

Diabetes 2008

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for the Study of Diabetes ■ Rome, Italy

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More ADVANCES



Important data on diabetes presented at the 44th Annual Meeting of the European Association for the Study of Diabetes comes to you in **Diabetes 2008**, a newsletter CME program that is being offered to you by Yale University School of Medicine. Fax or e-mail delivery to your office of **Diabetes 2008** will be followed by a **Diabetes 2008** booklet (EASD and AHA newsletters) in the mail. After successfully completing the quiz and evaluation therein contained, you will qualify for up to 5.5 AMA PRA Category 1 Credits™ to be issued by Yale University School of Medicine.

Diabetes 2008 is being offered to physicians practicing in the United States. After successfully completing this program, participants will be able to:

- Explain the pathogenesis of Type 2 diabetes, especially the coexisting roles of insulin resistance and insulin secretion.
- Recognize the clinical manifestations of the macrovascular and microvascular complications of diabetes and describe appropriate therapeutic interventions.
- Recognize the important association between insulin resistance/metabolic syndrome and atherosclerosis in patients with Type 2 diabetes.
- Identify evolving and emerging management strategies for diabetes (e.g., combination antihyperglycemic therapy, new insulin delivery systems, new glucose monitoring techniques, novel drugs).
- Describe the approach to managing dyslipidemia, hypertension, and cardiovascular risk factors in patients with diabetes.

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This past summer saw the presentation of three landmark studies which assessed the impact of intensive glycemic control on macrovascular endpoints in patients with Type 2 diabetes (T2DM): ADVANCE, ACCORD, and the VADT. These investigations demonstrated no benefit in the short-term (3 to 5 years) from intensive glucose lowering with regard to cardiovascular (CV) outcomes. Indeed, one study, ACCORD, actually suggested some risk from aggressive intensification of therapy in an older/high-risk population. In a presentation in the DaVinci Auditorium on the opening day of the EASD meeting in Rome, new data from the important *Action in Diabetes and Vascular Disease: Preterax and Diamicon Modified Release Controlled Evaluation* (ADVANCE) trial were reviewed and expanded. The glycemic control aspect of this study was presented in June at the American Diabetes Association meeting in San Francisco and simultaneously published in the *New England Journal of Medicine* (2008;358:256). 11,140 patients with T2DM were randomized to one of two anti-hyperglycemic treatment arms and one of two blood pressure (BP) treatment arms. This was a 2x2 factorial design (25% received more intensive BP lowering only, 25% more intensive blood glucose (BG) lowering only, 25% both strategies, and 25% neither). Patients were followed for 5 years. The primary endpoints were composites of major CV events (death from a CV cause, nonfatal myocardial infarction [MI], nonfatal stroke) and major microvascular events (new or worsening retinopathy or nephropathy); these endpoints were assessed both jointly and individually.

Dr. John Chalmers from Australia reviewed the published ADVANCE data. The mean age of the patients was 66±6 years, with a duration of diabetes of 8±6 years. 42-43% were female and 32% had a prior history of vascular disease, including 12% with MI and 9% with stroke. The mean weight was 78±17 kg and BMI 28±5 kg/m². A history of major microvascular disease (defined as retinopathy or macroalbuminuria) was present in 10%.

In the blood pressure arm of the trial, the results of which have already been reported

(*Lancet* 2007), patients were randomized to the combination of the ACE inhibitor, perindopril, plus the thiazide diuretic, indapamide. This study demonstrated relative benefits from the more aggressive program in the majority of the primary and secondary endpoints assessed: 14% less mortality, 18% less CV death, 21% less total renal events (most being new onset proteinuria), and 14% less total coronary events. New data from this arm presented by Dr. Chalmers included subgroup analyses. Irrespective of baseline BP, all patient groups experienced benefit, even those already below 130/80 mmHg.

Next, the BG control arm was reviewed. This randomization was between intensive control with the oral sulfonylurea, gliclazide, plus other drugs as required to achieve a HbA1c of <6.5% vs. conventional care. At baseline, the HbA1c was 7.5±1.5%. After a median of 5 years of follow-up, HbA1c levels in the standard care and intensive groups were 7.3% and 6.5%, respectively, with a consequent 0.8% difference between groups. To achieve this target, patients in the intensive group understandably required more pharmacotherapy. By the end of the trial, 90% of patients in the intensive group (vs. 70% in the standard care group) were still taking gliclazide, 41% (vs. 24%) were on insulin, and 17% (vs. 11%) were using a thiazolidinedione. The use of lipid-lowering agents, blood pressure medications, and aspirin were similar, however, between the two groups.

For the primary composite outcome of major micro- and macrovascular events, the hazard ratio (HR) was 0.90 (95% confidence interval 0.82-0.98) in favor of more intensive glucose lowering therapy (Figure 1). This difference was mainly driven by the microvascular events, chiefly worsening of nephropathy (HR 0.86 [0.77-0.97]), whereas there was no statistical difference in the macrovascular rates between groups (HR 0.94, [0.84-1.06]). No differences were seen in any of the macrovascular secondary endpoints, such as total mortality, all coronary events, or any peripheral vascular event. Notably, severe hypoglycemia occurred more commonly in intensively treated patients (2.7% vs. 1.5%, p<0.0001). The event

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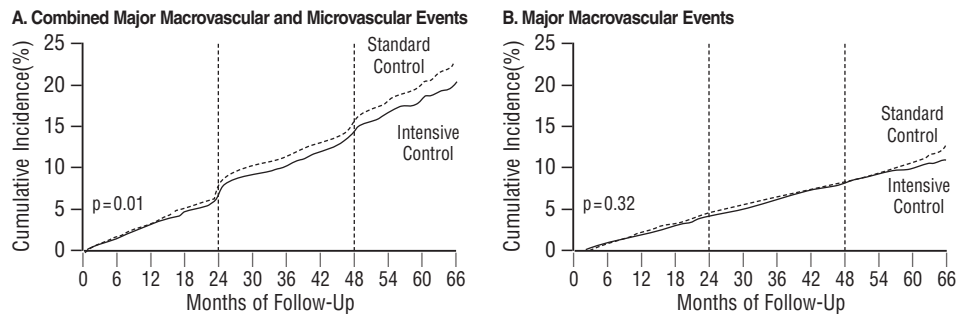
More ADVANCES

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rates for severe hypoglycemia were low, however: 0.7 and 0.4 per 100 patient-years in the intensive and standard care groups, respectively. These effects of intensive glycemic control were consistent across a wide variety of subgroups, stratified by baseline clinical criteria.

Additional new data presented by Dr. Chalmers included the effects of 'joint therapy'—i.e., the effects of combined aggressive BP and BG lowering therapy vs. those who received neither. One question—in light of the results from the ACCORD investigators, showing an increase in CV mortality in their more tighter controlled group—was whether tighter BG control might attenuate the benefits seen from more aggressive BP management. In ADVANCE, however, the answer was clearly "no." First, statistical tests (Cox modeling) for an interaction between BP and BG control therapies proved negative ($p > 0.1$)—that is, the effects of these strategies individually were not substantially affected by the other. Second, when the group of patients receiving both intensive strategies were compared to the group receiving neither, if anything, the risk reduction was even more impressive. For instance, while BP and BG reduction resulted in relative risk reductions for renal outcomes of 18% and 19%,

Figure 1. ADVANCE: Cumulative Incidences of Events by Glucose-Control Strategy



respectively, their combination led to a 33% risk reduction ($p = 0.005$). Similar trends were noted for CV and all-cause mortality. Dr. Chalmers concluded that when using a multifactorial approach involving careful attention to both BP and BG control, one may achieve a ~1/3 reduction in renal outcomes, ~1/4 less CV mortality, and a ~1/5 lower all-cause mortality rate.

One important difference between ACCORD and ADVANCE underscored by Dr. Chalmers, in addition to the different HbA1c targets in the intensive arms (<6% vs. <6.5%, respectively), was the rapidity of BG lowering in the former trial (target achieved in <1 year), as compared to the gentler approach used in the latter (target achieved in 3 years). In addition, the use of both

insulin and thiazolidinediones was much more widespread in ACCORD than ADVANCE.

At this point, it appears that a reasonable HbA1c target remains <7%. Although there is no convincing evidence that this by itself will protect against CV events, it certainly reduces microvascular risk and may, in light of today's disclosures, enhance the effects of aggressive BP control, which has its own substantial benefits on both micro- and macrovascular disease endpoints. We look forward to reviewing these latest analyses from ADVANCE once they are published, as well as the microvascular data from both ACCORD and the VADT. In addition, ACCORD's intensive BP lowering and lipid-lowering arms are continuing.



Nephropathy News



It is widely accepted that Type 2 diabetes is a major risk factor for chronic kidney disease (CKD). Several studies presented this week explored the epidemiology of this association as well as novel treatment paradigms.

Using data from the NHANES IV survey of patients with Type 2 diabetes who were ≥ 30 years of age at the time of their diagnosis and started insulin therapy more than one year after their diagnosis, Koro and Lee of the US determined the percentages of those meeting the criteria for Stage 1 through 5 CKD (Table 1) (abstract 1211). Overall, they observed that approximately 40% of these individuals could be considered to have CKD. Almost three-quarters of those were classified as Stage 2 or 3. The percentage of patients being treated with one antidiabetic medication increased from 36% in those with Stage 1 disease to 78% in those with Stage 5 CKD. Similarly, the percentage of insulin-treated patients also increased with increasing kidney disease severity, with 7% of those with Stage 1 and 58% of those with Stage 5 receiving insulin.

Table 1. Stages of Chronic Kidney Disease*

Stage	Description	GFR
Normal kidney function	Healthy kidneys	≥ 90 ml/min
Stage 1	Kidney damage with normal or high GFR	≥ 90 ml/min or more
Stage 2	Kidney damage and mild decrease in GFR	60 to 89 ml/min
Stage 3	Moderate decrease in GFR	30 to 59 ml/min
Stage 4	Severe decrease in GFR	15 to 29 ml/min
Stage 5	Kidney failure	<15 ml/min or on dialysis

GFR=glomerular filtration rate.

*Published by the National Kidney Foundation.

Albuminuria: A Predictive Marker for Kidney Disease

Diabetic patients almost always exhibit elevations in urinary albumin excretion prior to overt renal impairment, according to the findings of Karalliedde and English colleagues (abstract 44). In their retrospective analysis of the records of patients with Type 1 ($n = 96$) or Type 2 ($n = 516$) diabetes and diabetic kidney disease (defined using serum creatinine cut-points of >1.7 mg/dl

or >3.4 mg/dl) who were attending a specialist diabetes renal unit between 2005 and 2007, they found that all patients had a history of albuminuria prior to their diagnosis of renal impairment, regardless of the serum creatinine cut-point used. Among those with Type 1 diabetes, the mean duration of diabetes at the time of albuminuria was 24.6 ± 11.8 years, while in those with Type 2 diabetes the mean duration of diabetes at the time of albuminuria was 9.9 ± 8.3 years.

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Nephropathy News

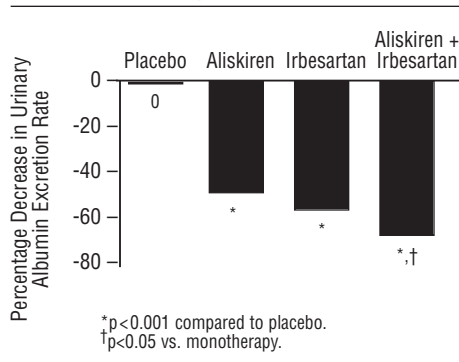
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Modulating RAS

There is evidence to suggest that the use of renin inhibitors may be renoprotective in patients with diabetes, with investigators at this meeting adding to the growing body of evidence supporting the use of these agents in this setting. In a study of 599 patients enrolled in a multinational, randomized, double-blind study, Parving and colleagues of Denmark and the US evaluated whether adding aliskiren, a novel oral direct renin inhibitor, to the angiotensin receptor blocker (ARB), losartan (thus providing 'dual blockade' of the renin-angiotensin system [RAS]), provides any additional renoprotective effect (abstract 45). Patients with hypertension, Type 2 diabetes, and nephropathy were treated for 3 months with open-label losartan 100 mg and were then randomized to 6 months of add-on treatment with placebo or aliskiren (150 mg daily for 3 months followed by forced titration to 300 mg daily for an additional 3 months). Reduction in early morning urinary albumin:creatinine ratio at 6 months was the primary outcome parameter. As compared to losartan/placebo treatment, losartan/aliskiren resulted in a 20% reduction in mean urinary albumin creatinine ratio (95% CI: 9% to 30%, $p < 0.001$). Among those treated with dual blockade, nearly one-fourth (24.7%) exhibited a $\geq 50\%$ reduction in urinary albumin creatinine ratio as compared to 12.5% of losartan/placebo patients ($p < 0.001$). Patients treated with losartan plus aliskiren also exhibited a trend toward better BP reduction ($p = 0.08$) and smaller decline in renal function ($p = 0.07$).

In a much smaller study, Persson and international colleagues assessed whether the use of aliskiren had any effect on albuminuria as compared to the ARB, irbesartan, and whether the use of combined therapy might be synergistic (abstract 1218). In their double-blind, randomized, cross-over trial, 24 patients with Type 2 diabetes, hypertension, and albuminuria (>30 mg/day) were randomized to four 2-month treatment periods. During these they received in random order placebo, aliskiren 300 mg once daily, irbesartan 300 mg once daily, or the combination. In addition, patients received a stable dose of long-acting

Figure 2. Effect of Aliskiren, Irbesartan, and their Combination on Urinary Albumin Excretion as Compared to Placebo



furosemide throughout the study. The primary endpoint was the change in urinary albumin excretion rate (AER). As illustrated in Figure 2, dual therapy provided a significantly greater reduction in urinary albumin excretion than monotherapy. Aliskiren and irbesartan monotherapy showed similar effects, each producing a significant reduction as compared to placebo. The effects on other cardiovascular parameters such as BP, however, were similar between the active treatment groups. Whether the use of renin inhibitors alone or in combination with other RAS blockers will have a long-term benefit on actual renal (or CV) outcomes is not yet known. Notably, in the recent ONTARGET study (*N Engl J Med* 2008; 358:1547), no benefit from the combination of the ARB, telmisartan, with the ACE inhibitor, ramipril, on CV disease endpoints was demonstrated in $>17,000$ patients with vascular disease and/or diabetes.

Table 2. Cockcroft-Gault and Modification of Diet in Renal Disease-4 Formulas to Estimate Creatine Clearance

Cockcroft-Gault Formula for Estimated Creatinine Clearance (eCl_{Cr})	
$eCl_{Cr} = \frac{(140 - \text{age}) \times \text{Mass (in kilograms)} \times (0.85, \text{ if female})}{72 \times \text{Serum Creatinine (in mg/dl)}}$	
Modification of Diet in Renal Disease-4 Formula for Estimated Glomerular Filtration Rate (eGFR)	
$eGFR = 186 \times \text{Serum Creatinine}^{-1.154} \times \text{Age}^{-0.302} \times [1.21, \text{ if black}] \times [0.742, \text{ if female}]$	

Ekinci and Australian colleagues found in a double-blind, randomized, placebo-controlled, crossover study, that the administration of sodium chloride tablets resulted in marked attenuation ($\sim 80\%$) of the expected AER decrease during ARB therapy (telmisartan) with or without thiazide treatment (abstract 1215). Their findings emphasize the importance of maintaining a low-salt intake in order to sustain the renoprotective effects of ARB therapy with or without a thiazide diuretic in those with diabetes.

Estimating Renal Function—Which Formula to Use??

Estimating renal function in obese patients is typically performed using the same mathematical equations as in individuals of normal weight, that is, the Cockcroft-Gault or the Modification of Diet in Renal Disease-4 (MDRD-4) formulas (Table 2). Joosten and colleagues of The Netherlands compared renal function determinations estimated with these two formulas to that more accurately calculated using 24-hour creatinine clearance data in a cohort of 380 women and 469 men with diabetes who were dichotomized into two groups: those with BMI $<$ and ≥ 30 kg/m² (abstract 1192). Between the BMI groups, the smallest difference in renal function determination was observed when it was assessed using the Cockcroft-Gault formula, as compared to the MDRD-4 formula. The investigators concluded that the actual recommended methodology for assessing renal function in the obese and the consequences linked to the resulting estimates of renal function need careful consideration.

HbA1c

HbA1c: A Diagnostic Tool?

HbA1c

In the last year, glycated hemoglobin (HbA1c) measurements were globally standardized to the International Federation of Clinical Chemistry (IFCC) reference method. The HbA1c is reliable,

relatively inexpensive, and can be measured conveniently during non-fasting conditions. It provides an estimate of overall glycemic control during the prior 2-3 month period. However, both the American

Diabetes Association (ADA) and World Health Organization (WHO) use either fasting glucose, random glucose, or glucose 2 hours (2hPG) following oral glucose tolerance test (OGTT) to define diabetes

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HbA1c: A Diagnostic Tool?

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mellitus. Three studies out of Denmark used different, existing large population databases to explore whether the use of HbA1c is appropriate for the diagnosis of diabetes mellitus.

Van't Riet *et al.* from Amsterdam looked within an established database of 2,748 subjects, 40 to 65 years of age, from the New Hoorn Study to determine how well HbA1c measurements correlated with fasting plasma glucose (FPG) and 2hPG following OGTT (abstract 391). Subjects were analyzed according to whether they had normal glucose tolerance (NGT); impaired hyperglycemia (IH; defined as impaired fasting glucose and/or impaired glucose tolerance); known diabetes (KDM2); or screen-detected, new diabetes (NDM2). In subjects with NGT, IH, and NDM2, the Spearman correlations between HbA1c and FPG were higher (0.26, 0.25, 0.51) than between HbA1c and 2hPG (0.14, -0.05, 0.45), but all correlations were quite low. On this basis, the researchers did not endorse the use of HbA1c for the diagnosis of diabetes. For subjects with known diabetes, the

correlation between HbA1c and FPG was much better at 0.78; between HbA1c and 2hPG, the value was even higher at 0.84.

Simonis-Bik and colleagues, also from Amsterdam, presented an analysis of 180 healthy, normoglycemic people who are twins or siblings of twins in the Netherlands Twin Register (abstract 387). They entered three different fasting glucose values and one HbA1c value for each subject into a 4-variate structure equation model to estimate heritability of each parameter. Again, a low correlation was found between HbA1c and fasting BGs. However, heritability explained 75% of the population variance in HbA1c, which likely reflects genes that influence the glycation of hemoglobin. Heritability of fasting BG varied between 40-66% depending on the setting where the sample was drawn. Of note, there was a gender difference: men had significantly higher mean fasting BGs as well as a higher HbA1c's when compared to women.

Finally, Vistisen and collaborators from the Steno Diabetes Center in Denmark addressed the association of macro- and microvascular complications in groups with diabetes or impaired glucose metabolism that were defined by either

HbA1c or OGTT (abstract 388). The investigators used a database of 6,258 people between the ages of 30 and 60 years. The macro-vascular risk factors of people defined by OGTT results versus those defined by HbA1c values were used to calculate a 10-year risk of developing ischemic heart disease (IHD). The HbA1c was found to be better at distinguishing between individuals at high and low risk of developing IHD over a 10-year period as compared with FPG and 2hPG. It was also noted that people with diabetes defined by HbA1c have a worse microvascular risk profile compared to those identified by either FPG or 2hPG.

In summary, in patients not diagnosed with diabetes, HbA1c values do not correlate as well as one might expect with either fasting glucose or post-challenge glucose. This may reflect varying hematological, metabolic, or genetic factors at play. However, in diabetic patients, HbA1c does show better correlation to macro- and microvascular complications than the glycemic values themselves. While it is not currently recommended to use HbA1c for the diagnosis of diabetes, a consensus statement by the ADA will soon address this issue.



How Low Can You Go?



It is well recognized that, for individuals with Type 1 diabetes, symptoms of hypoglycemia change over time and, following intensified insulin therapy, many actually lose their "early warning system"—adrenergic symptoms. More and more Type 2 diabetic patients are now also progressing to insulin therapy, and there is now evidence to suggest that they may also develop impaired awareness of hypoglycemia (IAH) over time. Schopman *et al.* from Edinburgh sought to ascertain the prevalence of IAH in 122 insulin-treated Type 2 diabetes patients and how it influences their exposure to hypoglycemia (abstract 681). Patients were of a median age of 67 years, with a mean diabetes duration of 15 years and insulin therapy duration of 6 years. Approximately one-half were male (63 of 122); mean HbA1c was 8.4±1.5%. Participants were asked to complete a detailed questionnaire and then capillary BG was prospectively recorded 4 times a day, over a 4-week period. Biochemical hypoglycemia (defined as BG <54 mg/dl) was identified and any associated symptoms were recorded and classified. Severe hypoglycemia (defined as that requiring external assistance) was estimated retrospectively over the preceding year. Overall, the prevalence of IAH was 9.8%. IAH was

associated with a 5-fold higher mean incidence of biochemical hypoglycemia (2.34±4.39 vs. 0.46±1.21 episodes in those with normal awareness; p<0.001). Moreover, in the year preceding the study, the incidence of severe hypoglycemia as reported by those with IAH was 17-fold higher than those without IAH (0.83±1.12 vs. 0.05±0.28 episodes per patient; p<0.001). The investigators concluded that while hypoglycemia unawareness occurs less commonly in Type 2 as compared to Type 1 diabetes, in those affected it is associated with a greatly increased risk of both biochemical and severe hypoglycemia. Hypoglycemic symptoms in any insulin-treated diabetic patient should therefore be evaluated routinely at each visit.

A concern of motor vehicle departments for many years is whether individuals with insulin-treated diabetes are a public liability while driving. Agencies that legislate in this area have historically restricted individuals with Type 1 diabetes from driving commercially operated vehicles, and some states demand a medical-fitness assessment prior to issuing a standard driving license. Clearly, IAH and impaired cognition during hypoglycemia might increase the propensity of insulin-treated individuals to car accidents. Moreover, studies

have shown that inducing controlled hypoglycemia in a driving simulator leads to driving abnormalities in individuals with Type 1 diabetes. In this light, Honkasalo and colleagues from Finland retrospectively determined in 2 medium sized Finnish communities (n=67,261) whether diabetic patients with recurrent (at least 3 or more) episodes of severe hypoglycemia during the previous year still held a valid driving license (abstract 679). A total of 1,776 medically-treated diabetic patients were identified and of these 1,326 (75%) completed a questionnaire. Data on the occurrence of severe hypoglycemia during the same year were collected from electronic patient records used in primary health care centers and local hospitals offering 24-hour emergency room service and from the 24-hour ambulance service registers of these 2 communities. Current driving license data were obtained from the local police authorities. Twenty-seven percent (27%) of the patients with Type 1 diabetes and 12% of insulin-treated patients with Type 2 diabetes reported at least 1 episode of severe hypoglycemia (incidence rates, 66.7 and 26.5 per 100 patient-years, respectively). Of the patients with Type 1 and Type 2 diabetes, 10.4% and 3.2%, respectively, needed ambulance care for the event. Of all insulin-treated patients,

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How Low Can You Go?

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56 (7.3%) reported 3 or more severe hypoglycemic episodes during the preceding year. Two-thirds (66%) of these patients still held a license to drive, and 20% of them also held a

license to drive commercial vehicles (truck or taxi). The researchers concluded that recurrent severe hypoglycemia occurs in a significant number of insulin-treated patients, and that the majority of these patients still hold a valid driving license—some even for commercial vehicles, in

violation of local governmental standards. However, it is important to note that there is currently no good evidence that, overall, individuals with insulin-treated diabetes have higher motor vehicle accident rates and some studies suggest accident rates may even be lower.



Secondary Diabetes



One of the more gratifying diagnoses to make is that of secondary diabetes—i.e., when hyperglycemia results from an underlying medical condition. Very often, when that condition is diagnosed and treated, the diabetes disappears or becomes much easier to control. Admittedly, the list of causes of secondary diabetes is something of a mixed bag of hormonal, pancreatic, and drug-related causes, along with certain known infectious illnesses and some hyperglycemic states associated with various genetic syndromes. (As we better understand the varied pathogenesis of typical Type 2 diabetes, it is quite likely that the number of recognized genetic syndromes will increase over the years.) Several studies presented this week focused on less common causes of diabetes.

Bonata *et al.* from Italy focused on post-renal transplant diabetes (abstract 367). In a group of 53 non-diabetic patients undergoing renal transplantation, diabetes occurred in 9% during the first year post-transplant, while 28% developed impaired fasting glucose (IFG), a form of pre-diabetes, during this same period. Patients developing dysglycemia post-transplant were older than those who maintained NGT. Both IGT and diabetes were seen more frequently in patients on tacrolimus vs. cyclosporine for their immunosuppressive regimen.

Patients with schizophrenia are at increased risk for Type 2 diabetes. Whether this is due to underlying lifestyle habits, anti-psychotic drug therapy, or other factors is not fully understood. Shaw *et al.* from several European countries examined BG levels and diabetes risk factors in 2,463 patients with schizophrenia (per DSM-IV criteria

(abstract 711). The mean age was 41 years, and 55% were male. 86 were being treated for diabetes, but an additional 75 had a fasting BG ≥ 126 mg/dl, for a total identified diabetes prevalence of 7.2%. An additional 25.8% had IFG. Multivariate logistic regression analysis revealed that age >40 (odds ratio [OR] 2.00 [95% CI 1.48-2.70]), waist circumference >95 cm (1.81 [1.23-2.66]), serum triglycerides >200 mg/dl (1.69 [1.23-2.33]), female gender (1.32 [1.07-1.64]), and clozapine therapy (1.90 [1.37-2.62]) were associated with an abnormal glycemic status. The newer anti-psychotic drug, amisulpride ($n=218$), was associated with a reduced risk (0.50 [0.33-0.75]). No overall differences were seen in the percentages of patients with hyperglycemia between those on classical vs. novel anti-psychotic agents. In the literature, members of the latter category have been associated with an increased risk for diabetes, although mainly in observational, uncontrolled studies (like the current investigation.) The investigators encouraged close follow-up of glucose levels in patients with schizophrenia.

Acute and chronic pancreatitis are both associated with diabetes. In an elegant pathological study, Menge *et al.* from Germany sought to determine the islet cell mass and turnover in patients with established chronic pancreatitis (abstract 541). They wondered if the association with diabetes is due to an overall reduction in β -cell mass and/or turnover and whether islets were more or less vulnerable to injury than the acinar (i.e., exocrine) pancreas. Pancreatic tissue specimens were obtained from 29 patients and 14 control subjects. These were stained for

insulin, glucagon, and markers of cell turnover and apoptosis (cell death). Islet-cell mass was estimated from the product of the fractional islet cell areas and the mean pancreas volume in each group, the latter being determined by CT scan. Mean pancreatic volume was 64.9 ± 4.3 cm³ in pancreatitis patients vs. 82.3 ± 6.7 cm³ in controls ($p=0.035$). Fractional beta-cell area was $0.64 \pm 0.09\%$ in the pancreatitis patients vs. $0.78 \pm 0.07\%$ in controls ($p=0.30$); beta-cell number was decreased ($p=0.0017$). Overall, β -cell mass was calculated to be reduced in pancreatitis by 34%. Alpha cells appeared similar, and no differences in the replication rates in beta, ductal, and acinar cells were noted between groups. In the chronic pancreatitis patients, the frequency of apoptosis was 10-fold higher in acinar cells than in beta cells.

The investigators concluded that beta-cell mass is reduced by about a third in patients with chronic pancreatitis, mainly due to a reduction in the total islet-cell number. The similar beta-cell replication rates in the two groups, despite a 10-fold increased apoptosis rate in the acinar cells from pancreatitis patients, suggests the autolysis in chronic pancreatitis is specific for the exocrine compartment. These findings might explain the typical sequence of exocrine then endocrine deficiency in patients with chronic pancreatitis.

Clinicians are urged to consider the diagnosis of secondary diabetes when a patient presents with atypical features. A careful diagnostic evaluation may reveal an underlying, correctable condition that, if treated, may improve patient outcomes.



So Many Posters, So Little Time....



Metcalf and other EarlyBird Diabetes Study investigators evaluated the direction of causality between physical activity and body fat in 185 children (104 boys, 81 girls) (abstract 670). Physical activity was measured annually between 6 and 9 years of age by 7-day accelerometry, an objective, validated method of directly measuring motion. Percent body fat was measured by whole-body DEXA at 7 and 8 years

of age. Body fat was associated more strongly with physical activity level measured 1 year later ($r = -0.20$) than 1 year earlier ($r = -0.10$), raising the interesting possibility that fatness may influence activity more so than vice versa. The weakness of the association and its direction of causality

could explain, at least in part, why attempts at reducing childhood obesity by promoting physical activity have been largely unsuccessful. If future studies confirm these findings, the focus of obesity prevention may need to focus predominately on excess calorie intake.

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