

Diabetes 2009

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At the Heart of Diabetes



Important data on diabetes presented at the 69th Annual Scientific Sessions of the American Diabetes Association come to you in **Diabetes 2009**, 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 2009** will be followed by a **Diabetes 2009** 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 AMA PRA Category 1 Credits™ to be issued by Yale University School of Medicine.

Diabetes 2009 is being offered to physicians practicing in the United States. After successfully completing this program, participants will be able to:

- Describe the mechanisms of β -cell failure, the progression of diabetes, and its complications.
- Implement strategies for the early diagnosis and treatment of diabetes.
- Recognize the manifestations of the macrovascular and microvascular complications of diabetes and describe appropriate therapies.
- Understand the interrelationship between insulin resistance, hyperglycemia, and atherosclerosis in patients with Type 2 diabetes.
- Compare the mechanisms of action of diabetes therapies, their risks, benefits, and proper roles in disease management.
- Identify evolving and emerging therapeutic strategies in diabetes care.
- Describe the approach to managing dyslipidemia, hypertension, and cardiovascular risk factors in patients with diabetes.

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Coronary heart disease (CHD) occurs so frequently in people with diabetes that their management should be focused upon reducing cardiovascular (CV) risk. In a symposium on managing heart disease risk in diabetes, David Matthews, MD from the University of Oxford and Jorge Plutzky, MD from the Brigham and Women's Hospital in Boston, MA, addressed the question of whether it matters how we get to blood pressure and lipid goals. Each speaker reviewed the multiple trials showing the benefits of lowering blood pressure and LDL-cholesterol in reducing CVD morbidity and mortality. In addition, they noted which agents may give further benefit. Dr. Matthews concluded that beta blockers have been superseded by angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers in their ability to provide additional protection from cardiac events and mortality. However, he emphasized that the literature would indicate that lowering of blood pressure to goal carries the largest impact on morbidity and mortality regardless of the agent used.

Dr. Plutzky reached a similar conclusion regarding lipid therapy—that it generally does not matter how cholesterol goals are specifically achieved, with lower LDL-cholesterol and higher HDL-cholesterol values almost routinely conferring CV protection. Clearly, statins are the most powerful reducers of LDL-cholesterol and have the best effect on CHD events. The sole exception to this paradigm appears to be torcetrapib, the cholesterol-ester transfer protein inhibitor, which showed adverse effects on blood pressure despite causing a marked increase in HDL-cholesterol. As a result, this drug appeared to have a deleterious effect on CV outcomes. Further development of this agent was subsequently terminated.

We would also add that some very alluring dual PPAR agonists (α/γ) had shown discouraging clinical results despite seemingly potent effects on plasma lipids. Moreover, while we agree with Dr. Plutzky as regards to LDL-cholesterol, we are less impressed with the results of studies targeting triglycerides and HDL (ie, fibrates), at least in diabetic cohorts.

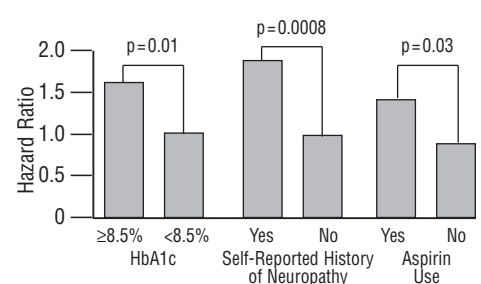
In contrast to blood pressure and most lipid therapies, recent investigations have not been able

to demonstrate a benefit on CV outcomes from more stringent glucose control. An update on the ACCORD trial and other CVD related topics were the focus of numerous poster and oral presentations, some of which are summarized below.

ACCORD Update

Intensive, as compared to standard, glycemic intervention has been shown to increase all-cause mortality in one study (Action to Control Cardiovascular Risk in Diabetes [ACCORD], target HbA1c <6%), but not in two others (Action in Diabetes and Vascular Disease: PreterAx and DiamicroN MR Controlled Evaluation [ADVANCE] and VA Diabetes Trial [VADT] of Glycemic Control and Complications in Diabetes Mellitus Type 2). Calles *et al.* analyzed the relationship between baseline characteristics of the ACCORD study patients and all-cause mortality at the time the intensive arm of the study was prematurely discontinued, with the objective of identifying if any clinical characteristics could be used to predict adverse outcomes (abstract 88-OR). A total of 460 deaths (257 intensive treatment, 203 standard treatment) occurred among 10,251 patients during 3.5 years of mean follow-up. A statistically significant interaction was observed between 3 baseline characteristics and increased mortality with intensive vs. standard therapy (Figure 1). Other variables (eg, diabetes duration, any oral agent, insulin use, use of an antihypertensive agent, statin use, history of prior cardiovascular disease [CVD]) did not have significant interactions

Figure 1. Baseline Characteristics Predict Increased Mortality in ACCORD



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with approach to glycemia treatment on mortality. On the basis of their findings, the investigators suggested that patients with Type 2 diabetes and an HbA1c >8.5%, a prior clinical history of neuropathy, and/or using aspirin may be less suitable for intensive glycemic control. The latter finding is somewhat counterintuitive and requires further study. Of note, the American Diabetes Association is currently revising its recommendations regarding routine aspirin therapy as prophylaxis against CVD events, based on several recent trials suggesting less overall benefit than had been anticipated from studies conducted in non-diabetic individuals.

Risk Factors

Chen *et al.* from Texas and New Jersey conducted a systematic literature review and meta-analysis to confirm the direct association between HbA1c in Type 2 diabetes patients and their risk of developing macrovascular diseases (abstract 704-P). A total of 19 prospective cohort studies and 20 randomized, controlled trials, published between 1966 and 2008, were identified and included in the analyses. In random effect models, the pooled estimates from prospective cohort studies showed a 14% increased risk of developing macrovascular complications per 1% increase in HbA1c level (relative risk [RR] 1.14, 95% CI 1.08-1.20). In the meta-analysis of randomized, controlled trials, lowering HbA1c led to a 21% reduction in the incidence of macrovascular events (RR 0.79, 95% CI 0.68-0.9), comparing intervention groups to control groups. The investigators concluded that, given that the majority (~75%) of deaths among diabetes patients are due to CVD, improved glycemic control should have a substantial, favorable impact on public health. It is notable, however, that the three aforementioned trials have not been able to demonstrate this very reasonable conclusion, ACCORD, actually showing increased mortality in the intensive therapy group. Meta-analyses notwithstanding, what is learned from epidemiological associations may not always translate therapeutically.

Results of the Carotid Intima-Media Thickness (CIMT) in Atherosclerosis Using Pioglitazone (CHICAGO) study demonstrated that pioglitazone significantly decreased CIMT progression compared to glimepiride in patients with Type 2 diabetes (Mazzone *et al.*, *JAMA* 2006;296:2572-81). At week 72, progression of mean CIMT was -0.001 mm and +0.012 mm for the thiazolidinedione (TZD) and sulfonylurea, respectively (p=0.02). This week, Davidson and US associates presented results of change in coronary artery calcium (CAC), a secondary endpoint of the study (abstract 717-P). CAC, a

marker for subclinical atherosclerotic disease, measured by electron beam computed tomography (EBCT), may be utilized in CVD risk stratification of patients; the amount of calcium within plaque was quantified with the Agatston scoring method. There was no significant difference between the TZD (n=146) and sulfonylurea (n=153) treatment groups in median change of CAC from baseline to end of treatment (up to 18 months). Factors associated with insulin resistance had the strongest association with CAC progression: age (p<0.0001), triglycerides, TG/HDL-cholesterol ratio, BMI, waist-hip ratio, visceral adipose tissue volume, and VCAM1 (vascular cell adhesion molecule-1) (all p<0.05). However, *change* in these variables over the course of the study was not related to CAC progression. Interestingly, baseline or change in CIMT were also not predictors of CAC progression. From these CAC data, one might conclude that pioglitazone has no effect on atherosclerosis as compared with sulfonylurea. However, this contradicts the primary endpoint findings of CHICAGO, and also those of PERISCOPE, which found differential effects (favoring pioglitazone) on coronary disease as measured by intravascular ultrasound (IVUS). It may also be that CAC scoring is not sensitive enough measure to reflect the possible changes induced by these therapies.

Gastaldelli and other RISC (Relationship between Insulin Sensitivity and Cardiovascular disease) study investigators reported on the association between CHD risk (Framingham score) and early carotid atherosclerosis (ie, CIMT) with certain metabolic parameters, insulin sensitivity (M/I, by euglycemic-hyperinsulinemic clamp), and physical activity (assessed by accelerometry) (abstract 673-P). RISC includes ~1300 European subjects (age 30-60 years, BMI 20-45 kg/m²) without diabetes, hypertension, or clinically manifest CVD. Since subjects with abdominal obesity and/or non-alcoholic fatty liver disease (NAFLD) have a higher risk of developing both diabetes and CVD, the investigators also evaluated the value of NAFLD in predicting CHD. Presence of NAFLD was estimated using the fatty liver index

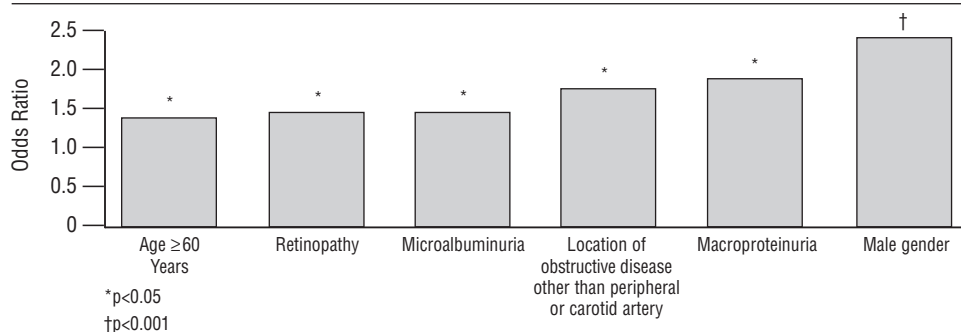
(FLI), which is comprised of waist circumference, BMI, triglycerides, and GGT level (FLI>60 indicates a >78% likelihood of NAFLD; FLI<20 indicates a >91% likelihood that NAFLD is *absent*).

The study cohort was at low overall risk for CHD (83% were at below average risk). According to multivariate analysis, the 10-year CHD score was positively and independently associated with BMI and waist circumference, and negatively associated with physical activity and M/I (R²=0.24, all p<0.01). Fatty liver index alone was related to CHD before (R²=0.23) and after (R²=0.26, p<0.0001) adjustments for physical activity. By multivariate analysis, independent determinants of CIMT were M/I (p=0.01), age, systolic blood pressure, LDL-cholesterol, and gender (all p<0.0001, R²=0.27). When the fatty liver index was added to the model, it was independently correlated to CIMT (p=0.0001), replacing M/I (R²=0.27). These findings suggest that in middle-aged, nondiabetic individuals, NAFLD is independently associated with increased CIMT and CHD risk. Calculation of fatty liver index from ordinary metabolic and anthropometric data may therefore be considered as a simple cardiometabolic risk score. These data confirm findings from other groups. The specific explanation for this phenomenon is unknown, but may be related to hepatic lipid metabolism.

Silent CAD

Cosson and French colleagues explored 781 asymptomatic diabetic patients with ≥1 risk factor for silent MI (eg, nephropathy, peripheral or carotid occlusive artery disease) with myocardial scintigraphy after exercise stress, dipyridamole injection, or both between 1992 and 2006 (abstract 639-P). Silent MI was found in 227 patients (29%). A clinical score to identify patients at high risk of silent MI was then tested in a cohort of 482 Type 2 diabetes patients who had also undergone scintigraphy. Predictive factors are shown in Figure 2. A clinical score (1 point for each factor, 2 points for male gender) ≥3 compared to <2 was predictive for silent MI (61% vs. 37%, OR 2.6 [1.9-3.6], p<0.0001), with a

Figure 2. Predictive Factors for Silent MI in Asymptomatic Diabetes Patients



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sensitivity, specificity, and positive and negative predictive values of 61%, 63%, 40%, and 80%, respectively. The area under the receiver operating curve (AROC) was 0.648, $p < 0.0001$. We would point out, however, that a recent randomized clinical study, DIAD (Young *et al.*, *JAMA* 2009;301:1547), found no ultimate change in CV outcomes between patients who had undergone screening myocardial perfusion imaging and those who were unscreened. Accordingly, even though routine stress testing may detect evidence of coronary disease, it is unclear if this leads to any ultimate benefit for patients, especially in an era of aggressive CVD risk factor reduction with statins, ACE inhibitors, etc.

In a related study, Umemoto and Japanese coworkers conducted a cross-sectional study to determine the value of multi-slice computed tomography coronary angiography (MCTCA) for the non-invasive detection and characterization of coronary atherosclerotic plaques in patients with diabetes (abstract 738-P). The presence of coronary narrowing, plaques, and calcifications was evaluated by 64-slice MCTCA in 96 consecutive patients (mean age 64.9, 71% male, HbA1c 7.1) who had no apparent ischemic symptoms or ECG abnormalities in the previous 5 years. No significant stenosis was observed in two-thirds of the study patients (66%, $n=63$), with 25% ($n=24$) having normal coronary arteries and 41% ($n=39$) having $<50\%$ luminal narrowing. In 7 (7%) patients, 50-75% stenosis was detected, although ischemia was excluded by exercise stress test. In 23 (24%) patients, more than 75% stenosis was detected by MCTCA, with stenosis confirmed by standard coronary angiography in 16 of 20 patients. In these individuals, the mean Hounsfield unit score, used to characterize the nature of plaques, was 154 ± 52 , suggesting that most of them were non-vulnerable, fibrous/lipid plaques. The Hounsfield unit score was similar between patients with $>75\%$ versus $<50\%$ stenosis. The investigators concluded that 64-slice MCTCA could provide important information for identifying not only the presence, but also the compositional nature of the plaques. We agree, although in light of the above discussion, it remains unclear even if this degree of information would necessarily result in any change in therapy, to say nothing of event rates themselves.

Cardiac Neuropathy

Diabetic autonomic neuropathy (DAN) (Table 1) is associated with a 5-fold increase in CV mortality. Since it is often irreversible at the time of diagnosis, screening and early detection may be

Table 1. Manifestations of Diabetic Autonomic Neuropathy

CV	<ul style="list-style-type: none"> ■ Resting tachycardia ■ Reduced heart rate variability ■ Orthostatic hypotension ■ Silent ischemia
GI	<ul style="list-style-type: none"> ■ Esophageal dysfunction ■ Gastroparesis ■ Diarrhea/constipation ■ Fecal incontinence
GU	<ul style="list-style-type: none"> ■ Neurogenic bladder ■ Erectile dysfunction ■ Retrograde ejaculation
Other	<ul style="list-style-type: none"> ■ Sudomotor dysfunction/gustatory sweating

important. With this in mind, Oleolo *et al.* from Great Britain evaluated spectral analysis of heart rate variability and dynamic pupillometry as early, non-invasive, screening tests for DAN in 48 patients with diabetes (Type 1, $n=16$; Type-2, $n=32$) and 16 age- and gender-matched healthy volunteers (abstract 239-OR). On the basis of standard cardiac autonomic function and baroreceptor sensitivity test results, the diabetes patients were classified as having no autonomic neuropathy ($n=14$), subclinical disease ($n=17$), or established disease ($n=17$). In spectral analysis of heart rate variability, subjects with subclinical illness had the lowest RR interval variation (volunteers 937.0 ± 114.1 , no-DAN 880.9 ± 138.8 , subclinical-DAN 677.2 ± 73.2 , established-DAN 830.9 ± 120.7 ; $p < 0.05$). Subjects in the subclinical and established DAN groups had the longest delay in latency to constriction time (0.26 ± 0.05 , 0.27 ± 0.07 , 0.34 ± 0.04 , and 0.34 ± 0.08 ms for the respective groups; $p=0.02$). So, both spectral analysis of heart rate variability and dynamic pupillometry may have a role in detecting autonomic dysfunction in asymptomatic diabetic patients who have otherwise normal cardiac autonomic function. Prospective studies will be required, however, to determine whether earlier identification of DAN, prior to the onset of symptoms, and targeted intervention will improve long-term outcomes. The obvious question is whether the onset of this form of neuropathy is at all modifiable outside of standard glucose control recommendations.

Lipid Therapy & Gender

Fenofibrate (200 mg/day) significantly reduced total CVD events, hospitalization for acute coronary syndromes, amputations, the need for coronary or carotid revascularization, laser therapy for diabetic retinopathy, and progression of proteinuria in the placebo-controlled FIELD (Fenofibrate

Intervention and Event Lowering in Diabetes) trial into which 9,795 patients (3,657 women) with Type 2 diabetes and not taking statin therapy were enrolled (Keech *et al.*, *Lancet* 2005;366:1849-61). In analyses conducted by D'Emden and Australian coworkers, fenofibrate conferred more favorable effects in women for selected endpoints (abstract 662-P): Mean reduction in LDL-cholesterol was larger in women (16.5% vs. 9.4% in men; $p < 0.001$), although the effects on HDL-cholesterol were not different between the genders. After adjustment for CVD medication, uptake of statin therapy, and baseline covariates (weight, use of estrogen), CVD event reductions with fenofibrate were more than 2-fold greater in women (29% vs. 13% for men; interaction $p=0.1$). These new findings suggest that fibrate therapy may have a greater impact in women than in men—the reasons for which remain unclear. We would remind our readers, however, that there was no overall effect from fenofibrate therapy on FIELD's primary endpoint, CHD death and non-fatal MI (0.89 [95% CI, 0.75-1.05]).

More Benefits from Exercise

Inflammation plays a central role in the initiation and progression of atherosclerotic disease and in the occurrence of atherothrombotic events. Belalcazar and US co-investigators of Look AHEAD (Action for Health in Diabetes) compared the impact of intensive lifestyle intervention (using behavior modification) to diabetes support and education on levels of high sensitivity C-reactive protein (hs-CRP), a biomarker of sub-clinical chronic inflammation (abstract 694-P). hs-CRP levels were measured at baseline and at 1 year in a subset of 1,759 overweight/obese individuals with Type 2 diabetes. Based on multiple linear regression, change in hs-CRP was significantly greater in the intensive lifestyle intervention group than in the group provided solely support and education (-38% vs. -8% , $p < 0.0001$). Median hs-CRP levels were 4.2 mg/dl at baseline, 2.4 mg/l at 1 year for intensive lifestyle intervention, and 3.5 mg/l at 1 year in the control group. Decreases in hs-CRP were greater in women (-29% vs. -19% in men, $p=0.0032$). A significant decrease in hs-CRP was seen in subjects who experienced greater improvements in adiposity measures, fitness, glucose control, triglycerides, and HDL-cholesterol level. The investigators concluded that lifestyle intervention in obese diabetic patients can lead to the modulation of chronic subclinical inflammation. This is an extremely important finding, especially given the increasing obesity rates in our society. It would follow logically, but remains to be proven, that lifestyle interventions in these individuals would translate to a long-term benefit on CV events.

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Musings on Medalists

Geltman *et al.* from Boston and Cleveland studied a large cohort (n=351) of patients with long-standing (≥ 50 years) Type 1 diabetes (referred to as 'medalists') (abstract 742-P). While the investigators previously reported that this unique group of patients has lower rates of microvascular complications (retinopathy and nephropathy) than expected, they found their prevalence of CVD to

be higher (48.5%) compared to age-matched patients with Type 2 diabetes from the NHANES (46.1%) and patients with shorter duration of Type 1 diabetes as reported by the EDC (23.1%), DCC (5.8%), and EURODIAB (6.5%). The risk factors associated with CVD among the medalists were similar to those among Type 1 and Type 2 diabetes patients with disease of shorter duration, contrary to the pattern of risk factors associated with nephropathy and retinopathy. After adjustments for potential confounders (lipid lowering medications, nephropathy, HbA1c), age, diabetes duration,

diastolic blood pressure, heart rate, inflammatory factors, male gender, the advanced glycation end product (AGE) carboxyethyl-lysine, and LDL-cholesterol were significantly associated with CVD ($p < 0.05$). Thus, it appears that although surviving patients with prolonged Type 1 diabetes may be somehow protected from small vessel disease, they do not appear to be protected from CVD, despite a generally non-atherogenic lipid profile. Other typical risk factors combined with factors related to AGE metabolism may increase the risk of CVD in this cohort.



Get a Move On It!



In an afternoon symposium entitled "How to Get Inactive People to Exercise," Chairperson Judith Regenstein, PhD, presided over four distinct presentations related to the topic. Jill Kanaley, PhD, exercise physiologist, Syracuse, led the session differentiating between exercise and physical activity, the former being more planned and structural. Technology has diminished physical activity for the average individual, who is now sedentary for a significant portion of an average day. Despite even a morning exercise routine, for example, many individuals remain relatively sedentary throughout the remainder of the day. Research demonstrates that there are acute and chronic physiologic effects of such sedentary behavior. Thus, all individuals, but especially those with diabetes, should not only be coached to exercise each day, they should also be encouraged to increase activity and expend energy throughout the day.

When exercise is prescribed, both aerobic activities and resistance training should be included as each is associated with significant benefits. An individualized approach is key. Aerobic activities include biking, swimming, and/or walking, with a gradual increase in duration and frequency over time. When instructing on resistance training, Dr. Kanaley suggests beginning with 8-10 exercises that target larger muscle groups in both the upper and lower body, with a frequency of 2-3 times weekly. Both endurance and strength result from resistance training. One critical component of resistance training is teaching proper technique for weight lifting. Patients must be supervised to perform slow controlled motions, complete full range of motion of joints, and proper breathing. When targeting endurance, increased repetition is key. To improve strength, increases in intensity are recommended. Although programs must be designed specifically for each patient, Kanaley suggests initially targeting burning 1000 calories/week by exercising 3-4 days per week at 30 minutes per day and increasing physical activity by 2.5 hours/week.

One method of aerobic exercise testing is to evaluate recovery heart rate. The rate of decrease in heart rate after exercise is related to fitness and is actually inversely proportional to survival statistics. Ideally, one should decrease

heart rate by 20 beats per minute within the first or second minute after exercising.

Additional recommendations include encouraging patients to stretch, in particular, the Achilles tendon, to minimize pain in the initial stages of

Table 2. Key 2008 Physical Activity Guidelines for Americans

Adults

- All adults should avoid inactivity. Some physical activity is better than none, and adults who participate in any amount of physical activity gain some health benefits.
- For substantial health benefits, adults should do at least 150 minutes (2 hours and 30 minutes) a week of moderate-intensity, or 75 minutes (1 hour and 15 minutes) a week of vigorous-intensity aerobic physical activity, or an equivalent combination of moderate- and vigorous-intensity aerobic activity. Aerobic activity should be performed in episodes of at least 10 minutes, and preferably, it should be spread throughout the week.
- For additional and more extensive health benefits, adults should increase their aerobic physical activity to 300 minutes (5 hours) a week of moderate intensity, or 150 minutes a week of vigorous intensity aerobic physical activity, or an equivalent combination of moderate- and vigorous-intensity activity. Additional health benefits are gained by engaging in physical activity beyond this amount.
- Adults should also do muscle-strengthening activities that are moderate or high intensity and involve all major muscle groups on 2 or more days a week, as these activities provide additional health benefits.

Older Adults

The Key Guidelines for Adults also apply to older adults. In addition, the following guidelines are just for older individuals:

- When older adults cannot do 150 minutes of moderate-intensity aerobic activity a week because of chronic conditions, they should be as physically active as their abilities and conditions allow.
- Older adults should do exercises that maintain or improve balance if they are at risk of falling.
- Older adults should determine their level of effort for physical activity relative to their level of fitness.
- Older adults with chronic conditions should understand whether and how their conditions affect their ability to do regular physical activity safely.

People With Chronic Medical Conditions

- Adults with chronic conditions obtain important health benefits from regular physical activity.
- When adults with chronic conditions do activity according to their abilities, physical activity is safe.
- Adults with chronic conditions should be under the care of a health-care provider. People with chronic conditions and symptoms should consult their health-care provider about the types and amounts of activity appropriate for them.

Source: <http://www.health.gov/paguidelines/guidelines/summary.aspx>

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Get a Move On It!

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walking/running, thereby promoting adherence to the program. Dr. Kanaley emphasized the need for proper fitting shoes that are well constructed and replaced regularly. Most running shoes, if worn regularly, break down in as early as 3-4 months and subsequently lack proper support. Motivators for patients may include pedometers and walking or running with dogs. She also suggests advising patients to find creative places to increase physical activity.

Peter Cavanaugh, PhD, DSc, University of Washington, next discussed exercise, foot care, and safety in the patient with diabetes. He noted the ADA guidelines regarding exercise in patients with severe peripheral neuropathy (*Diabetes Care*, 2009), suggesting it to be a relative contraindication, predisposing patients to injury. Cavanaugh then contrasted the view of exercise from the perspective of an exercise physiologist and that of a biomechanist. The latter sees exercise as the forces upon various parts of the body, including the feet. Various types of activities considered comparable by the exercise physiologist from a basal oxygen uptake (MET) perspective, are very different with respect to the stress they exert at the level of the feet. Thus, equivalent 4 MET exercises (swimming 0.25 mph, biking 9 mph, and walking 4 mph) may be metabolically identical, yet, from a biomechanical point of view, are very different activities as far as

the feet are concerned, especially in anyone with underlying neuropathy or joint deformities. Such an approach to exercise evaluation would therefore not necessarily eliminate the diabetic patient with even severe peripheral neuropathy as a candidate for an exercise program.

Dr. Cavanaugh concluded his presentation with several recommendations for the patient with peripheral neuropathy in whom exercise is pursued: educate patients about the potential risks; prior to any program, begin with a foot exam; and, examine footwear closely (proper length, socks, etc.). It has been demonstrated that only 1 in 4 patients with diabetes has correctly sized shoes; patients who develop ulcers are 5 times more likely to have had poorly-fitting shoes. Additional recommendations include offering diverse activities; do not arbitrarily limit walking; promote foot self-exams, including temperature monitoring; and, encourage regular foot care.

Dr. Allison Kirk, University of Strathclyde, Glasgow, Scotland, continued the symposium sharing motivational techniques to promote exercise. The first is to encourage patients to walk more, especially given the data demonstrating its numerous health benefits in patients with diabetes. These include decreases in all-cause and CV mortality as well as economic benefits resulting from decreased prescriptions and overall healthcare costs. Pedometers may assist in promoting walking activities. Encourage patients to minimize sedentary behavior. One technique that has shown

positive results at an institutional level is the 'point-of-choice prompt.' An example of this technique is the placement of signage near an elevator reminding an individual of the location of the stairs. She cited one investigation that demonstrated that point-of-choice prompts increased stair use by 54%. Finally, incorporate behavioral strategies such as goal setting, self-monitoring, feedback, and stimulus control.

Lastly, William Haskell, PhD, Stanford University, reported on the recently revised federal guidelines entitled *2008 Physical Activity Guidelines for Americans* (Table 2). Dr. Haskell described the meticulous process for the development of the guidelines, stating that the primary goal is physical activity as it relates to public health. The guidelines recommend avoiding inactivity, consistent with the message provided by all the symposium presenters. The guidelines recommend that adults participate in 150-300 minutes of moderate-intensity or 75 minutes of vigorous-intensity aerobic exercise each week. Studies have confirmed that the benefits of aerobic activity are identical regardless of whether the activity is one 150-minute interval versus 5 x 30 minute events each week. It is also suggested to mix moderate and vigorous intensity along with resistance training twice weekly. The complete guidelines may be accessed at www.health.gov/paguidelines and will benefit all of our patients, not solely those with diabetes.



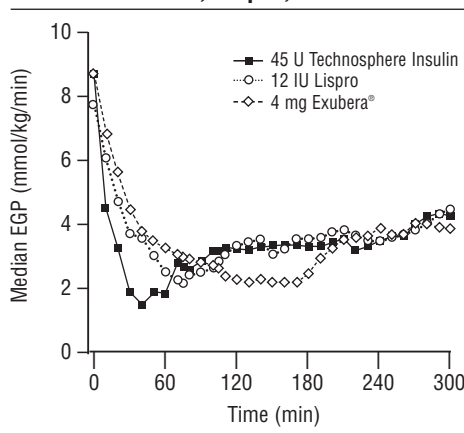
New Twists to Insulin Therapy



Insulin therapy is obviously required by all patients with Type 1 diabetes and by a substantial proportion of patients with Type 2 diabetes, whose beta-cell secretory capacity has faltered, typically late in the disease course. In the latter group, insulin therapy is frequently delayed for many reasons, one of which is the perception that insulin is an inconvenient therapeutic option. Accordingly, there has been sustained interest in non-invasive or somehow easier delivery systems for this important hormonal therapy.

Despite the recent commercial failure of Exubera® and the subsequent termination of several large development programs in inhaled insulin, there continues to be some interest in pulmonary delivery. Potocka *et al.* from Great Britain and the US compared 45 units Technosphere® insulin (Afresa™) by inhalation with 12 IU subcutaneous insulin lispro and 4 mg inhaled human insulin (Exubera®) in an open-label, single-dose, 3-way crossover study of 18 insulin-treated patients with Type 2 diabetes and normal pulmonary function

Figure 3. Median Endogenous Glucose Production (EGP) Following Single Dose Technosphere® Insulin, Lispro, and Exubera®



(abstract 232-OR). Suppression of endogenous glucose production (mainly, liver) occurred markedly

earlier with inhaled Technosphere® insulin, followed by lispro and Exubera® (40, 75, and 130 minutes, median profiles) (Figure 3). Significant differences up to 40 minutes were observed between Technosphere® insulin and lispro ($p < 0.002$) and up to 2 hours with Exubera® ($p < 0.05$). Median total areas over the endogenous glucose production (EGP) curve and median postprandial blood glucose areas under the curve were comparable across the treatment groups. These data suggest that the pharmacokinetic profile of Technosphere® insulin—achieving peak insulin levels within 12 to 14 minutes of dosing—may result in a more physiologic suppression of endogenous glucose production.

Other injectable medications may also be delivered with the same technology. Also using a Technosphere® particles system, Costello *et al.* from the US and The Netherlands reported on a study of 1.5 mg MKC253, a glucagon-like peptide (GLP)-1 analogue, which was administered by oral inhalation to 6 healthy subjects in one study, and in a second study, was given to 15 patients

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New Twists to Insulin Therapy

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with Type 2 diabetes (and compared to inhaled placebo in 5 Type 2 diabetes patients), all non-smokers with normal lung function (abstract 446-P). MKC253 produced a transient decrease in glucose of 14 mg/dl in the healthy subjects, with minimum levels observed ~15 minutes after inhalation and at baseline again by 1 hour. Response in Type 2 diabetes patients was directly related to level of baseline hyperglycemia, ranging between 14 and 22 mg/dl. This proof-of-concept study may lead to new options for incretin-based therapy delivery.

Polermo and Italian investigators reported that a 12 unit dose of buccal spray insulin (Generex Oral-lyn™), administered before and 30 minutes after a standard 75 gram oral glucose tolerance test (OGTT) to 15 Caucasian subjects with impaired glucose tolerance (IGT), resulted in a 31% decrease in mean plasma glucose at 2 hours (from 179.0 to 124.0 mg/dl, $p=0.01$) and a 28% decrease at 3 hours (from 126.8 to 86.5 mg/dl, $p=0.04$) (abstract 233-OR). There was also a trend for increased insulin levels, reaching statistical significance at 30 minutes (from 59.6 to 76.4 μ U/l, $p=0.04$).

In a related study Geho *et al.* from Pennsylvania and Texas observed a positive impact of oral hepatic-directed vesicle-insulin (HDV-I) treatment on post-meal glucose (abstract 424-P). This insulin is specifically formulated to exert its major effect within the hepatocyte. Six Type 2 diabetes patients (mean age = 55 ± 8 years, fasting plasma glucose = 161.3 ± 25.2 mg/dl, and BMI = 34.1 ± 3.4 kg/m²) being treated with metformin prior to enrollment, received add-on, single 5 U doses of study drug orally on successive days at different times before a standard test meal (ie, 0, 15, and 30 minutes). Compared to placebo, all 3 dose timings reduced postprandial glucose excursions and incremental glucose AUC_{0-4h}, with the 15-minute pre-meal dose timing showing

the largest reduction (73%, $p=0.01$), followed by 30 minute per-meal dosing (60%, $p=0.05$) and 0 minutes (39%, $p<0.001$).

Ito and Japanese coworkers conducted a study of Insulin Micropile Array Tips (MAT), a new transdermal therapeutic system of insulin (abstract 431-P). The MAP device measures 1 cm x 1 cm, containing 100 self-dissolving insulin-containing 'micropiles' with a mean length of 493 μ m. After administration of the insulin formulation (6.8 ± 0.8 IU) to the abdominal and dorsal skin of 4 dogs, a maximum $34 \pm 3.8\%$ reduction in glucose was observed 1.4 \pm 0.2 hour, with no difference in hypoglycemic effect based on administration site. The C_{max} for insulin of 140.0 ± 33.6 mIU/ml was observed at 0.8 ± 0.1 hours. Relative bioavailability compared to subcutaneous injection was $72.4 \pm 8.3\%$. The MAT dissolved immediately after administration. The investigators commented that they are studying dextran, hyaluronic acid, and albumin, as alternatives to chondroitin sulfate as the base polymer, which was used in this study.

Thibaudeau and Canadian colleagues reported results of their study of PC-Insulin, the product of covalently conjugating recombinant insulin to recombinant human albumin (abstract 435-P). PC-Insulin was developed with the objective of improving upon the pharmacokinetics of currently available basal insulins, which may still have a labile pharmacokinetic profile in certain patients. A dose-dependent decrease in glucose was observed for up to 48 hours after a single subcutaneous dose in diabetic rats. In another rat study in which study drug was compared to insulin glargine after repeated injections, a similar reduction in glucose was observed with both insulins up to 8 hours after dosing, but glucose levels at 24 hours were only normalized in animals treated with PC-Insulin. In the same model, PC-Insulin also demonstrated a long-lasting decrease in circulating free fatty acids. According to the investigators, evidence from animal pharmacokinetic studies (mice, rats, mini-pigs, and monkeys) suggests that PC-Insulin

may be dosed daily or even 3 times weekly in humans, with low variability in glucose at steady-state.

In a phase 2, 4-way crossover study, Hompesch *et al.* from California compared the pharmacokinetics and postprandial glucose response to subcutaneous insulin lispro and regular human insulin, each alone or co-injected with recombinant human hyaluronidase (rHuPH20) following a liquid meal challenge in 22 Type 1 diabetes patients (15 male, mean age 40.7, BMI 24.2 kg/m²) (abstract 456-P). The hyaluronidase allegedly enhances insulin absorption in subcutaneous tissues. Patients fasted (10 hours) and refrained from insulin for 12 hours before dosing. Starting 2 hours before a liquid meal challenge (60 g carbohydrates), patients were titrated to a glucose target of 100 mg/dl with glucose/insulin infusion. rHuPH20 co-administration accelerated insulin exposure with a reduction of t_{max} from 49 to 30 minutes ($p<0.001$) and increased C_{max} from 45 to 62 pM/IU ($p=0.0007$). Greater early and reduced later postprandial exposures were also observed. This change in insulin pharmacokinetic profile improved glycemic control as the mean 2-hour postprandial glucose level was reduced from 139 to 124 mg/dl ($p=0.116$) and the postprandial glucose peak of 174 mg/dl was reduced to 147 mg/dl ($p=0.002$) when combination therapy was used. The most common adverse event was hypoglycemia, which was reported at a similar rate in the two treatment groups.

Most of the above reports concern early investigational agents. We would point out that over the past 9 years of these newsletters, we have seen many novel insulin delivery technologies come and go. To date, the only approved way to use insulin by outpatients is through standard injections, either with older syringes, through pen devices, or via continuous subcutaneous insulin infusion (the insulin pump).



So Many Posters, So Little Time....



Braza *et al.* from Texas conducted a cross-sectional study of 76 consecutive adult Hispanic patients with Type 2 diabetes who had taken metformin for at least 1 year (mean = 5 years) (abstract 569-P). 31 patients (41%) had low-normal levels or were frankly vitamin B12 deficient. B12 deficiency did not correlate with either the duration of metformin use or an abnormal MCV. Peripheral

neuropathy was documented in 7% of the patients with normal B12, 23% in those within the low/normal range, and 77% in patients with a B12 deficiency. On the basis of these findings, the researchers recommended that Type 2 diabetes patients should be either screened for B12 deficiency or supplemented with vitamin B12 after being on metformin for 1 year. They also recommended

B12 deficiency screening for all Type 2 diabetes patients with peripheral neuropathy who are being treated with metformin. This is an often forgotten effect of metformin therapy. While there continues to be controversy regarding the implications of low vitamin B12 in metformin-treated patients, routine supplementation seems to be an easy intervention and a very reasonable recommendation.

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