

DIABETES CENTER OF EXCELLENCE

NEWSLETTER

Section of Endocrinology, Diabetes and Nutrition



NEWSLETTER NO. 6

AUGUST 2011

HIGHLIGHTS FROM THE AMERICAN DIABETES ASSOCIATION 71ST SCIENTIFIC SESSIONS

More than 17,500 top scientists, physicians and other health care professionals from around the world attended the American Diabetes Association's 71st Scientific Sessions, June 24-28, in San Diego, CA. The overall philosophy of the ADA is to present and share cutting-edge research which will advance the field of diabetes, research and improve patient care.

THE BANTING MEDAL FOR SCIENTIFIC ACHIEVEMENT Congratulations, Dr. Barbara Corkey!

The Banting Medal for Scientific Achievement is the Association's highest scientific award and honors an individual who has made significant, long-term contributions to our understanding of diabetes, its treatment and/or prevention. The award is named after Nobel Prize winner Sir Frederick Banting, who co-discovered insulin.

This year's recipient of the Banting Medal was Barbara E. Corkey, PhD, Vice Chair for Research and Professor of Medicine and Biochemistry at Boston University School of Medicine. Dr. Corkey presented a lecture on the role of hyperinsulinemia in type 2 diabetes.

In Dr. Corkey's words,

"My model proposes that environmentally induced, elevated background levels of insulin, or what I refer to as basal hyperinsulinemia, is the root cause of insulin resistance, obesity, and diabetes."

Dr. Corkey's research model explains how basal hypersecretion of insulin occurs and considers possible ways to treat or prevent hyperinsulinemia. A review of her data suggests that monoacylglycerols and artificial sweeteners in foods can stimulate basal insulin secretion. She also explains that reactive oxygen species (ROS) and cytosolic redox are among the key players in insulin hypersecretion.

Studies suggest *"high fuels and foreign agents that increase redox or generate ROS result in stimulation of basal insulin secretion. These data further indicate*

that hypersecretion of insulin can be caused directly by ROS. Further research into the role of hyperinsulinemia could lead to “radically different and novel strategies to the treatment of insulin resistance and type 2 diabetes.”

The Annual Kelly West Lecture ***Diabetes and Race in America - 1898 to 2011***

Dr. Frederick Brancati, Professor of Medicine and Epidemiology and Director of Diabetes Prevention & Control Core at John Hopkins University discussed racial disparities at the annual Kelly West Lecture, *Diabetes and Race in America - 1898 to 2011*. The lecture was named for Kelly West, MD, a diabetes epidemiologist who concluded that the growing disparity in diabetes between Caucasian and African American populations was a result of environmental factors, not race or biology. More than thirty years later, the argument continues.

Compared to the Caucasian population, African Americans, Hispanics and other non-Caucasian groups have a significantly higher rate of diabetes. African Americans have between 32% and 45% excess risk for diabetes based solely on health characteristics such as fasting glucose and blood pressure. From 1989 – 2011, the change in incidence reflects a history of slavery, poverty, migration, poor nutrition, poor education, less access to healthy foods and disparities in health care. Although race may play a role, environmental factors account for nearly all of the race-based disparity in diabetes, diabetes care and diabetes outcomes. Recent studies suggest that race accounts for about 1% of the diabetes gap. The Diabetes Prevention Program found that lifestyle interventions were similarly effective in Caucasians, African Americans, and Hispanics.

Nutrition studies have found markers such as serum potassium levels that show racial differences that mimic racial differences in diabetes. Food surveys in Baltimore found that poor neighborhoods, largely African American, have a poor supply of fresh fruits and vegetables, low fat milk and other healthy foods while wealthier neighborhoods are well-supplied with nutritious food.

Access to health care also makes a difference. *Project Sugar 1*, a study comparing intervention by a nurse case manager, a community health worker, or both, found that more intensive intervention produced better A1C and blood pressure results. Dr. Brancati said, “*when they worked as a team, the effect was more than additive. When we expanded into a randomized controlled trial, we saw a 20% improvement in ER use and hospital admits from the combined intervention compared to usual care. A later study found that tailoring diabetes self-management education materials to the patient’s education level also made a significant difference in diabetes outcomes.*”

“The key message is that if it is environmental, it is modifiable. I would confirm Dr. West’s conclusion that the disparity is due to environment, not biology and we can do something about that.”

New Drugs for the Treatment of Type 2 Diabetes

Several new drugs are currently under investigation or have recently been approved for the treatment of type 1 and type 2 diabetes. These drugs include once-weekly exenatide, two new DPP-4 inhibitors, a handful of SGLT2 inhibitors, and an ultra-long acting insulin. Although it appears that some of these medications are close to approval by the FDA, it is hard to predict when they might become available for use

Once-weekly exenatide (Bydureon) is a glucagon-like peptide-1 receptor newly available in Europe and has been shown to sustain glycemic control and weight loss for up to two years. Exenatide (Byetta) has been in use for several years, but it needs to be injected twice a day. If approved, the once-weekly form would be much more convenient to use by patients with type 2 diabetes, especially those who are resistant to taking medications by injection.

Trials of linagliptin (Tradjenta) and alogliptin (Nesina), two new depeptidyl peptidase-4 (DPP-4) inhibitors, have shown that these agents improve insulin secretion and reduce hyperglycemia. By inhibiting an enzyme that breaks down the incretin GLP-1, they increase GLP-1 action and improve insulin secretion by the beta cell. Linagliptin has already received FDA approval and is available for use. Alogliptin is still under review by the FDA.

Dapaqliflozin and canagliflozin, two new sodium-glucose-co-transporter-2 (SGLT2) inhibitors are under development and can reduce A1C concentrations and body weight. These medications increase excretion of glucose by the kidney, thereby lowering blood glucose levels.

Insulin degludec, the investigational, ultra-long-acting basal insulin lasts up to 40 hours and thus may be able to reduce the frequency of insulin dosing. It is currently in studies to compare its effectiveness with other basal insulins, like insulin glargine (Lantus) and insulin detemer (Levemir.)

The Look AHEAD Trial and Four-Year Outcomes of an Intensive Lifestyle Intervention in Type 2 Diabetes

The key message presented from the Look AHEAD trial was that lifestyle interventions can effectively reduce risk factors in type 2 diabetes, but expect adherence fatigue. Dr. Xavier Pi-Sunyer, MD, MPH, Professor and Chief of Endocrinology, Diabetes and Nutrition at Columbia University College of Physicians and Surgeons, NY, reported that we have lost some of the impact on weight loss and risk factors that was seen in year one. Look AHEAD is a 13 ½ year randomized controlled trial that compares standard lifestyle counseling and

care for overweight and severely obese patients with type 2 DM with an intensive lifestyle intervention program.

- ❖ Year one data showed strong improvements in A1C levels, weight, exercise, and other parameters. The severely obese population had lost about 9% of their initial body weight.
- ❖ Years 2, 3, and 4 showed continued differences from the control group, but progressive regression.
- ❖ Year four data showed that the severely obese population lost approximately 5% of their initial body weight.
- ❖ More importantly, about 25% of the severely obese patients showed a 10% or greater weight loss at four years.
- ❖ Nearly 50% of those who lost more than 10% at year one sustained that magnitude of weight loss at year four.

Look AHEAD found that a significant number of type 2 patients can achieve complete reversal of diabetes signs and symptoms using lifestyle modification alone, and were subsequently able to stop taking medications. An even larger number of patients showed a substantial improvement in A1C and were able to reduce medication use.

- ❖ At one year, about 11% of the intensive lifestyle intervention population had an A1C of <6.5 and were not taking medications versus 2% in the control group – about a 5-fold difference.
- ❖ At four years, about 8% of patients continued to not have diabetes without medication compared to less than 3% in the control group.

If patients can achieve and maintain these changes in weight loss and activity, there is an opportunity for many of them to no longer have diabetes signs and symptoms.

Drug-Induced Dysglycemia

Dr. Charles Ponte, PharmD, Professor of Clinical Pharmacy and Family Medicine at the West Virginia University Schools of Pharmacy and Medicine presented an overview along with strategies to both prevent and manage drug induced disruptions of glycemic control. He noted that a variety of common medications, with neuroleptic agents and statins can contribute to dysglycemia. All are associated with increases in diabetes, and there may be differential effects associated with different agents within each class of drugs.

Dr. Ponte advised, *“If you have a patient who must be on an agent that can affect glucose regulation, prospective monitoring is paramount. If you do see an adverse effect, stop the drug if you can, reduce the dose if you cannot stop it, and provide supportive care. Any disruption of glycemic regulation has consequences not to be taken lightly.”*

Patients with mental illness are at increased risk of diabetes with or without drug treatment, as first noted in the 19th century and reaffirmed in the 1920s and 1930s. Clinicians who used insulin coma therapy noted that patients with mental illness were more resistant to insulin than the general population. There are clearly some individuals who develop diabetes shortly after starting antipsychotic medications that may go into remission if the drug is stopped. One obvious mechanism is the weight gain often seen in antipsychotic drug use. But there appear to be other mechanisms, including increased insulin resistance and possibly an effect on beta cell function.

David Preiss, a Research Fellow at the University of Glasgow's BHF Glasgow Cardiovascular Research Centre, Scotland explored multiple large randomized trials that have shown a 9% to 10% increase in the incidence of diabetes in patients taking statins compared to patients on placebo, with even higher increases on intensive regimens. Dr. Preiss stated, *"I don't want to give the impression that we shouldn't be using statins. Benefit is definitely there if you are treating people at moderate to high risk of future cardiovascular events. What we don't know are the risk-benefit considerations as you treat people at lower and lower cardiovascular risk, but higher diabetes risk. It may be that statins come out strongly on the side of benefit, but we cannot say for sure."* There are currently no convincing theories to explain the association between statins and diabetes, but the data are convincing."

AMPK Symposium and Related Lectures

AMPK is a fuel sensing enzyme that is activated by a decrease in a cell's energy state as reflected by an increase in the AMP/ATP ratio. Early studies (prior to 2000) revealed that when activated, AMPK restores a cell's energy state by increasing processes that generate ATP and decreasing others that consume ATP. Another key early finding was that many of the metabolic changes in skeletal muscle induced by exercise (e.g. increased glucose transport, fatty acid oxidations and mitochondrial function and gene expression) were AMPK-mediated. More recently, it has become apparent that AMPK can also inhibit a wide array of potentially pathological events in cells including increased inflammation, mitochondrial dysfunction, apoptosis and senescence. In exerting these effects, AMPK has been shown to interact with a wide variety of transcriptional activators, some of which are linked to the increase in longevity caused by caloric restriction.

From a clinical perspective, interest in AMPK increased dramatically, with the discovery that two of the major classes of drugs used to treat diabetes, the biguanides (metformin) and the thiazolidinediones (pioglitazone and rosiglitazone), like exercise, may exert their beneficial effects, at least in part, by activating AMPK. At the ADA, a symposium was devoted to AMPK as a mediator of the action of metformin and of adiponectin, an adipokine (a hormone released from adipose tissue) that has been implicated in the activation of AMPK by thiazolidinediones. The following are brief summaries of some of the lectures presented in this symposium.

T. Kadowaki: University of Tokyo Kadowaki was one of the early investigators to show that the hormone adiponectin may have beneficial effects in preventing atherosclerotic-vascular disease and combating diabetes in insulin-resistant rodents. In addition AMPK activation accounts for many of its biological actions and adiponectin mediates many of the therapeutic benefits, as well as the activation of AMPK, by thiazolidinediones.

Philip Scherer, University of Texas Scherer first identified adiponectin in 1994. In his lecture he reviewed his work and that of others showing that:

- 1) Loss of adiponectin: produces clinically relevant abnormalities, (e.g. insulin resistance and steatosis) in animals on a high-fat (but not a high carbohydrate) diet.
- 2) Adiponectin increases insulin sensitivity in fat-fed mice
- 3) Adiponectin can exert some of its beneficial effects (e.g. lowering blood glucose, diminishing apoptosis) in mice even when it doesn't increase AMPK, suggesting it acts by more than one mechanism.

Benoit Viollet: Inserm, France: Viollet pioneered the development of genetically modified rodents in which AMPK is knocked down or overexpressed in whole animals (mice) or specific organs.

In his lecture he reviewed the evidence that metformin exerts its biological actions by activating AMPK.

- 1) Zhou et al (2001) demonstrated that metformin activates AMPK in the liver (rodents).
- 2) In 2010, Foretz and Viollet (JCI) – demonstrated that metformin can decrease hepatic gluconeogenesis in mice in which it does not activate AMPK. It appeared to do so in these mice by diminishing the cells energy state.

Barbara Kahn: Beth Israel Deaconess, Boston: Kahn is a leader in studying the effects of AMPK on the hypothalamus that regulate food intake. In her lecture she reviewed the evidence that leptin, a hormone released by adipose tissue is responsible for the suppression of food intake after meals. She also discussed the evidence that leptin acts by decreasing AMPK activity in the hypothalamus, and that in doing so decreases the synthesis and release of NPY, a neuropeptide that increases food intake

Dr. Kahn also presented new evidence from her lab that at a molecular level leptin down-regulates AMPK by activating a unique signaling pathway. She showed in mice that a phosphorylation process is involved in the down-regulation of the activity of the enzyme.

Causes of Diabetic Retinopathy at the Cellular Level

The incidence of diabetes is increasing worldwide at an alarming rate. It is estimated that the current rate of 1 in 10 adults with diabetes in the US will increase to 1 in 3 by year 2050. With the upsurge in this population, the incidence of diabetic complications, including diabetic retinopathy, is expected to rise. Currently there is no cure for this problem, the leading cause of blindness in the working age population. Treatment to prevent the development of lesions of diabetic retinopathy would be extremely useful. Chronic hyperglycemia-induced retinal vascular cell loss is a hallmark lesion in the development and progression of diabetic retinopathy. However, the underlying mechanism(s) for the retinal cell loss remains unclear.

Dr. Sayon Roy's laboratory showed that mitochondrial dysfunction could contribute to oxidative stress and subsequent retinal vascular cell loss in diabetic retinopathy. Chronic hyperglycemia triggers apoptosis (cell death) in retinal endothelial cells and pericytes that may cause the acellular capillaries that are seen in diabetic retinopathy. This is the first report implicating a special mitochondrial transporter protein. This transporter protein is localized on the mitochondrial inner membrane and is involved in several key cellular processes including maintenance of cellular iron homeostasis. It is also a mitochondrial iron transporter involved in traffic of iron ions across the mitochondrial membrane and may have implications for iron overload. Abnormalities of the transporter protein may thus influence iron homeostasis and promote subsequent oxidative stress in the diabetic retina.

Diabetes and the Elderly

The Growth in Population Size and Costs of Diabetes for Medicare

Type 2 diabetes is a growing problem among older adults. By 2050, one third of adults over 50 will have the disease. One half of Medicare dollars will be spent on diabetes care. Patients contracting diabetes at 51 years old face a 3.7 year loss of life expectancy, 5.7 year loss of healthy life expectancy and \$75,000 additional lifetime medical expenditures. Early intervention in the near-elderly population can achieve improvements in lifetime outcomes. Potential scenarios might include intensifying treatment substantially increasing the use of insulin in people over age 50, utilizing more effective oral agents than existing drugs and eliminating imperfect medication adherence.

The Challenges of Treatment Decisions in Older Diabetes Patients

The Diabetes and Aging Study looked at control of blood glucose, complications and death in older diabetic patients. The objective was to identify the range of glucose levels associated with the least amount of complications and mortality in this group. This was a retrospective study with 71,000 patients who had type 2

diabetes with a mean age of 71 years. The mortality curve showed the highest death rate in those with A1C levels of <6%. The findings support a target of A1C levels <8% in this patient population.

Beyond Recent Trials: The Next Frontiers in Diabetes Management

Complications of diabetes and disability are important and occur in both middle and old age. This adds to the complexity in caring for patients with diabetes. Complex medication regimens may not be appropriate for the older adult with diabetes. Goals for glycemic control need to be revisited on a regular basis as the patient ages. Additionally, 22% of adults over the age of 51 have characteristics that make diabetes self management more challenging.

Redesigning Clinics to Deliver Geriatric Diabetes Care

Goals for glycemic control in this population should include helping these patients identify barriers to care. Regimens need to address the barriers of depression, deconditioning and social isolation. Management plans can be modified while considering cognitive issues and physical disabilities. Various tools are useful in the outpatient setting to distinguish dementia from depression. These include the Mini Mental Status Exam, the Clock in the Box Test and the Modified Clock Drawing Test. Health literacy as well as polypharmacy can be additional barriers to optimal care of older adults with diabetes.

The Role of the GI Tract in Obesity

The relatively new field of study known as the “gut microbiome” was well represented at the ADA sessions, and was placed into context of the national and global obesity epidemic. The human microbiome is the totality of organisms (bacterial, viral, helminth, etc) living in or on an individual, most often commensally. The GI tract is the host to the largest microbiome of most animals, and this is true of humans. Since the obesity epidemic is thought to have genetic and environmental underpinnings, leading researchers of the human microbiome have recently focused attention on obesity as a potentially relevant link between chronic human disease and the gut microbiome. In addition to changes in diet and exercise, recent data point to the gut microbiome as a major feature of the environmental changes driving the epidemic

While recent evidence suggests that trillions of bacteria that normally reside within the human GI tract affect nutrient acquisition and energy regulation, and that the obese and leans have different gut microbiomes, the details of these differences are challenging to uncover, and once uncovered, difficult to describe in a meaningful way. One presenter described certain bacterial species that, when cohabitating in one animal, equip themselves to synthesize and metabolize fats to support their own existence, while simultaneously affecting the animal’s fat absorption (and therefore calorie absorption). It is clear that microbiomes contain unique clusters of organisms that can differ from human to human. Investigators

have identified that somewhat specific bacterial groupings, named “enterotypes,” are distributed differently in the obese vs. lean, or following a high fat diet vs. low fat diet. In controlled feeding studies in humans using stool for PCR analysis, it has been found that enterotype distribution can shift with high calorie/high fat feeding – suggesting either an adaptive or maladaptive response of the gut microbiome to increased energy intake. Enterotypes may possible change as we age as well, and following other life changes – many investigations are ongoing in this exciting area.

While the gut microbiome is clearly relevant to human health and disease, the field is young and complex. Therapeutic interventions targeting the microbiome are likely to evolve, and many expect these to be minimally toxic, such as probiotic or food-based therapies.

PEOPLE IN THE NEWS

Incretin-Based Therapy and Pancreatitis-What is the Risk?

Sternthal E. Endocr Pract. 2011 Jul 8:1-12. [Epub ahead of print] No abstract available.

Weight-based, insulin dose-related hypoglycemia in hospitalized patients with diabetes.

Rubin DJ, Rybin D, Doros G, **McDonnell ME.** Diabetes Care. 2011 Aug;34(8):1723-8. Epub 2011 Jun 23.

A woman with severe lupus nephritis and difficult to control diabetes mellitus.

Buhaescu I, **Rhee S,** York MR, **McDonnell M,** Merkel PA. Arthritis Care Res (Hoboken). 2011 Apr;63(4):623-9. doi: 10.1002/acr.20403. No abstract available.

Elevated proinflammatory cytokine production by a skewed T cell compartment requires monocytes and promotes inflammation in type 2 diabetes.

Jagannathan-Bogdan M, **McDonnell ME,** Shin H, Rehman Q, Hasturk H, **Apovian CM,** Nikolajczyk BS. J Immunol. 2011 Jan 15;186(2): 1162-72. Epub 2010 Dec 17.

Decreased AMP-activated protein kinase activity is associated with increased inflammation in visceral adipose tissue and with whole-body insulin resistance in morbidly obese humans.

Gauthier MS, O'Brien EL, Bigornia S, Mott M, Cacicedo JM, Xu XJ, Gokce N, **Apovian C, Ruderman N.** Biochem Biophys Res Commun. 2011 Jan 7;404(1):382-7. Epub 2010 Dec 3.

The evolution of insulin resistance in muscle of the glucose infused rat.

Brandon AE, Hoy AJ, Wright LE, Turner N, Hegarty BD, Iseli TJ, Julia Xu X, Cooney GJ, Saha AK, **Ruderman NB,** Kraegen EW. Arch Biochem Biophys. 2011 May 15;509(2):133-41. Epub 2011 Mar 21.

High Glucose-induced Altered Basement Membrane Composition and Structure Increases Trans-endothelial Permeability: Implications for Diabetic Retinopathy.

Chronopoulos A, Trudeau K, **Roy S,** Huang H, Viores SA, Roy S. Curr Eye Res. 2011 Aug;36(8):747-53.

Fenofibric acid reduces fibronectin and collagen type IV overexpression in human retinal pigment epithelial cells grown in conditions mimicking the diabetic milieu: Functional implications in retinal permeability. Trudeau K, **Roy S**, Guo W, Hernández C, Villarroel M, Simó R. Invest Ophthalmol Vis Sci. 2011 Jun 29. [Epub ahead of print]

Comparison of diabetes control among Haitians, African Americans, and non-Hispanic whites in an urban safety-net hospital. Vimalananda VG, **Rosenzweig JL**, Cabral HJ, David MM, Lasser KE. Diabetes Care. 2011 Jan;34(1):58-60. Epub 2010 Oct 26.

We would like to take this opportunity to thank the faculty of the Section of Endocrinology, Diabetes and Nutrition, for their contribution to this newsletter:

Roberta Capelson, MS, ANP
Karen A. Chalmers, MS, RD, CDE
Dr. Marie E. McDonnell
Dr. James L. Rosenzweig
Dr. Sayon Roy
Dr. Neil B. Ruderman