In January of 2010, the American Diabetes Association (ADA) endorsed new criteria for the identification of glycemic disorders, based upon glycated hemoglobin (HbA1c) cut-points: ≥6.5% for diabetes and 5.7-6.4% for pre-diabetes (Table 1). The original criteria based on fasting plasma glucose (FPG) and 2-hour glucose after an oral glucose tolerance test (OGTT) remain valid tests as well—the ADA did stipulate that one test is superior to another. Multiple presentations this week noted something that many clinicians across the country have observed—that HbA1c and FPG may not always necessarily agree. Furthermore, interesting differences in the characteristics of persons identified by the two tests are emerging.

In a symposium dedicated to the diagnosis of diabetes by HbA1c, Dr. Ed Gregg from the CDC addressed the challenges inherent in defining cut-points for pre-diabetes, given that the risk for subsequent diabetes lies along a continuum of FPG, 2-hour plasma glucose during an OGTT, as well as HbA1c. These cut-points are, therefore, driven by the choice of intervention and resources available since the ‘optimal’ thresholds remain in question. Dr. Gregg asked several questions: “What HbA1c levels correspond to prior FPG/OGTT criteria?”; “At what HbA1c levels are prevention efforts effective?”; “What is the relationship between HbA1c and future diabetes incidence?”; and “What cut-points provide potential for the greatest health impact?”

First, Dr. Gregg shared data from the 2003-2006 NHANES examination in which 14% of individuals were identified with pre-diabetes by HbA1c and 26.2% by FPG (i.e., having impaired fasting glucose). However, 6% of individuals were identified by HbA1c but not by FPG (favoring non-Hispanic blacks, women, and older persons) and 17% by FPG but not by HbA1c. He underscored that significant discordance exists between the two tests. Secondly, in the successful Diabetes Prevention Program (DPP), the largest lifestyle intervention trial, the mean HbA1c was 5.9%. A recent analysis from this trial suggests that effectiveness of diet and exercise was similar in those with higher and lower HbA1c levels. Accordingly, patients with HbA1c’s in the range denoted by the ADA for pre-diabetes are reasonable. Third, a systematic review (Zhang et al., in press) evaluating HbA1c at baseline and subsequent diabetes risk showed no distinct threshold, with increases in relative risk of ~10-20 fold at HbA1c of 5.5-5.9% and of ~20-40 fold at HbA1c of 6.0-6.4% (as compared to those in the lowest HbA1c range of <4.5%). Of note, FPG and HbA1c together were more predictive than each one alone. Lastly, the decision for particular cut-points depends to some degree upon the intent of intervention. In a hypothetical example using the DPP as a model, a HbA1c cut-point of 5.7% would require 24 persons thus identified to undergo lifestyle intervention in order to prevent one case of diabetes. The higher the HbA1c, the more cost effective the strategy, and vice versa. Dr. Gregg concluded that HbA1c is a strong and continuous risk factor for diabetes. However, discordance between HbA1c and glucose-based tests suggests that neither can be viewed as ideal.

Dr. Robert Cohen from the University of Cincinnati next reviewed biological aspects of HbA1c and the basis of the frequent disagreement between glucose- and HbA1c-based testing. HbA1c is an indirect measure of glycemia based upon the glycation of hemoglobin within red blood cells. Therefore, HbA1c depends upon how much glucose enters the red blood cell, the rate of glycation, and the red blood cell life span. Seminal work showing how well glucose and HbA1c relate comes from the A1c Derived Average Glucose (ADAG) study by Nathan et al. (Diabetes Care 2008;31:1473-8). Dr. Cohen pointed out that when glucose is plotted against HbA1c, one can easily see that an HbA1c of 7.0% corresponds to an average glucose ranging between 130 and 200 mg/dl and, likewise, an average glucose of 150 mg/dl corresponds to an HbA1c anywhere between 5.9 and 7.5%. The term “glycation gap” has been applied to this phenomenon of imperfect representation of glucose by HbA1c. In elegant experiments, Dr. Cohen and others have shown...
that glucose does not penetrate the red cell in the same way in all people, and although glycation appears to be constant over the red blood cell lifespan, the lifespan itself varies considerably. He emphasized the racial and ethnic differences in HbA1c and concluded that confirmation of diabetes requires consistency among tests and a single cut-point is not sufficient for all individuals.

In a counter-argument, Dr. Jonathan Shaw from the University of Melbourne stated that HbA1c and glucose are actually equally valid tests for diagnosing dysglycemic states. He acknowledged that there are problems with HbA1c—it is not a sensitive test and estimations of prevalent diabetes based on it may not be correct; the assay is variable; ethnic/age differences exist in its relationship to glucose; and many conditions may interfere in the performance of the assay (hemoglobinopathies, anemia, renal failure). However, fasting glucose has its own set of limitations: specimens need to be processed promptly; day-to-day variability is in the range of 12-15% (compared to <2% for HbA1c); and, fasting is required. Therefore, each test has its own conceptual challenges, and neither exactly and reliably matches the concept of chronic glycemia. The sensitivity of HbA1c as compared FPG is being reported in the range of 35-80% depending on the population studied. The discordance, Dr. Shaw noted, is now well-established—but is it important? He argued that it would be if we knew which test was the ’gold standard’, and we don’t.

Dr. Shaw showed that each test for diabetes predicted the diabetes complication of retinopathy very well. In the DETECT-2 project pooling 47,000 people from 13 studies, moderate non-proliferative diabetic retinopathy (as assessed by retinal photography) was extremely rare below HbA1c-6.5%, FPG ~126 mg/dl, and 2-hour OGTT ~200 mg/dl, but rose sharply with increasing values. The discriminatory value of these tests was almost identical. Therefore, while the choice of the test might depend on many factors, including availability, reliability, cost, and the prevalence of underlying hemoglobinopathies, in general, each one is intrinsically valid.

In related presentations this week, several investigators noted the differences in diagnosis of diabetes and pre-diabetes based upon HbA1c and the more traditional, glucose-based measures. In the Insulin Resistance Atherosclerosis Study (IRAS), Haffner et al. from Texas found that 15.9% of individuals had diabetes based upon the new ADA criteria, but out of these individuals, only one-third were identified by HbA1c, about one-half by FPG, and the vast majority by OGTT (424-PP). Discordance was also noted in those at risk for diabetes, with men, African Americans, and non-Hispanic whites more frequently identified by FPG, women or Mexican-Americans more frequently identified by OGTT, and very few whites being identified by HbA1c. Similarly, Lipska et al. from Connecticut (1136-P) noted poor sensitivity of HbA1c compared to FPG (57%) for diabetes diagnosis in a cohort of older Americans (mean age 76.5 years) in the Health ABC study. Differences between the two tests were accentuated by race and gender. The white/black differences were further evaluated by Selvin et al. from Hopkins based on the Atherosclerosis Risk In Communities (ARIC) study (1135-P). Interestingly, levels of HbA1c, fructosamine, and glycated albumin were all higher in blacks than whites, with and without diabetes, at similar FPG levels. However, 1,5-anhydroglucitol (which is reduced with postprandial hyperglycemia) trended lower in blacks. This study suggests that ambient glycemia, rather than alterations in glycation or other genetic factors, may explain black/white disparities in HbA1c levels.

Despite this controversy, support for the strong relationship between HbA1c and clinical outcomes was confirmed in several late-breaking presentations. Selvin’s group analyzed data from 11,092 participants in the ARIC study who did not have cardiovascular disease or diabetes at baseline (44-LB). Over 15 years of follow-up, in adjusted analyses, HbA1c 5.7-6.4% was associated with increased risk for subsequent diagnosed diabetes (HR 3.0), coronary artery disease (HR 1.6), ischemic stroke (HR 1.6), and all-cause mortality (HR 1.4). Notably, HbA1c predicted risk of these clinical outcomes even after adjustment for FPG.

In summary, while there appears to be significant discordance between HbA1c and glucose measures for the diagnosis of dysglycemic states, both glucose and HbA1c measures show a strong relationship with subsequent clinical outcomes. The optimal method for diagnosis remains hotly debated, and this controversy may not soon be reconciled.

**ACCORD Update**

ACCORD (Action to Control Cardiovascular Risk in Diabetes) is a multi-center, randomized, controlled trial with a factorial design evaluating intensive glycemic, lipid, and blood pressure strategies in 10,251 individuals with Type 2 diabetes at high risk for cardiovascular disease. The primary outcome was a composite of first occurrence of nonfatal MI, nonfatal stroke, or cardiovascular (CV) death. The trial was halted due to the higher risk for CV death and all-cause mortality in the intensive glucose arm. During the closing symposium of the 2010 ADA Scientific Sessions, investigators of the trial presented updated findings.

Dr. William Cushman from the University of Tennessee addressed whether targeting systolic blood pressure (SBP) <120 mmHg compared to <140 mmHg reduces CV events. Based on data from 4,733 eligible participants followed for 4.7 years (baseline mean age 62 years, BP 139/76 mmHg, Cr 0.9 mg/dl, HbA1c 8.3%, BMI 32 kg/m², 34% with prior CV disease, diabetes duration 10 years), intensive therapy did not significantly reduce the primary outcome (HR 0.88, 95% CI 0.73-1.06) with resultant mean SBP of 134 mmHg (2.1 medications).
in the standard and SBP 119 mmHg (3.4 medications) in the intensive groups (NEJM 2010;362:1575-85). In a subgroup analysis, stroke risk was reduced (HR 0.59, 95% CI 0.39-0.89) in the intensive group, but this effect needs to be confirmed in future trials. Overall, there was no evidence that targeting SBP <120 mmHg compared to <140 mmHg reduced CV events.

Dr. Henry Ginsberg from Columbia University reported on the main results of the lipid trial (NEJM 2010;362:1563-74). There were 5,518 eligible participants (LDL-cholesterol [C] 60-180 mg/dl, HDL-C <55 mg/dl for women and blacks and <50 mg/dl otherwise, triglycerides [TG] <750 mg/dl if on no therapy and TG <400 mg/dl otherwise). Randomization was to open-label simvastatin (20-40 mg/day) with addition of fenofibrate (54-160 mg/day based on renal function) vs. placebo. Participants (similar characteristics to that in the blood pressure study above, with mean LDL-C 101, HDL-C 38, TG 162 mg/dl) were followed for an average of 4.7 years. Addition of fenofibrate was not associated with reduced risk for the primary outcome (HR 0.92, 95% CI 0.79-1.08) compared to statin therapy alone. In subgroup analyses, there was heterogeneity in treatment effect according to sex, with a benefit for men, but possible harm for women (p = 0.01 for interaction). Although much has been made of apparent benefit in the prespecified lipid subgroup with both high TG (>204 mg/dl) and low HDL-C (<34 mg/dl) (see Cholesterol Chronicles, Issue 4, page 2), the interaction here was of only borderline significance (p = 0.057 for interaction).

Dr. Mertzel Gerstein from MacMaster University in Canada reported on the effects of 3.7 years of intensive glycemic control on CV outcomes after 5 years of total follow-up, providing additional information about the participants after the intensive glycemic strategy was halted. The median HbA1c was 7.5% at the end of intervention and increased to 7.6% at the end of follow-up in the standard group, and was 6.4% increasing to 7.2% in the intensive glycemic group. Rates of severe hypoglycemia (requiring assistance) decreased from 3% of participants/year in the intensive and 1%/year in the standard groups to 0.8%/year in both groups at the end of follow-up. The primary outcome at the end of follow-up was not significantly reduced, but CV death risk continued to be higher in the intensive arm (HR 1.29), with non-fatal MI risk reduced (HR 0.82). These findings are very similar to those observed when the intensive glycemic strategy was abandoned and show no reduction in the overall risk for CV events with intensive glucose therapy.

Dr. Faramarz Ismail-Beigi from Case Western Reserve University discussed the effect of intensive glycemia treatment on development and progression of microvascular outcomes (Lancet, June 29, 2010). In this analysis, several prespecified secondary composite outcomes were assessed: 1) dialysis or renal transplantation, high serum Cr (>3.3 mg/dl), or retinal photocoagulation or vitrectomy, 2) peripheral neuropathy and the first composite outcome; and 3) 13 other prespecified outcomes relating to kidney, eye, and nerve function. (Although not mentioned in this presentation, it is important to note that investigators and participants were aware of treatment group assignment.) The first and second outcomes were not significantly different between treatment groups (first outcome: HR 1.00, 95% CI 0.88-1.14; second outcome: HR 0.96, 95% CI 0.89-1.02). There were also no differences in individual outcomes for these renal or renal complications between the groups. Intensive therapy was, however, associated with reduced rates of microalbuminuria, macroalbuminuria, fall in eGFR, fall in visual acuity measures, and loss of pressure sensation. Notably, with so many comparisons, the probability of finding a positive association is greatly increased. In summary, intensive glycemic strategy did not improve advanced measures of microvascular disease. Whether improvements in some of the surrogates (such as microalbuminuria) translate to clinically meaningful outcomes is not clear in this older group of patients.

Dr. Emily Chew from the National Institutes of Health presented results of intensive glycemic, blood pressure, and lipid control on progression of diabetic retinopathy in a sub-study of the ACCORD trial (NEJM June 29, 2010). Out of 3,472 participants enrolled in the eye study (no history of photoagulation or vitrectomy), 2,856 (82%) completed baseline and year 4 follow-up. The primary endpoint here was progression of diabetic retinopathy by 3 or more steps on the Early Treatment Diabetic Retinopathy Study Severity Scale (ETDRSS) or progression of retinopathy necessitating photoagulation or vitrectomy. Intensive glycemic control was associated with reduced odds for the primary endpoint (OR 0.67, 95% CI 0.51-0.87), as was intensive lipid therapy with addition of fenofibrate (OR 0.60, 95% CI 0.42-0.86), but not intensive blood pressure control (OR 1.23, 95% CI 0.84-1.79).

In summary, intensive glycemic control in the ACCORD trial did not significantly reduce the primary outcome, significantly increased all-cause mortality, and reduced nonfatal MI, did not delay composite microvascular outcome measures, but did delay several measures of microvascular disease and reduced retinopathy progression. Blood pressure control to the normal range did not significantly reduce the primary outcome, significantly reduced stroke in a subgroup analysis, and did not affect retinopathy progression. Lipid treatment did not significantly change the primary outcome, showed some heterogeneity of effect in a few subgroups, and reduced retinopathy progression.

The GLP-1 receptor agonists were the subject of a Monday afternoon symposium as well as numerous oral and poster presentations. The session addressed several facets of GLP-1 based therapy, including potential CV benefits, newer long-acting agents, and possible links to acute pancreatitis and C-cell hyperplasia. Each speaker began their presentation with a summary of the unique physiologic actions of these novel, injectable compounds, as shown in Figure 1.

Dr. Allison Cohen, from the Joslin Diabetes Center began the session with a discussion of GLP-1 agonists & Modulation of Islet Function.

Continued on page 4
**GLP-1 Agonists...**

Continued from page 3

GLP-1 added to standard therapy in patients (n=12) with NYHA Class III/IV heart failure, comparing LVEF to a control group (n=9) who received standard therapy (J Card Fail 2006; 12:694-99). The GLP-1 arm significantly improved LVEF (21±3% to 27±3%, p<0.01), independent of a diagnosis of diabetes. Long-term, large-scale prospective trials are needed to truly assess any potential role in this area.

Dr. Carol Wysham of the University of Washington led the next presentation that reviewed the newer, long-acting GLP-1 agonists. As compared to exenatide, newer GLP-1 agonists, including liraglutide, exenatide LAR, taspoglutide, and albiglutide, have better glycemic effects (an additional 0.3-0.4% decrease of HbA1c), and some (e.g., liraglutide, exenatide LAR, albiglutide) have been shown to have fewer GI side effects, perhaps due to lesser effects on gastric emptying (GE).

Wysham also discussed that the longer acting agents appear to have a decreased impact on postprandial glucose excursions in comparison with twice-daily exenatide. While not specifically known, it may be also related to a lack of continued effect on GE. This was demonstrated in a study by Knudsen and Danish investigators who assessed the impact of acute and chronic exposure of liraglutide and exenatide twice daily on GE, food intake, and body weight in rats (591-P). GE was quantified using a standard acetaminophen release assay. Area under the curve (AUC) measurements were assessed after a single IV injection and after 14 days of twice-daily doses of exenatide, liraglutide, or placebo. Both compounds decreased AUC acutely versus placebo (p<0.001), suggesting an immediate impact on GE. After two weeks, AUCs were lower for placebo and liraglutide (9362±429 and 8135±380, p<0.02), yet exenatide continued with a profound decrease in GE (591±137, p<0.001). Each active treatment continued to have comparable effect on body weight at 14 days versus placebo (p<0.0001). From these data, the researchers suggested that slowed GE is not the primary mechanism for weight loss due to GLP-1 agonists, rather regulation of appetite signals in the brain may be responsible. Accordingly, the difference in long-term GE may explain the lesser impact on postprandial glucose excursions with the longer acting agents.

Wysham concluded her presentation noting that it is likely the GLP-1 agonists will be used with one to two concomitant oral agents. Sulfonylureas enhance the likelihood of hypoglycemia when used concomitantly, which may be solely a function of the sulfonylurea. In a related poster, a meta-analysis was presented at this week’s meeting comparing hypoglycemia rates between glimepiride and liraglutide. Gough, along with UK and Danish colleagues, evaluated the rates of hypoglycemia of liraglutide alone and in combination with other oral agents using data from six Phase 3 randomized, controlled trials (n=3,967) (764-P). At 26-weeks, liraglutide 1.8 mg and 1.2 mg was associated with a 91% reduced risk of hypoglycemia compared with glimepiride at HbA1c of 7% (p<0.0001). A reduced risk of ~95% of hypoglycemia was observed for 1.8 mg and 1.2 mg doses when the HbA1c reached 6.5% (Figure 2).

The third presenter, Dr. Kathleen Dungan from Ohio State University, discussed recent concerns of acute pancreatitis and C-cell hyperplasia that have been attributed to incretin mimetic drugs. The FDA issued safety alerts in 2007 for exenatide (and in 2009 for the DPP-4 inhibitor, sitagliptin), advising health care professionals that these agents have been associated with reports of acute pancreatitis. It has been debated whether the incretin drugs actually cause pancreatitis or whether this may merely be a reflection of increased risk in patients with Type 2 diabetes. Pendergrass and Chen of New Jersey evaluated claims data in 13 million subjects, 2 million with diabetes, enrolled in Medco Health Solutions (587-P). Subjects receiving a new prescription for exenatide (n=9,951), sitagliptin (n=23,951), metformin, sulfonylurea and/or thiazolidinedione (n=24,255) and a non-diabetic control group (n=111,392) were identified. They were followed until the earliest of the following: development of pancreatitis, discontinuation of index medication, or the end of the observation period (6-18 months). According to Cox proportion hazards model of time to first acute pancreatitis adjusted for baseline risk factors, there was no increased risk of pancreatitis with either exenatide (adjusted HR, 0.86, CI: 0.60-1.24, p=0.42) or sitagliptin (adjusted HR, 1.01, CI: 0.77-1.31, p=0.97), compared to the diabetes control group. The researchers concluded that their analysis does not support an increased risk with incretin mimetics. Dungan echoed the conclusions of the poster presentation.

The FDA recommends a conservative approach to this issue: maintain a low threshold of suspicion for acute pancreatitis in patients receiving GLP-1 agonists or DPP-4 inhibitors and avoid rechallenging patients with the medications in whom the condition is confirmed.

With respect to C-cell hyperplasia and the risk for medullary thyroid cancer, Dungan shared that the relationship between rodent and human data is unknown. More research will be needed.

Among the most heavily studied of the antihyperglycemic drug classes, GLP-1 receptor agonists’ role continues to evolve. Potential CV benefits are now proposed but more data are needed. The availability of longer-acting compounds on the market will likely expand their use, but any emerging concerns about potential toxicities will require careful consideration.
Both sulfonylureas (SUs) and dipeptidyl peptidase 4 (DPP-4) inhibitors work within the pancreatic beta cell to stimulate insulin release, albeit through very different mechanisms. Although the SUs may be more potent across the range of HbA1c, both drugs are comparable in Type 2 diabetes patients with milder hyperglycemia. Given the increasing popularity of the latter class, the question posed in a debate on Sunday was “Will the DPP-4 Inhibitors Replace the Sulfonylureas?”

Dr. Michael Nauck of Germany began by extolling the virtues of the DPP-4 inhibitors as the preferred class of oral anti-hyperglycemic agents. DPP-4 inhibitors have the mechanistic advantage of prolonging the half-life of GLP-1, which has insulino tropic activity only upon glucose stimulation. These drugs have, accordingly, low rates of hypoglycemia, and are weight neutral in contrast to the more traditional insulin secretagogues. In addition, there is early data suggesting that DPP-4 inhibitors may protect beta cells from apoptosis, and possibly even protect cardiac myocytes from ischemia during vascular occlusion. He concluded that DPP-4 inhibitors are a safer alternative to SUs. In an era of increasing CV vigilance, the side effect profile of SUs, which includes hypoglycemia, weight gain, and potential effects on ischemic preconditioning, make them a less attractive oral agent class.

Dr. David Matthews from Oxford, England gave an entertaining defense of the tried and true SUs. He was forthright in stating that SUs are not necessarily better medications than DPP-4 inhibitors, but they have over 40 years of use in clinical settings and have demonstrated safety and efficacy in lowering blood glucose. He reviewed more than five large, longitudinal randomized control trials, including the UGDP (University Group Diabetes Program), UKPDS (UK Prospective Diabetes Study), ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Dia micron Modified Release Controlled Evaluation), and ADOPT (A Diabetes Outcome Progression Trial). SUs have demonstrated their abilities in head-to-head trials with other drugs, as well as their role in preventing microvascular disease. Dr. Matthews agreed that hypoglycemia is the main problem with these agents, and it is clear that DPP-4 inhibitors have significantly lower rates. However, he felt that the risk is acceptable, and clinicians may adjust the dosing to prevent the likelihood of this adverse effect. He concluded that SUs are well validated and cost a small fraction of the newer agents. In the global pandemic of Type 2 diabetes, we need a safe and cheap treatment strategy, so SUs will remain one of this disease’s core agents.

Defining “Normal” in GDM

Since the third trimester of pregnancy is associated with increased insulin resistance, placing metabolic stress on pancreatic beta cells, it can serve as a unique window into future diabetes risk. Retnakaran et al. from Toronto reported that women with glucose intolerance in pregnancy experienced beta-cell function decline, even within the first year postpartum (13-OR). They assessed 392 women with a glucose challenge test (GCT) and oral glucose tolerance test (OGTT) during pregnancy, and then a repeat OGTT at 3 and 12 months postpartum. The women were divided based on initial OGTT into four groups: GDM (n=107), gestational impaired glucose tolerance (GIGT, n=75), abnormal GCT with normal glucose tolerance (NGT) (n=137), and normal GCT with NGT (n=73). The prevalence of abnormal glycemia at 3 months and then again at 12 months postpartum increased progressively across the baseline defined groups from GCT/NGT (2.7% and 2.7%, respectively) to abnormal GCT/NGT (10.2% and 11.7%), GIGT (18.7% and 17.3%), and GDM (34.6% and 32.7%) (p<0.0001 for comparisons across groups at both time intervals). Between 3 and 12 months postpartum, the subgroups showed significant differences in beta-cell function, as calculated by the Insulin Secretion Sensitivity Index-2 (ISSI-2) (Figure 3, p=0.0036), with ISSI-2 declining in both the GDM and GIGT groups. Notably, this occurred without any changes in insulin sensitivity.

These results indicate a continuous relationship between abnormal glucose metabolism in pregnancy and future beta-cell decline. The concerning feature of this study is how quickly beta-cell abnormalities become manifest in otherwise young, healthy women.

The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study also found a continuous, linear association of abnormal glucose metabolism in pregnancy and adverse neonatal and maternal outcomes. In particular, the association was strongest with fasting plasma glucose (FPG). At this meeting Metzger et al. reported on a subgroup analysis of women with a FPG ≤79 mg/dl, which represented the cohort mean (160-OR). They sought to determine whether this fasting glucose level could serve as a cut-point in excluding gravidas from undergoing an OGTT. They divided the women into non-GDM and GDM based on their 1- and 2-hour OGTT values. They then compared the prevalence of adverse neonatal and maternal outcomes in each group. In the GDM subgroup with FPG ≤79 mg/dl, frequencies of outcomes tended to be similar to those of the HAPO cohort overall and substantially lower than found in the all HAPO GDM group. However, the results did not provide enough evidence for the investigators to recommend not performing an OGTT in pregnant women with such a low FPG. More research is required to better elucidate an appropriate cut-off, which is difficult given the linear and continuous relationship between glucose and adverse outcomes in this population.

Lastly, Neutrakul, et al. from Chicago evaluated the relationship of sleep disturbances to abnormal glucose tolerance in pregnancy (11-OR). They administered three different measures of sleep quality to 157 pregnant women on the same occasion as their screening 50g OGTT. No significant differences were found in reported sleep quality between women with normal glucose metabolism and those with impaired glucose metabolism.
Hypoglycemia continues to be the most frequent adverse event in the management of diabetes. But what are the long-term consequences of hypoglycemia? Two studies examined this in a Type 1 and 2 diabetes population.

Asvold, et al. from Norway presented a 16-year follow-up study on cognitive function in people with Type 1 diabetes and exposure to severe hypoglycemia before the age of 10 years (29-OR). Twenty-seven children with Type 1 diabetes were matched with a control of the same sex, age, and social background, and followed into adulthood. Nine of the children had been exposed to severe hypoglycemia, and 18 had not. Cognitive assessment was performed and reported as a standard deviation (SD) from the control subjects. Diabetic patients with early severe hypoglycemia were found to have reduced cognitive ability, with an overall score of -1.0 SD (95% CI -0.5 to -1.5), whereas diabetic patients without severe hypoglycemia were similar to controls (-0.1 SD, 95% CI -0.4 to 0.2). Specifically, they scored lower in problem solving (-2.2 SD), verbal function (-1.5 SD), and psychomotor efficiency (-1.3 SD). In addition, cognition scores were lowest in those who were exposed to hypoglycemia before 6 years of age (overall -1.3 SD). The researchers concluded that early severe hypoglycemia was associated with reduced cognitive function across several domains in adulthood.

In another study, hypoglycemia was found to be independently associated with an increased risk of acute CV events in people with Type 2 diabetes. Johnston et al. from the US did a retrospective analysis of 860,845 people with Type 2 diabetes within a large healthcare claims database, examining the association between ICD-9-CM coded hypoglycemic events and acute CV events (30-OR). The CV events included acute myocardial infarction, coronary artery bypass grafting, revascularization, percutaneous transluminal coronary angioplasty, and new unstable angina. Using a multiple logistic regression model with adjustment for confounding variables, they found that people with hypoglycemic events had a 79% greater risk of CV sequelae (OR 1.79, 95% CI 1.69-1.89) than people without hypoglycemia. Only two other variables, age (OR 13.25 for age 65+) and prior CV disease (OR 2.87) held a greater risk for acute CV events than hypoglycemia. Both of these studies underscore the importance of avoiding hypoglycemia as much as possible in our treatment of diabetic patients, particularly those on insulin therapy.

So Many Posters, So Little Time....

Bariatric Surgery

Roux-en-Y gastric bypass surgery (RYGB) has been associated with a hypoglycemic syndrome characterized by postprandial hypoglycemia and hyperinsulinemia. To assess the etiology, Kim et al. from California compared glucose-stimulated insulin secretion rate in 8 RYGB patients who developed post-operative hypoglycemia to that in 34 non-diabetic, nonsurgical individuals (54-OR). The investigators observed that patients with hypoglycemia post-RYGB appeared to have appropriate insulin secretion rates in response to intravenous glucose (similar to the insulin-sensitive control subjects). They concluded that the hyperinsulinemic/hypoglycemic episodes in these patients are likely secondary to the bypass surgery, per se, without any intrinsic change in pancreatic β-cells. These data do not rule out a possible derangement of incretin physiology, as others have proposed.

Hirsch et al. from Brazil conducted a study to characterize the underlying mechanisms related to non-resolution of Type 2 diabetes after RYGB, despite significant postoperative weight loss. This occurs in ~20% of patients undergoing the bariatric procedure (379-OR). At a mean of 41 months following RYGB, 28 diabetics patients underwent mixed meal tolerance testing. The subjects whose diabetes resolved post-operatively appeared identical to those whose diabetes did not with regards to age, disease duration, degree of weight loss, fat distribution, and underlying beta-cell function. The investigators, however, observed a combination of greater insulin resistance, chronic subclinical inflammation, and impaired incretin response to meals in the patients whose diabetes persisted.

Fiber Facts

Johansen and Sørensen from Norway conducted a case-control study of 362 subjects without a diagnosis of diabetes mellitus or impaired glucose tolerance (IGT) to determine the prevalence of idiopathic reactive hypoglycemia (IRH) (abstract 1761-P). IRH was defined by 1h- or 2h- post-load (oral glucose tolerance test, OGTT) glucose <70 mg/dl or 1h- or 2h- glucose < fasting glucose and no evidence of Type 2 diabetes or IGT. IRH was found in 12.4% of subjects, who had higher fasting but lower 2h-glucose, but were similar to controls based on age and BMI. In a second part of their investigation, 12 subjects with documented IRH participated in a four-week crossover study—two weeks each with and without 20g of long-chain soluble fiber (fructo-oligosaccaride) diet supplementation. Added fiber clearly improved the reactive glucose pattern of a 4-hour OGTT. Fasting plasma glucose and total cholesterol levels were also significantly reduced.

Chromium Ineffective

Chromium is widely marketed to the public with diverse health claims pertaining to muscle mass, weight control, glucose metabolism, insulin action, and diabetes prevention. Ali et al. from Connecticut conducted a double-blind, modified cross-over study in which they randomized 59 subjects with impaired fasting glucose, impaired glucose tolerance, or metabolic syndrome to 6-month sequences of supplemental chromium picolinate or placebo at one of two dose levels (500 or 1000 mcg daily), then vice versa, followed by a six-month post-intervention assessment (abstract 1763-P). No changes were seen in serum insulin levels, HOMA-IR, 2-hour postprandial glucose, or fasting plasma glucose after six months of chromium, at either dose level, compared to placebo. Chromium supplementation had absolutely no effect on insulin resistance or impaired glucose metabolism parameters, and thus is unlikely to attenuate diabetes risk.

Silvio E. Inzucchi, MD
Robert S. Sherwin, MD

Editors, Yale University,
New Haven, Connecticut