular events (vascular mortality, cardiac death, non-fatal myocardial infarction or stroke, CABG, percutaneous coronary intervention, or non-coronary revascularization) were recorded. Event rate in those with neither Type 2 diabetes nor CAD was similar to that among patients with Type 2 diabetes and no CAD, higher in those without Type 2 diabetes but with CAD, and highest among those with both conditions (Figure 3). Although Type 2 diabetes is still thought to be a ‘coronary artery disease risk equivalent’, in this study, Type 2 diabetes patients without CAD had a significantly lower event rate than their non-diabetic peers with established coronary heart disease (p = 0.017). Importantly, the decision to perform angiography may differ based upon diabetes status and could not be taken into account in this study. However, these data, and others, suggest that, in the context of aggressive, modern risk factor reduction strategies, the rate of appearance of coronary risk in our diabetic patients may actually be slowing.

Asymptomatic patients with diabetes are felt to be at higher risk for cardiovascular events. Screening asymptomatic patients for CAD remains controversial, with some investigators showing no benefit on clinical outcomes (DIAD Study, Young et al., JAMA 2009). Several small studies at the EASD meeting assessed the presence of sub-clinical CVD in patients with diabetes. Mokan and colleagues from Slovakia examined 47 patients (20 with Type 1 diabetes, 27 with Type 2 diabetes) without a history of CVD for the presence of cardiomyopathy, hypoperfusion, and cardiac autonomic neuropathy (abstract 1142). Treadmill testing was negative in all patients. Echocardiography showed diastolic dysfunction in 10% and 11% of patients with Type 1 and Type 2 diabetes, respectively. Hypoperfusion by 99mTc-tetrofosmin-gated SPECT was found in 35% and 60% of the respective cohorts. Cardiac autonomic dysfunction (based
on heart rate variability, spectral analysis, and a battery of tests developed originally by Ewing was diagnosed in 60% and 77%, respectively. Overall, the investigators found that a large proportion of patients with diabetes had hypoperfusion by SPECT and cardiac autonomic dysfunction, whereas more conventional testing with treadmill and echocardiography identified few patients with abnormal findings, although this study did not contain a control group.

In another study, Valensi and French colleagues evaluated 263 asymptomatic patients with at least one cardiovascular risk factor who had silent myocardial ischemia (SMI, here defined as an abnormal stress myocardial scintigraphy) (abstract 1257). These patients subsequently underwent coronary angiography: 93 individuals had CAD (defined as a stenosis >70%) on angiography. Of these individuals, 29 had percutaneous coronary intervention, 7 coronary artery bypass (CABG), and 56 were treated medically. After a mean follow-up of 5.5 years, 8 cardiac deaths occurred, 23 acute coronary syndromes, 3 revascularizations, 1 cardiac failure, and 1 ventricular fibillation. The incidence of events was lowest in patients with SMI but no CAD on angiography, intermediate in the group treated with revascularization, and highest in those with CAD who were subsequently treated medically. In the subgroup of patients with 3-vessel disease (n=17), the incidence of events was lower in those who underwent CABG than in those treated medically. This study adds to the recognition of poor prognosis in patients with SMI, but because of its retrospective, non-randomized design, specific recommendations regarding revascularization cannot yet be made. In the DIAD study noted above, which was randomized and involved more than 1,000 patients, no difference in morbidity and mortality was found between a screened and unscreened group, with cardiac event rate in the entire study being very low at <1%/year.

Although SMI has long been associated with diabetes, its relationship to pre-diabetic states is less clear. Intzilakis and colleagues from Denmark studied 596 non-diabetic individuals (age 55-75) without known CVD or cancer for the presence of SMI (defined as ST depression ≥1mm for at least 1 minute during 48-hour continuous ECG monitoring) and prediabetes (based upon fasting plasma glucose [FPG] 100-125 mg/dl) at baseline (abstract 1236). During follow-up (median 6.3 years), 77 individuals developed the primary endpoint of acute myocardial infarction and/or death. This occurred in 36% of individuals with prediabetes and SMI at baseline, 15% with prediabetes but no SMI, 12% with normal glucose and SMI, and 10% with neither abnormal glucose nor SMI. Subjects in the combined prediabetes/SMI cohort had a higher risk for the primary endpoint (HR 4.0, 95% CI 2.0-8.1) compared to those with normoglycemia/no SMI, even after adjustment for many cardiovascular risk factors, although the risk was attenuated (HR 2.5, 95% CI 1.2-5.2). Prediabetes may raise the risk of cardiovascular events in patients with silent ischemia.

Finally, although there is consensus regarding high cardiovascular risk in patients with diabetes, the optimal treatment targets in these patients remain controversial. Hemmingsen and colleagues from Denmark conducted a meta-analysis of 19 randomized clinical trials evaluating intensive vs. conventional glycemic control in patients with Type 2 diabetes (abstract 1250). To be included, trials had to pre-specify different targets of blood glucose control in patients. Data on 29,977 patients with a duration of intervention up to 12.5 years were analyzed. The primary outcomes of all-cause mortality and CVD mortality did not differ between the two groups (RR 1.00, 95% CI 0.93-1.08 and RR 1.05, 95% CI 0.95-1.17, respectively). The risk for all-cause mortality did not differ by disease duration, HbA1c, or fasting glucose at baseline. For secondary endpoints, intensive therapy was associated with a reduced risk of non-fatal myocardial infarction (RR 0.86, 95% CI 0.78-0.93), amputation of lower extremity (RR 0.64, 95% CI 0.44-0.95), nephropathy (RR 0.89, 95% CI 0.70-0.91), retinal photocoagulation (RR 0.79, 95% CI 0.69-0.91), and all microvascular complications combined (RR 0.85, 95% CI 0.78-0.93), but not of non-fatal stroke, cardiac or peripheral revascularization. Serious adverse events were more frequent in the intensively-treated patients and the risk for severe hypoglycemia was increased (RR 2.71, 95% CI 2.42-3.02).

It remains unclear how to weigh the potential risks and benefits of intensive glucose control in everyday clinical practice, and more work is needed to define which patients derive more benefit than harm from intensive control. As has been emphasized in the latest guidelines, individualization of therapeutic targets in diabetes is of increasing importance.

**Insulin – An Oldie but Goodie**

Multiple studies presented at the EASD this week focused on optimizing insulin therapy with currently available formulations in a variety of combinations and dosing regimens. UK investigators, Hope et al. (abstract 995) inquired whether patients with a long history of Type 2 diabetes develop absolute insulin deficiency, which in turn would alter the therapeutic approach for them. Urinary C-peptide:creatinine ratio (UCPCR) from a single urine sample has been previously shown to be a non-invasive indicator of endogenous insulin production. UCPCR values in patients with Type 2 diabetes (n=171) who started insulin at least one year post-diagnosis were evaluated. Subjects with a UCPCR of ≤0.2 nmol/mmol were considered to have an absolute insulin deficiency. This occurred in 13.5% (23/171) of patients. Characteristics of these patients included longer
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non-randomized design of the study. caution over interpretation, given the open-label, without increasing weight or hypoglycemia. glycemic control and enhances patients’ satisfaction, regimen was being converted from twice daily pre-mixed regimen in a real-world setting improves in mean HbA1c, FPG, self-monitoring results, weight, at goal HbA1c (≤ 7%) 6 months following the regimen. Described as a "real world" clinical trial setting, patients with Type 2 diabetes patients to glargine plus glulisine (The Belgium) from premixed insulin, dosed hormone insulin deficiency, may play a significant role in optimizing their therapeutic management. How do advanced insulin strategies compare beyond the simple, basal-only approach? This was the question asked by Storms and researchers from The Netherlands and Belgium. The group conducted a 6-month, prospective observational study evaluating the efficacy and safety of switching patients to glargine plus glulisine (The Netherlands) or glargine and any rapid-acting insulin (Belgium) from premixed insulin, dosed twice daily (abstract 962). Described as a “real world” clinical trial setting, patients with Type 2 diabetes (n = 214) were enrolled if their insulin regimen was being converted from twice daily premixed to a basal-bolus regimen. The primary aim was to determine the proportion of patients at goal HbA1c (≤7%) 6 months following the conversion. Additional measures such as changes in mean HbA1c, FPG, self-monitoring results, weight, insulin dose, hypoglycemia rates, and patient satisfaction were also assessed. The percent of patients achieving goal HbA1c significantly improved at month 6 upon switch to basal-bolus, as did other measures (Table 4). Weight did not differ significantly, yet the incidence of nocturnal and severe hypoglycemia was reduced. Patient satisfaction scores also improved (p<0.0001), as measured by diabetes treatment satisfaction questionnaires. The researchers concluded that conversion to basal-bolus insulin dosing from a pre-mixed regimen in a real-world setting improves glycemic control and enhances patient satisfaction, without increasing weight or hypoglycemia. These data are of some interest, but we would caution over interpretation, given the open-label, non-randomized design of the study.

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<th>Table 4. Patient Parameters Upon Conversion from Pre-Mixed Insulin Dosing to Basal-Bolus Regimens</th>
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<td>% of patients with HbA1c &lt; 7% (95% CI)</td>
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<td>HbA1c (%)</td>
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<td>Fasting plasma glucose (mg/dl)</td>
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<td>7-point SMBG (mg/dl)</td>
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<td>Basal dose (glargine, units/day)</td>
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<td>Bolus dose (rapid-acting insulins, units/day)</td>
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<td>Hypoglycemia: patient-reported reduction from baseline</td>
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SMBG = self-monitored blood glucose.

Combined insulin-oral agent therapy was the topic addressed by Pfutzner and German colleagues. These investigators conducted an interim analysis of the POComb study, assessing the metabolic benefits of insulin plus pioglitazone versus insulin plus metformin (abstract 899). Type 2 diabetes patients (n = 78) on prior insulin therapy were transitioned to an individualized and optimized regimen of glargine, then randomized to additionally receive pioglitazone 30 mg/day, metformin 1700 mg/day, or a combination of both oral agents. Baseline and 6-month measures of various parameters were measured (Table 5). HbA1c was stable in the two drug groups, but no differences in hypoglycemic event rates among the three treatment arms. The pioglitazone combinations resulted in increased insulin sensitivity, reduced insulin dose, and improved biomarkers of cardiometabolic syndrome (e.g., adiponectin, CRP).

While the standard approach with the newer analogs (i.e., detemir, glargine) is generally once daily dosing, Dhatariya and co-investigators from the UK examined whether twice daily dosing would provide better glycemic control (abstract 977). In a retrospective case analysis, HbA1c data were collected from 206 patients with Type 1 or Type 2 diabetes: 38% (78/206) taking glargine once daily and 62% (128/206) on twice daily at baseline. Those who switched from another insulin regimen to once daily glargine had a 0.27% reduction in HbA1c; a mean decrease of 0.49% occurred when they were switched to bid glargine. Based on these findings, the investigators suggested that twice daily dosed glargine may confer additional HbA1c benefit over once daily administration in selected patients.

Detemir, the other long-acting basal insulin, was the subject of an investigation by Zachariah and UK colleagues (abstract 981). Noting that detemir has been associated with less weight gain than other insulins, these investigators sought to determine the potential mechanism. In a 32-week, open-label crossover study, 23 patients with Type 1 diabetes managed with a basal-bolus (aspart) regimen were randomized to receive either detemir or NPH as their basal insulin for 16 weeks, then crossed over to receive

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<th>Table 5. Parameters at Baseline and Endpoint with 3 Insulin-Based Regimens</th>
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<tr>
<td>HbA1c (%)</td>
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<td>Daily insulin dose (units)</td>
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<td>HOMA-IR</td>
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<td>Adiponectin (mg/l)</td>
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<td>hsCRP (mg/l)</td>
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*p<0.05 vs. baseline (HOMA-IR, a measure of insulin resistance.)

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the other basal for an additional 16 weeks. Measures of energy intake/expenditure along with glycemetic control parameters and satiety hormones were collected at various intervals. After the first treatment period, the impact on weight with detemir was -0.69 vs. +1.7 kg with NPH (p = 0.0006). Total energy expenditure (measured by double-labeled water) was not significantly different between groups, whereas energy intake (measured by 7-day food diary) was significantly lower in detemir patients (2,016 vs. 2,181 kcal/day, p = 0.026).

Finally, these days many patients require very high-dose insulin therapy. In such circumstances, human regular U500 has been useful to maintain the total dose needed, but with mini-
mization of injection volume. U500 is 5-times as concentrated as U100, so that 10 ‘units’ on an insulin syringe (i.e., 0.1 ml) actually comprises 50 units of insulin. Its time course of action is somewhere between Regular U100 and NPH, with dosing typically 2-3 times per day. Despite being on the US market since 1997, there are few studies characterizing the pharmacokinetic (PK)/pharmacodynamic (PD) properties of this insulin.

Linnebjerg and US researchers evaluated 24 healthy obese subjects (weight 98.1 kg, BMI 34.4 kg/m²) in a randomized, double-blind, crossover, euglycemic clamp study of U500 and U100, each given at two fixed doses, 50 and 100 units. Serum immunoreactive insulin and glucose infusion rates were measured for PK/PD analy-

Gut Microbiota and Metabolism

In animal models, obesity has been shown to be associated with alterations in the microbiology of the gut. Vrieze et al. from the Netherlands and Finland conducted a double-blind study in which 18 male subjects with newly diagnosed and untreated metabolic syndrome (BMI ≥30 kg/m², FPG >100 mg/dl, triglycerides >142 mg/dl) underwent bowel lavage through a duodenal tube followed by randomization to either autologous fecal transplantation (from lean males, n=9) or autologous fecal transplantation (reinfusion of own collected feces, n=9) (abstract 90). At 12 weeks after the procedure, fasting triglycerides (as measured by TG/ApoB ratio) were significantly reduced (1.43 ± 0.21 to 1.11 ± 0.18, p<0.01) among the subjects who received autologous donor feces (from lean subjects), but not after autologous feces infusion. Likewise, there was improvement in both peripheral insulin sensitivity as measured by clamp (from 26.2 to 45.3 umol/kg/min, p=0.02) and hepatic insulin sensitivity (suppression of endogenous glucose production; from 51.5% to 61.6 %, p=0.08) at 6 weeks after the procedure in the allogenic group, but not in the autologous group. These results suggest a potential role of gut flora in the disturbances of glucose and lipid metabolism in obesity and could provide pathophysiological insights into their origins. The therapeautic technique will require a bit more refinement, however!

So Many Posters, So Little Time....

Implications of Islet Autoimmunity at Diagnosis in T1DM

In a large cohort of children with Type 1 diabetes prospectively followed, Holl et al. from Germany and Austria assessed the association between measured islet autoimmunity at disease onset and future insulin requirements and metabolic control (abstract 139). Of 3,302 patients who had onset of Type 1 diabetes prior to age 12 and continu-

Less Stringent Targets in the Aged?

van Hateren et al. from The Netherlands determined the impact of glucose control on cardiovascular mortality over a 10-year period in a prospective, observational study of Type 2 diabetes patients older than 75 years (abstract 398). In patients with diabetes for less than 5 years, each 1% increase in HbA1c was associated with an increase in all-cause and cardiovascular mortality risk of 40% and 66%, respectively.

According to results of a Cox proportional hazard model, including age, gender, smoking status, BMI, diabetes duration, serum creatinine, overt macrovascular complications, albuminuria, systolic blood pressure, total cholesterol/HDL ratio, and insulin use as potential confounders, glycemic control (HbA1c ≤7%) was associated with decreased risks of all-cause mortality (HR 0.56, 95% CI 0.33-0.95) and cardiovascular mortality (HR 0.28, 95% CI 0.11-0.69), compared to poor control, in elderly patients with diabetes for less than 5 years, but not among those with diabetes for a longer period of time. These data are consistent with several large, randomized clinical trials that were presented in 2008 (ACCORD, ADVANCE, VADT, see Diabetes 2008, volume 17). Based on these, there are increasing calls for less rigid targets in the elderly, particularly those with established vascular complications.

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