

Diabetes 2007

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Incretin Modulation



Important data on diabetes presented at the 67th Annual Scientific Sessions of the American Diabetes Association come to you in **Diabetes 2007**, a newsletter CME program that is being offered to you by Yale University School of Medicine with the support of Takeda Pharmaceuticals North America, Inc., Merck & Co., Inc., Novo Nordisk Inc., and Amylin Pharmaceuticals, Inc./Eli Lilly and Company. Fax or e-mail delivery to your office of **Diabetes 2007** will be followed by a **Diabetes 2007** booklet (ACC and ADA newsletters) in the mail. After successfully completing the quiz and evaluation therein contained, you will qualify for up to 5.5 Category 1 credits towards the Physician's Recognition Award of the American Medical Association to be issued by Yale University School of Medicine.

Diabetes 2007 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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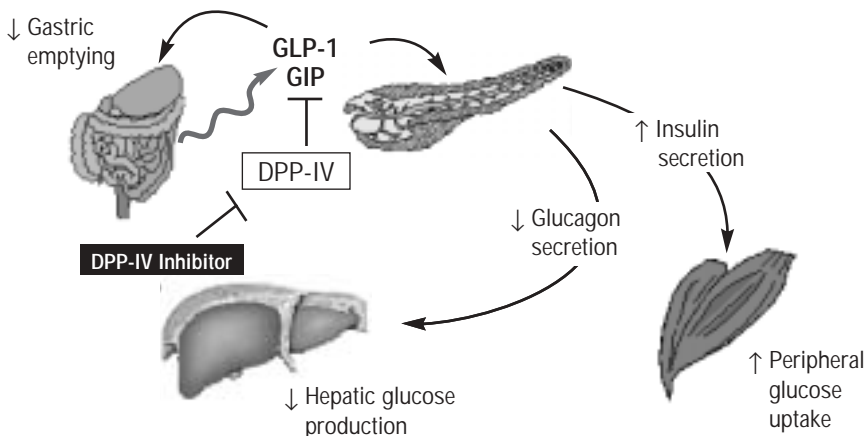
Drugs focusing on the incretin system continue to emerge. These agents exert their anti-hyperglycemic effect by mimicking the effect or increasing the concentration of the gut hormones, Glucagon Like Peptide (GLP)-1 and Glucose-Dependent Insulinotropic Peptide (GIP). These "incretins" enhance insulin secretion in response to food. GLP-1 is also known to suppress glucagon secretion, slow gastric emptying, and enhance satiety. Drugs developed to date either activate GLP-1 receptors (e.g., exenatide) or inhibit DPP-IV, the enzyme responsible for degradation of GLP-1 and GIP (e.g., sitagliptin). Incretins also appear to increase β -cell mass (in animal studies) which may, over time, preserve insulin secretory capacity.

Dr. Robert Ratner chaired the Monday symposium, "Pros and Cons of GLP Agonists versus DPP-IV inhibitors." Although billed as a debate, each of the speakers essentially agreed that both classes of drugs, the GLP agonists and DPP-IV inhibitors, are useful in the appropriate patient population. Dr. Ralph DeFronzo of the University of Texas, San Antonio, primarily addressed the GLP-1 agonists and began with a review of the pathogenesis of Type 2 diabetes and incretin pathophysiology (Figure 1). GLP-1 and GIP have overlapping activities and account for 90% of the

incretin effect. Exenatide, the first GLP-1 mimetic to be approved, improves first-phase insulin secretion and its actions are glucose dependent. It is therefore not associated with hypoglycemia. Three-year follow-up data support the durability of exenatide, with sustained reductions in fasting and post-prandial plasma glucose and HbA1c. Two new products are on the horizon, liraglutide and exenatide long-acting release (LAR), the former permitting once daily dosing and the latter given just once weekly, although both still by injection. Dr. DeFronzo closed the presentation with a discussion of additional advantages of exenatide including its effective suppression of hepatic glucose production and accumulating evidence that it may increase cardiac output and confer cardioprotection during ischemia. The latter preliminary findings will certainly require further study.

Dr. Richard Pratley of the University of Vermont, Burlington, followed with an overview of the DPP-IV inhibitors. He too agreed that there is little debate: patients with diabetes will benefit from new, safe therapies. He described the pharmacology of the DPP-IV inhibitors in great detail. DPP-IV is a member of a large family of proteases of which several have been identified (DPP-6, DPP-8, DPP-9, etc.). To minimize untoward side effects, specificity

Figure 1. Physiology of the Incretin System: Key Regulator of Post-prandial Glucose Metabolism



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from inhibition of DPP-IV is a key issue in the development of these drugs. There are, however, still several substrates for DPP-IV, including IL-2, IL-1 β , bradykinin, and substance P. The impact of DPP-IV inhibition on these substrates is not yet known and will require further investigation. Currently there are 12 different DPP-IV inhibitors in some phase of development, and 55 (!) abstracts at these ADA Scientific Sessions were devoted to this topic. Pratley shared clinical data on both sitagliptin and vildagliptin. Each appears to have comparable efficacy, resulting in significant decreases in HbA1c, post-prandial glucose, and, to a lesser extent, fasting glucose. Upon review of the adverse drug event data, Pratley commented on how remarkably safe the compounds appear to be, at least given the early experience with them. He closed by identifying three groups of patients in whom the DPP-IV inhibitors may be particularly beneficial: (1) the elderly, due to minimal hypoglycemia, good safety profile, and decreased likelihood of drug-drug interactions; (2) those with renal insufficiency, as initial data demonstrate safety and efficacy when dose-adjusted; and (3) heart failure patients, given the lack of edema as seen with thiazolidinediones (TZDs). In summary, the GLP agonists and DPP-IV inhibitors are safe and effective as monotherapy and as add-on therapy for patients with Type 2 diabetes.

The following abstracts further confirm some of the information provided by the symposium speakers. Three-year follow-up data on exenatide, via an open-label extension study, were presented by John Buse *et al.* from Chapel Hill, NC (283-OR). In 217 patients with Type 2 diabetes, exenatide (10 mcg BID) demonstrated a sustained reduction in HbA1c (-1.0 \pm 0.1%, $p < 0.0001$) and fasting plasma glucose (FPG) (-23.5 \pm 3.8 mg/dl, $p < 0.0001$) when compared to baseline and continued weight reduction (-5.3 \pm 0.4 kg, $p < 0.0001$ versus baseline). HOMA- β , a marker of β -cell function, also continued to improve when compared with baseline (+17%, $p < 0.0001$, in 92 patients receiving, in addition, metformin or sulfonylureas).

Trautmann and German colleagues assessed the incidence of hypoglycemia with exenatide versus insulin glargine in patients receiving the agents in combination with metformin or a sulfonylurea (172-OR). Patients received exenatide (5 mcg BID x 4 weeks, then 10 mcg BID x 12 weeks) or glargine (targeting a fasting blood glucose ≤ 100 mg/dl) for two 16-week periods in a crossover design. Similar reductions in HbA1c were achieved in exenatide- or glargine-containing regimens, with weight reduction only seen in the exenatide group.

Table 1. Incidence of Hypoglycemia in Exenatide vs. Insulin Glargine Combination Regimens

	Exenatide +		Insulin Glargine +	
	Metformin	Sulfonylurea	Metformin	Sulfonylurea
Change in: HA1c		-1.43%		-1.41%
Weight		-2.6 %		+1.8%
Hypoglycemia	2.6%	30%	17.4%*	34%
Nocturnal hypoglycemia	1.3%	7%	13%*	16%

* $p < 0.05$ vs. exenatide + metformin

Overall, the incidence of nocturnal hypoglycemia was lower in both exenatide treatment groups (exenatide + metformin, exenatide + sulfonylurea), but significantly lower in exenatide + metformin versus insulin glargine + metformin (Table 1). Seven severe hypoglycemic episodes were recorded in three patients, each of whom was receiving glargine. The authors concluded that, in their patients, exenatide combined with metformin was as effective as glargine + metformin on HbA1c, while avoiding hypoglycemia. (This clearly depends on the starting HbA1c, however, given the comparatively greater glucose-lowering power of insulin in patients with higher degrees of hyperglycemia.)

Dokken and colleagues of Tucson, Arizona evaluated the impact of GLP-1 on myocardial infarct size when administered during the reperfusion period after cardiac ischemia (58-OR). Following thoracotomy with occlusion of the left anterior descending coronary artery in age-matched rats, those receiving GLP-1 ($n=5$) experienced a decrease in infarct size (17% versus 74% of left ventricle, $p < 0.05$) as compared with the control group ($n=4$). The researchers concluded that further investigation of the mechanism of myocardial protection, as well as similar testing in diabetic animals, is needed.

Several sessions were devoted to the DPP-IV inhibitors. Sitagliptin is the first of class to be FDA-approved and is now commercially available for use as monotherapy, and in combination with metformin or TZDs. Many investigations involved evaluation of sitagliptin in combination with metformin. Additive effect was supported by an investigation conducted by Hermansen and colleagues of Denmark (535-P). 441 patients with Type 2 diabetes poorly controlled (HbA1c 7.5% -10.5%) on glimepiride alone or glimepiride and metformin were randomized to receive sitagliptin 100 mg daily or placebo in addition to their baseline oral regimen for 24 weeks. Sitagliptin therapy resulted in a statistically significant ($p < 0.001$) lowering of HbA1c (-0.7%), FPG (-20 mg/dl), and 2-hour post-prandial glucose

(-36 mg/dl) relative to placebo for the entire cohort. Patients on glimepiride alone and those on glimepiride + metformin experienced a placebo-subtracted baseline change in HbA1c of -0.6% and -0.9%, respectively.

Migoya *et al.* of New Jersey evaluated the complementary effects of sitagliptin and metformin on GLP-1 concentrations in healthy volunteers (286-OR). In a blinded, four-period crossover trial, monotherapy with each was compared with combination and placebo. Both metformin and sitagliptin increased active GLP-1 concentrations by 1.5- to 2-fold independently when compared with placebo, and the combination appeared synergistic resulting in a greater than 4-fold increase ($p < 0.001$). Of note, metformin increased total GLP-1, as well, consistent with an increase in GLP-1 release from the gut. Sitagliptin, in contrast, decreased total GLP-1, suggesting a negative feedback from the higher active GLP-1 concentrations. Such complementary actions may prove uniquely beneficial.

Vildagliptin, a DPP-IV inhibitor in Phase 3 trials, was added to existing glimepiride therapy in a double-blind, placebo controlled trial of 276 patients with Type 2 diabetes. Garber *et al.* of Houston, Texas assessed two different doses of vildagliptin (50 mg daily or BID) over a 24 week period (501-P). Once daily vildagliptin resulted in an adjusted mean change in HbA1c from baseline to week 24 of -0.7 \pm 0.1% ($p < 0.001$) versus placebo. Twice daily dosing did not confer additional benefit. There were no significant differences in the vildagliptin groups versus placebo with respect to hypoglycemia, weight gain, and adverse events. The authors suggest that a 50 mg once daily dose of vildagliptin is effective and well tolerated when added to a sulfonylurea.

Yet another investigational DPP-IV inhibitor, saxagliptin, was evaluated by DeFronzo *et al.* in 743 Type 2 diabetes patients with inadequate glycemic control (HbA1c ≥ 7.0 and $\leq 10.0\%$) on a stable metformin dose (285-OR). Patients were randomized to one of three saxagliptin doses

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(2.5, 5, or 10mg) or placebo, in addition to metformin in all groups, over a 24-week period. Statistically significant decreases in HbA1c and FPG occurred in all three treatment groups relative to placebo (Table 2). Saxagliptin was not associated with increased hypoglycemia rates and was weight neutral for all doses relative to placebo.

Modulators of the incretin system comprise a new (albeit relatively expensive) avenue to glycemic

Table 2. Impact of Saxagliptin Added to Metformin vs. Placebo

Saxagliptin Dose	HbA1c*	Fasting Plasma Glucose *
2.5 mg	-0.73% [†]	-16 mg/dl [†]
5 mg	-0.83% [†]	-24 mg/dl [†]
10 mg	-0.71% [†]	-21 mg/dl [†]

* Adjusted-mean placebo subtracted difference.

[†] Each, p < 0.0001.

control in our patients with Type 2 diabetes. As our clinical experience grows with these agents, and as more

research is conducted by the scientific community, we will certainly be learning more about their optimal role.



Renal Alphabet Soup: NKF, RAS, & CKD



Diabetic nephropathy occurs in 20-40% of patients with diabetes and is the single most common cause of end-stage renal disease (ESRD). Persistent albuminuria in the range of 30-299 mg/24h (microalbuminuria) is the earliest stage of diabetic nephropathy and a marker for the development of renal failure. It is also now a recognized marker for increased cardiovascular disease risk. Improved glycemic control with intensive insulin therapy, aggressive blood pressure management, and renin-angiotensin system (RAS) blockade have all been shown to reduce the development and/or progression of diabetic nephropathy. But, are these interventions aggressive enough and are we intervening early enough? These were questions addressed at a well-attended symposium, entitled "Hot Topics in Renal Disease."

To set the stage of the debate that was to follow, Dr. Robert Nelson, Phoenix, AZ reviewed the recently published clinical practice guidelines developed by the National Kidney Foundation (NKF). The development of the guidelines was based on the Kidney Disease Outcome Quality Initiative (KDOQI), which attempted to produce a unified definition of diabetic kidney disease. The guidelines aim to improve outcomes in diabetic patients with chronic kidney disease (CKD), by providing strategies for diagnosis and management. The guidelines take an evidence-based approach and each recommendation is graded accordingly (A to C based on the quality of the evidence). In all, five guidelines were developed (available at www.kidney.org), the first of which deals with the diagnosis of and screening for CKD, the other four dealing with its management. The guideline recommends screening for CKD annually in individuals with Type 1 diabetes of ≥5 years duration, and annually from diagnosis in Type 2 diabetes.

Screening can be done simply using the albumin:creatinine ratio (ACR) on a spot urine. Dr. Nelson reminded the audience that there is considerable variability in ACR measures and, as such, multiple tests may be required. He also commented that while estimated Glomerular Filtration Rate (eGFR) is helpful in monitoring disease progression, it is much less useful as a screening test and can only detect CKD stage 3 or worse. The stages of kidney disease are shown in Table 3.

The other guidelines concern the management of other co-morbid conditions that can accelerate disease progression; namely hyperglycemia, hypertension, dyslipidemia, and nutrition. Consistent with other national guidelines, they recommend targeting a HbA1c of <7.0%, blood pressure <130/80 mmHg, LDL-cholesterol <100 mg/dl, and limiting protein intake to 0.8g/kg body weight per day. Dr. Nelson briefly commented on the evidence base supporting each recommendation. He noted that physicians should be aware of the potential for lactic acidosis in subjects on metformin, of fluid retention for those on a TZD, and the increased risk of hypoglycemia from sulfonylureas (and also insulin) because of reduced drug clearance. He recommended an ACE-inhibitor or an angiotensin-receptor blocker (ARB) plus diuretic therapy as first-line treatment

for hypertension, but noted that subjects with CKD are likely to need three to four medications to control their blood pressure. Statins were advised as first-line therapy for dyslipidemia, with the proviso that they may not be indicated in patients on hemodialysis. Finally, dietary protein reduction has been shown to have clinical benefit and restricted protein intake is also endorsed by the guidelines once CKD is established. As Dr. Nelson pointed out, protein restriction to 0.8 g/kg body weight per day is actually the RDA for protein in all individuals and, as such, they are not recommending restriction as much as avoiding excess intake.

A review of these new guidelines provided the framework for the remaining speakers to address the more controversial areas of CKD management in diabetes. Dr. Hsueh presented data regarding RAS blockade for patients with microalbuminuria. Rodent and human studies appear to indicate that, in clinical practice, we may actually be using doses of ACE-inhibitors and ARBs that are too low to adequately block the effects of tissue angiotensin. In the DROP (Diovan Reduction of Proteinuria) study for instance, doses of valsartan up to 640 mg per day seemed optimally effective in reducing urine albumin excretion rates. Dr. Hsueh also revealed

Table 3. Stages of Kidney Disease Based on GFR

Stage	Description	GFR (ml/min per 1.73 m ² BSA)
1	Kidney damage with normal or increased GFR	≥90
2	Kidney damage with mildly decreased GFR	60-89
3	Moderately decreased GFR	30-59
4	Severely decreased GFR	15-29
5	Kidney failure	<15 or dialysis

BSA=body surface area; GFR-glomerular filtration rate.

Renal Alphabet Soup...

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data from animal studies suggesting that renin and pro-renin might independently cause proliferation of renal mesangial cells and be suitable additional targets for therapy. Similarly, TZDs may act on the nuclear transcription factor, PPAR γ in mesangial cells to reduce disease progression. Finally, she commented that we need to develop techniques for diagnosing the condition earlier and welcomed research on newer screening methodologies such as urinary podocyte detection that might enable earlier detection of CKD in diabetic patients.

The final two speakers, Dr. Vlassara of Mount Sinai Medical School in New York, and Dr. Cooper of Australia, reviewed the growing literature on the role of oxidative stress in the pathogenesis of CKD. The evidence points to depletion and exhaustion of defense systems in CKD leading to the build-up of reactive oxygen species (ROS) and advanced glycated end-products (AGEs). Dr. Cooper noted that while ROS and AGEs have a role to play in normal cellular processes, in excess they become toxic, and, independently of glucose, could accelerate CKD. Dr. Vlassara pointed out that while all the research focus has been on these pathways and mechanisms for reducing ROS production, little attention has been paid to the

Table 4. Prevalence of Anemia in Diabetes Patients Based on Kidney Function

CKD Category	eGFR >60	CKD Stage 3	CKD Stage 4	CKD Stage 5
N	477	206	52	30
Anemia (%)	29 (6.1)	56 (27.2)	23 (44.2)	23 (76.7)
Number on ESA	0	17	14	15
% Anemic on ESA	0	30	61	65

CKD=chronic kidney disease; ESA=erythropoiesis-stimulating agent.

amount of exogenous AGEs (mainly from cooked foods) we ingest on a daily basis. She showed some interesting mouse data where altering the diet to reduce AGEs intake dramatically reduced the progression of CKD. Both concluded by saying that increasing knowledge of these pathways might lead to the development of novel therapeutic strategies to limit the progression of CKD in diabetes.

Another risk factor for the progression of CKD is anemia, which occurs earlier when the renal disease is in the setting of diabetes. Aung and colleagues, Manchester, UK, measured hemoglobin levels in all blood samples collected for HbA1c in their general diabetic population over a six-week period (767-P). Most recent creatinine and eGFR (calculated with the MDRD formula) were collected, as was the use of erythropoiesis-stimulating agents (ESA). Their results are shown in Table 4.

The investigators concluded that anemia is common in individuals with diabetes and CKD Stage 3 or higher, but that erythropoetic stimulators appear to be underutilized in this population. They recommended screening for anemia in all diabetic individuals with eGFR <60. Caution is advisable, however—we are not aware of any evidence that such aggressive treatment reduces morbidity or mortality specifically in diabetic subgroups of CKD patients.

It is hoped that the development and widespread utilization of national guidelines will allow a more consistent and evidence-based approach to the management of CKD in our diabetic patients. Certainly for cardiovascular disease prevention, such guidelines have had a marked effect on disease progression—similar benefits in CKD may help slow the development of this very disabling complication of diabetes.



Striking Back at Stroke



Over the past several years, there has been increasing interest in the relationship between cerebrovascular disease, insulin resistance, and diabetes. Usman and British colleagues studied the prevalence of glucose intolerance in patients with acute stroke but no known prior history of glucose dysregulation (684-P). In all, 58 consecutive patients (50% female; mean age 79.2 ± 10.5 years) with acute stroke documented by CT scan were administered a 75-g oral glucose tolerance test (OGTT). Testing was conducted between 7-21 days after the event to avoid the potential effects of acute stress on glucose metabolism. Impressively, 67.2% of patients had abnormal glucose metabolism on OGTT (3.4% with impaired fasting glucose [IFG] only; 41.4% with impaired glucose tolerance [IGT] only; 8.6% with both IFG + IGT; and 13.8% with diabetes.) The mean fasting glucose in the group was 99 ± 14 mg/dl. Notably, fasting glucose itself failed to identify almost 59% of patients found to have glucose intolerance. The presenters concluded

that glucose dysregulation is widely prevalent in an acute stroke population, for which routine fasting glucose determination is a highly insensitive marker. They suggested that their data support the need to perform OGTTs to better evaluate glucose metabolism in patients with cerebrovascular disease. We would offer two criticisms. First, it's not clear if those patients studied within a week or two of their stroke event may still have been suffering from "stress hyperglycemia" due to insulin resistance from the stress hormones of acute illness. Unfortunately, there are few data to inform us as to how long to wait to optimally assess glucose tolerance after stroke. Secondly, while the results are interesting, they cannot speak to whether these patients might benefit from such identification for purposes of, presumably, therapy. We need more information regarding the benefits of treatment for mild glucose abnormalities in this older group of patients.

Insulin resistance has been proposed as one explanation for the high rates of atherosclerotic

events, including stroke, in the Type 2 diabetic patient. Increased carotid intima-media thickness (IMT), a sonographic surrogate marker for atherosclerotic burden, has been documented in patients with a variety of glucose abnormalities. The relationship between insulin resistance and carotid IMT has not been rigorously assessed. Park and Korean colleagues measured carotid IMT in 3,144 patients with Type 2 diabetes (51.4% male, mean age 56.8 ± 10.3 years) (269-OR). Insulin sensitivity was measured with an insulin tolerance test, using the rate constant for plasma glucose disappearance after the intravenous injection of 0.1 units/kg of regular insulin. IMT was then measured by B-mode ultrasound. Multiple regression analysis was used to test for an independent association of insulin resistance and IMT, adjusting for potential confounders. Carotid IMT decreased step-wise with increasing insulin sensitivity. After controlling for gender, age, BMI, blood pressure, and LDL-cholesterol, the association between insulin sensitivity and IMT persisted. The odds ratio for

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carotid atherosclerosis was 1.61 (95% confidence intervals [CI] 1.21-2.12) for men and 2.14 (95% CI 1.60-2.86) in women in the lowest quartile of insulin sensitivity, as compared to those in the highest quartile. The presenters concluded that insulin resistance is an independent risk factor for carotid atherosclerosis in patients with Type 2 diabetes.

Sulfonylureas close ATP-sensitive potassium channels, thereby causing insulin secretion from pancreatic beta cells. These channels are widely expressed throughout the body, including brain, and it's been suggested that they may serve a protective role during cerebral hypoxia. Recently,

activating the sulfonylurea receptor in an animal model of stroke was shown to have a neuroprotective effect by reducing cerebral edema and infarct volume. Theodorakis *et al.* from Greece studied 570 patients with Type 2 diabetes with a first stroke event who were receiving oral anti-diabetic agents, and compared them to 250 patients treated with insulin or diet alone (703-P). Of those on oral agents, 58% were taking sulfonylurea drugs. A standardized stroke scale was employed to assess for neurological impairment. Higher stroke scale scores, indicative of less impairment, were seen in the group taking sulfonylureas. Prior sulfonylurea use was the only independent predictor of neurological severity by linear

regression analysis. Also, those taking sulfonylureas were less prone to MRI-detected lacunar infarcts, as compared to the non-sulfonylurea patients (19.6% vs. 25.6%, $p < 0.001$). The group concluded that prior sulfonylurea use was associated with less severe immediate neurological deficits in Type 2 diabetic patients with stroke. Further studies will be needed to confirm these findings. Conceivably, however, targeting sulfonylurea receptors may provide a new therapeutic approach in acute stroke care.

Understanding the epidemiology, pathogenesis, and potential therapies for diabetic patients with stroke should eventually open up new avenues of care.



The Heart of the Matter



Wackers *et al.* from New Haven, CT presented follow-up data from their Detection of Ischemia in Asymptomatic Diabetics (DIAD) study (263-OR). This group has previously reported a 22% prevalence of silent myocardial ischemia in 522 patients with Type 2 diabetes, aged 50-75 years with normal ECG and no history, symptoms, or signs of coronary artery disease. Ischemia was detected using adenosine sestamibi SPECT stress imaging (DIAD-1). At three years of follow-up, repeat SPECT was performed in 356 patients (DIAD-2). 166 had no repeat study due to coronary events, revascularization, new co-morbidities, refusal, or loss to follow-up. In those who had repeat SPECT, the abnormality rate was similar to the original group at 20%. On repeat SPECT, 79% of patients with silent myocardial ischemia in DIAD-1 showed resolution of their original abnormality in DIAD-2. Of the patients with a normal original study, only 10% developed a new abnormality reflective of new ischemia. The SPECT scans were interpreted by a blinded expert panel, and confirmed through a

computer quantification program. The entire DIAD cohort was more aggressively treated over time, likely due to increasingly rigid recommendations concerning cardiovascular risk factor reduction from national organizations, including the ADA. Patients with resolution of ischemia in DIAD-2 had more aggressive management of cardiovascular disease (CVD) risk factors, with greater duration of time (68 ± 30 vs. 52 ± 30 total drug-months, $p = 0.04$) on the composite of a statin, ACE-inhibitor and/or aspirin. These data were surprising to the investigators who predicted more ischemia over time, but are consistent with recent data from the INSPIRE and COURAGE trials, demonstrating that aggressive medical management has substantive benefits on CVD outcomes. The DIAD investigators are continuing to follow their patients for a total of five years to examine event rates vs. a natural history cohort of patients on whom baseline demographic and laboratory data was obtained but who did not undergo SPECT imaging.

Reaven *et al.* presented provocative data

from the VA Diabetes Trial (VADT) study, correlating the presence and degree of retinopathy to sub-clinical atherosclerosis as measured by coronary artery calcium (CAC) scores on CT scan (268-OR). The study cohort consisted of 211 veterans (95% male, mean age 62.1 ± 9.2 years, diabetes duration 12.5 ± 8.5 years, HbA1c $9.2 \pm 1.4\%$). After multivariable adjustments, which included established cardiovascular risk factors, the presence of proliferative diabetic retinopathy (PDR) was significantly associated with coronary atherosclerosis, with a 3.2-fold increase in CAC if PDR was present. Patients with PDR were more than eight times more likely to have a CAC score of >400 , considered a clinically relevant high-risk group. These data demonstrate a surprisingly strong relationship between retinopathy and the extent of coronary atherosclerosis. First, this suggests that the identification of patients with retinopathy identifies a high-risk group of patients. It also suggests that microvascular and macrovascular disease may share common risk factors and origins.



So Many Posters, So Little Time....



A Calcium-Diabetes Connection?

Florez and coworkers evaluated the association of daily calcium intake and 25-hydroxy-vitamin D (25[OH]Vit D) levels with fasting hyperglycemia (serum blood glucose ≥ 126 mg/dl) in 168 adult South Floridians (63% female, 72% Hispanics, mean age = 56.1 years, BMI = 30.5 kg/m^2) (68-OR). After adjusting for demographic variables, sun exposure, vitamin D intake, BMI, and hypertriglyceridemia, a low vitamin D level was associated with higher risk (OR = 2.7, 95% CI 1.02-7.2) and sufficient total calcium intake (i.e., $\geq 1\text{g/day}$) was associated with

lower risk (OR = 0.46, 95% CI 0.22-0.97) of fasting hyperglycemia. The mechanisms here are not known.

Pramlintide + Insulin for Type 2 Diabetes

In a 16-week, double-blind study, Lutz *et al.* from San Diego randomized 211 Type 2 diabetes patients using insulin glargine \pm oral hypoglycemic agents to the amylin analogue pramlintide (60 or 120 μg) or placebo injections with major meals (536-P).

Benefits from the addition of pramlintide included modest improvements in glycemia (mean HbA1c change of $-0.70 \pm 0.11\%$ vs. $-0.36 \pm 0.08\%$ with placebo, $p < 0.05$; mean post-prandial glucose excursions $-24.4 \pm 3.6 \text{ mg/dl}$ vs. $-0.4 \pm 3.0 \text{ mg/dl}$ with placebo, $p < 0.0001$) and weight loss ($-1.6 \pm 0.3 \text{ kg}$ vs. $+0.7 \pm 0.3 \text{ kg}$ with placebo, $p < 0.0001$). Despite improved glycemic control, the risk of hypoglycemia was not increased (57% vs. 55%).

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