

# Diabetes 2005

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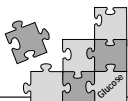
Important data on diabetes presented at the 65th Annual Scientific Sessions of the American Diabetes Association come to you in **Diabetes 2005**, a newsletter CME program that is being offered to you by Yale University School of Medicine with the support of Takeda Pharmaceuticals America, Inc. and Eli Lilly and Company. Fax or e-mail delivery to your office of **Diabetes 2005** will be followed by a **Diabetes 2005** booklet (ACC and ADA newsletters) in the mail. After successfully completing the quiz and evaluation therein contained and remitting a \$10 certificate fee to the Yale Office of Continuing Education, 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 2005** is being offered to physicians practicing in the United States. After successfully completing this program, participants will be able to:

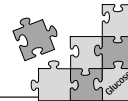
- Explain the pathogenesis of Type 2 diabetes, especially the coexisting roles of insulin resistance and insulin secretion.
- Recognize the clinical manifestations of the macrovascular and microvascular complications of diabetes and describe appropriate therapeutic interventions.
- Recognize the important 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.

Yale University School of Medicine is accredited by the Accreditation Council for Continuing Medical Education to sponsor continuing medical education to physicians. Yale University School of Medicine designates this continuing medical education activity for a maximum of 5.5 Category 1 credits towards the AMA Physician's Recognition Award. Each physician should claim only those hours of credit that he/she actually spent in the educational activity.

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## Metabolic Syndrome: Treating the Parts, Not the Sum

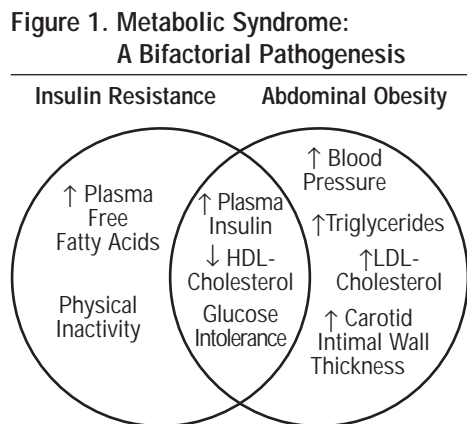


More than two decades ago, the concept of a cluster of metabolic abnormalities that included obesity, high triglyceride and reduced HDL-cholesterol concentrations, hypertension, and glucose intolerance was described. The level of interest in this "metabolic syndrome" has increased substantially over the past five years, reflected in a 100-fold increase in the number of related publications! In over 5000 publications to date, we have had five competing definitions of the syndrome. In addition to the four (NCEP ATP III, WHO, CDC, EGIR) reviewed in *Diabetes 2004* (Volume 10, Issue 4), the International Diabetes Federation (IDF) recently unveiled their own definition of metabolic syndrome that stratified waist circumference cut-points by ethnicity. However, despite a plethora of definitions, have we really made any progress in understanding the pathophysiology, its treatment, or its consequences? These were the focus of an opening day symposium.

### Competing Definitions & Determinants

In the first of four presentations, Dr. Ele Ferrannini of Italy reviewed the competing definitions. Since insulin resistance and abdominal obesity appear in some but not all of the definitions, he reviewed the pathophysiologic links between these two components and the metabolic

syndrome in a population of non-diabetic patients. The role of other determinants (e.g., free fatty acid levels, physical activity, blood pressure, lipid levels, plasma insulin, glucose tolerance, and early atherosclerosis as measured by common carotid intimal medial thickness) were also assessed. Overall, he concluded that the pathogenesis of the metabolic syndrome may be bifactorial; insulin resistance and abdominal obesity both contributing to its development. These two principal factors include several pathogenic determinants that are in part overlapping and in part independent (Figure 1). In the following presentation, Dr. Michael Stern of Texas reviewed the importance of using adequate methods of assessment in predicting the risk of cardiovascular disease in patients with diabetes or the metabolic syndrome. The use of relative risk, odds ratio, and hazard ratio may have serious limitations in assessing the clinical and public health significance of risk factors. In contrast, he pointed out that the use of sensitivity, false positive rate, and area under the receiver operator characteristics (ROC) curve may identify risk factors that are the most discriminating. Using a decision tree model with these risk parameters, he presented data indicating that presence of the metabolic syndrome is inferior to other parameters (such as history of cardiovascular disease, small dense LDL-cholesterol, and C-reactive protein levels) in identifying diabetic patients who are at high risk for cardiovascular disease. In the third presentation, Dr. David Eddy suggested a "moratorium" on new definitions of metabolic syndrome for a variety of reasons. First, among the current definitions, there are discrepancies in certain definitions of the parameters (i.e., obesity, glucose, hypertension). More importantly, while the metabolic syndrome may help identify patients at risk, treatment should be targeted to each of the individual components using existing guidelines. He recommended the use of the DiabetesPHD risk assessment tool (available at [www.diabetes.org](http://www.diabetes.org)), which uses personal health information to predict one's current risk for diabetes,



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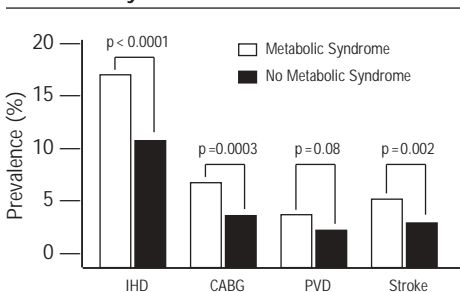
## Metabolic Syndrome: Treating the Parts Continued from page 1

heart attack, stroke, renal failure, as well as foot and eye complications. In the closing presentation, Dr. Pirjo Ilanne-Parikka of Finland reviewed findings of a two year extension of the Finnish Diabetes Prevention Study. The investigators noted that a population of individuals with metabolic syndrome given intensive individualized dietary and exercise counseling fared better in terms of weight loss, metabolic syndrome regression, and decreased development of diabetes compared to a control group provided general dietary and exercise information on an annual basis.

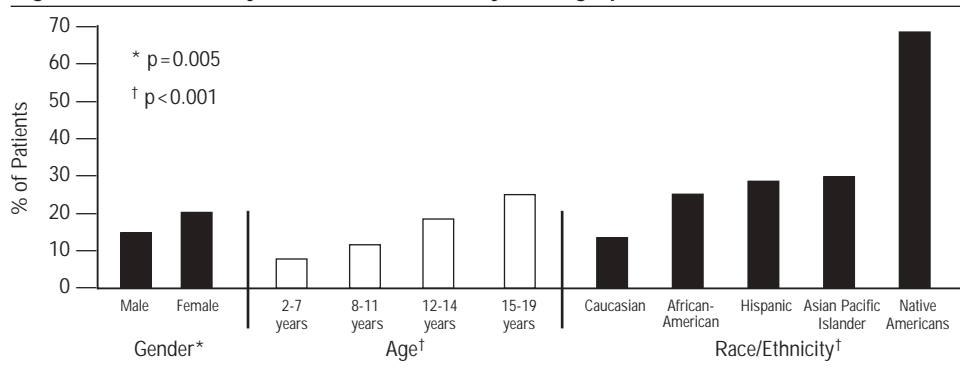
## Cardiovascular Impact

The close association between the metabolic syndrome and its clinical consequences, specifically cardiovascular disease, has created a large interest in when precisely primary prevention treatment should be initiated. Wong and Australian collaborators assessed whether the presence of metabolic syndrome (defined by WHO criteria, which includes insulin resistance) can be used to stratify cardiovascular risk in 5298 subjects with Type 2 diabetes (255-OR). Overall, 72% of subjects had metabolic syndrome, with a consistent prevalence across age groups. Those with and without metabolic syndrome were of similar age (mean 59.2 years), duration of diabetes (3.8 years with vs. 3.4 years without), and ethnicity (~38% Anglo-Celtic). Across all age groups, those with metabolic syndrome had a significantly higher prevalence of ischemic heart disease, CABG, and stroke compared to those without metabolic syndrome (Figure 2). Between the age groups, the investigators made the interesting observation that those with metabolic syndrome had cardiovascular disease prevalence rates that were similar to those observed in non-metabolic syndrome subjects who were 10 years older. This finding

**Figure 2. Effect of Metabolic Syndrome on CVD Events**



**Figure 3. Metabolic Syndrome Prevalence by Demographic Parameters**

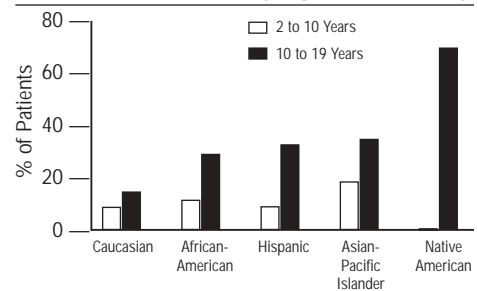


suggests that treatment intervention might need to begin a decade earlier in those with metabolic syndrome in order to properly mitigate risk.

## Metabolic Syndrome: Not Just for Grown-Ups

The prevalence of metabolic syndrome has been determined primarily in populations ranging from young adults (i.e., 20 years) to the elderly (i.e., > 70 years). Data in children and adolescents thus far have been limited. Rodriguez *et al.* studied 2436 participants of SEARCH, a multi-center, national study of youth between 0 and 19 years of age with diabetes, to determine the prevalence and correlates of the metabolic syndrome as defined by the NCEP ATP III (262-OR). The overall prevalence of metabolic syndrome was 18%, with significant differences observed by gender, age, and race/ethnicity (Figure 3). Children with a parental history of diabetes were also at significantly higher risk for metabolic syndrome compared to those without (32% vs. 14%,  $p < 0.0001$ ). Using a biochemical algorithm based on the presence of diabetes antibodies (DA) and fasting C-peptide (FCP)

**Figure 4. Metabolic Syndrome Prevalence by Age and Ethnicity**



level, the investigators assessed the prevalence of metabolic syndrome by diabetes type. The prevalence was 10% in Type 1 (DA-negative, FCP < 0.8 ng/ml), 15% in those with Type 1A (DA-positive, FCP < 3.7 ng/ml), 89% in those with Type 2 (DA-negative, FCP ≥ 3.7 ng/ml), and 65% among "hybrids" (DA-positive, FCP ≥ 3.7 ng/mL) ( $p < 0.001$ ). The investigators also observed a near doubling or more of metabolic syndrome prevalence between ethnic populations 2 to 10 years of age and those between 10 to 19 years (Figure 4).

**Table 1. Association between Insulin Sensitivity, Plasma Insulin, and PAI-1 and Recurrent MI**

	Total Glucose Disposal (mg/kg/min)	Plasma Insulin (mU/l)	PAI-1 (U/ml)
T2DM with recurrent MI (n=18)	2.1 ± 0.2	29.3 ± 3.7	7.1 ± 0.6
T2DM with single MI (n=22)	3.4 ± 0.4	20.4 ± 3.2	5.3 ± 0.5
p-value	<0.01	<0.05	<0.05
Non-diabetic with recurrent MI (n=20)	3.2 ± 0.4	17.7 ± 1.8	6.3 ± 0.4
Non-diabetic with single MI (n=24)	4.4 ± 0.3	11.9 ± 1.4	4.4 ± 0.5
p-value	<0.01	<0.05	<0.05

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## **Metabolic Syndrome: Treating the Parts** *Continued from page 2*

### **A Prothrombotic State**

The metabolic syndrome and specifically insulin resistance, a component of the WHO criteria, have been linked to increased platelet aggregation and decreased thrombolysis, in part related to increases in plasminogen activator inhibitor-1 (PAI-1). Lalic and Yugoslavian colleagues compared the insulin sensitivity (expressed as total glucose disposal rates during

an insulin clamp procedure), plasma insulin (PI), and PAI-1 levels in four groups of patients: those with Type 2 diabetes with recurrent myocardial infarction (MI), those with Type 2 diabetes and a single MI, non-diabetics with recurrent MI, and non-diabetics with a single MI (710-P). Glucose disposal rates (reflecting greater insulin resistance) were significantly lower among both diabetic and non-diabetic subjects with recurrent MI vs. the corresponding subjects with a single MI (Table 1). Not unexpectedly, both PI and PAI-1 levels were significantly higher in both

groups with recurrent vs. single MI. No differences in total cholesterol, its subfractions, and triglyceride levels were detected between groups. These findings indicate that MI recurrence in both Type 2 diabetic patients and non-diabetic patients may be more strongly dependent on insulin resistance and hypofibrinolysis than on lipoprotein levels. This statement is provocative and will require confirmation by others. Clearly, however, both insulin resistance and disordered coagulation play key roles in the progression of atherosclerosis.



## **Insulin Administration: New Routes (Even Snouts)**



Landmark studies, such as the Diabetes Control and Complications Trial (DCCT), the United Kingdom Prospective Diabetes Study (UKPDS), and the Epidemiology of Diabetes Interventions and Complications (EDIC) trial, have shown that intensive insulin treatment with strict glycemic control significantly reduces the long-term microvascular risk of diabetes. In Type 2 diabetes, recommendations are for the initiation of insulin therapy alone or in combination with oral agents once the latter fails to adequately control glucose. Unfortunately, due to many barriers, insulin is often started too late in the course of disease, and also at insufficient doses. These barriers include the frequent need for multiple daily injections and fingersticks for glucose monitoring, as well as fear of hypoglycemia and weight gain. As a result, patients are often reluctant to initially accept insulin therapy. To address at least some of these barriers, information on newer insulin analogs as well as several innovative non-invasive delivery systems was presented at this week's meeting.

### **Basal Analogs**

After nearly 85 years, we are just now learning how to utilize insulins in a more physiologic manner. Worldwide, most patients are still using forms of intermediate-acting insulin that were developed over a half century ago. These older formulations, such as Lente and NPH, are limited by their inadequate duration of action as well as their unpredictability. The more recent availability of the basal insulin analogue, glargine, has allowed for more physiological insulin replacement regimens in many patients. In an oral symposium presentation, Dr. Malcolm Natrass of the University of Birmingham described strategies that are being used to develop other basal insulin analogs with low variability, high reproducibility, and extended durations of action. These strategies include

modifying the molecular structure to increase hexameric formation and albumin binding (such as with insulin detemir) or changing the isoelectric point such that precipitation occurs at a physiologic pH of 7.4 (used to develop glargine). In the case of insulin detemir, the fatty acid (myristic acid) side chain binds to albumin in the injection depot as well as in the circulation and results in a longer duration of residence time and delivery to target organs. Studies in patients with Type 2 diabetes have consistently noted that, as compared to NPH, detemir produces greater improvements in fasting plasma glucose, similar effects on HbA1c, and decreased risk for hypoglycemic episodes. Additionally, an abstract at this week's meeting noted that Type 2 diabetic insulin-naïve patients treated with detemir gained less weight compared to those treated with NPH ( $p=0.01$  for the linear regression of change in body weight vs. baseline BMI) (271-OR). Similar results have been noted in studies of patients with Type 1 diabetes as illustrated by the results of Heller and Danish colleagues (487-P) who in a meta-analysis of four multicenter, open-label, randomized clinical trials of patients treated with insulin detemir ( $n=1180$ ) or NPH insulin ( $n=810$ ) found that the former was associated with a 22% lower overall risk for hypoglycemia (relative risk 0.78). The lowered risk for hypoglycemia with detemir compared with NPH insulin was observed at all levels of HbA1c, with the relative reduction in risk increasing with improving HbA1c. Insulin glargine has also been observed to produce similar effects on HbA1c and rates of hypoglycemia in patients with Type 1 (587-P) and Type 2 diabetes (583-P, 1246-P).

### **Puff Away!**

The sheer combined absorption area of the alveoli (between 100 m<sup>2</sup> and 140 m<sup>2</sup>, or the size of the average tennis court) suggests that delivery of insulin through the lungs may be a viable mode

of administration. In the last several years, selected products have continued through the development process while numerous others have been abandoned. The major differences among those currently under development are the formulation of insulin for inhalation (i.e., dry powder, liquid, particle) and the device used to deliver the insulin. In an oral symposium presentation, Dr. Jay Skyler from Miami reviewed the mechanics of several of these devices. In general, the time action profiles of all the currently studied inhaled insulin products are similar, with all having a more rapid onset of action compared to subcutaneous (SC) insulin. In smokers these formulations tend to have a faster onset compared to non-smokers. Upper respiratory tract infection appears to have little to no effect on absorption. Those with asthma display decreased bioavailability, whereas the effect of chronic obstructive pulmonary disease remains unknown. In terms of safety, he reported that the short-term or long-term use of inhaled insulin has little to no effect on pulmonary function and that, despite a small rise in insulin antibodies, these effects are still substantially lower than those seen with previous non-purified forms of insulin.

These findings were supported in several other oral presentations and posters at this week's meeting. Peterson and Danish associates (359-OR) compared the onset and duration of action of the AERx iDMS® inhaled insulin formulation to that of SC insulin in a study of 15 patients with Type 1 diabetes. The subjects were randomized to receive a dose (0.3 U/kg) of inhaled insulin, insulin aspart SC, and human regular insulin SC on three different dosing days in randomized order. A 10-hour isoglycemic glucose clamp (clamp level of 7.2 mM) was performed and the glucose infusion rate recorded for 10 hours post-dosing. The onset of action of the inhaled insulin formulation did not differ

## Insulin Administration..

*Continued from page 3*

from that of insulin aspart (66 minutes), but was significantly faster compared to that of human regular insulin (72 vs. 89 minutes;  $p = 0.01$ ). The duration of action of the inhaled insulin was longer than that of insulin aspart (291 vs. 209 minutes,  $p < 0.01$ ) and similar to that of human regular insulin (297 minutes).

Exubera<sup>®</sup>, another inhaled insulin delivery system, which appears to be closest to market, was compared with SC short-acting insulin, combined with once- or twice-daily intermediate- or long-acting insulin for 12 weeks in a study of 226 patients with Type 1 diabetes by Dumas *et al.* (355-OR). Similar effects on HbA1c were observed (7.5% for both groups) with those treated with inhaled insulin having a higher hypoglycemic event rate (6.8 vs. 5.5 events/patient-month in the inhaled insulin and SC arms; RR 1.24; 90% CI 1.17-1.31). Severe hypoglycemia, however, occurred in fewer inhaled insulin-treated patients compared to SC insulin-treated patients (9 vs. 17 patients; RR 0.52, 90% CI 0.30, 0.86). While overall adverse event profiles were similar, cough was reported in 30.9% of inhaled insulin patients compared with 7.8% of SC patients. Cefalu and colleagues (356-OR) reported the two-year efficacy and safety profile of Exubera<sup>®</sup> from three studies (two controlled, one uncontrolled) performed in adults with Type 2 diabetes. In the two controlled trials, patients received inhaled insulin plus oral agents ( $n = 158$ ) or oral antidiabetic agents ( $n = 146$ ). The third study was an extension of three controlled phase 3 trials in patients previously on diet/exercise alone, oral agents, or insulin regimens ( $n = 384$ ). In each of the studies, inhaled insulin produced a decrease in HbA1c that was comparable to oral antidiabetic agents (Table 2). The rate of hypoglycemic events was higher in the uncontrolled study compared with the controlled trial; however, these patients did attain a lower HbA1c value. No significant between-treatment changes in lung function (FEV<sub>1</sub> or DL<sub>CO</sub>) were observed. Insulin antibody levels rose in all three studies, but were not associated with any changes in glycemic control or other adverse events.

The Technosphere<sup>®</sup> system delivers pulmonary insulin via a small MannKind<sup>™</sup> inhaler, and exhibits a bioavailability that mimics normal, meal-related, first or early-phase insulin release. In a multicenter study, Rosenstock and American colleagues (357-OR) randomized 119 patients with Type 2 diabetes inadequately controlled on

diet or oral agents (HbA1c 6.6% to 10.5%) to prandial inhaled Technosphere insulin or placebo. In the intent-to-treat population a mean change from baseline HbA1c of 0.72% ( $p < 0.001$ ) was observed, with no induction of antibodies or severe hypoglycemic events reported.

The Lilly/Alkermes system<sup>®</sup> delivers inhaled insulin using a small, breath-actuated device. In a 12-week, open-label, non-inferiority crossover study the inhaled system was compared to SC insulin (361-OR). Patients with Type 1 diabetes (mean age 39 years, baseline HbA1c 8.1%) were randomized to preprandial inhaled insulin or SC insulin plus insulin glargine once daily. Based on HbA1c values, the treatments were considered equivalent (difference between treatments -0.11,  $p = 0.17$ ). The inhaled insulin produced lower fasting blood glucose levels (145 vs. 163 mg/dl,  $p = 0.01$ ) at the expense of an increased incidence of nocturnal hypoglycemia (4.2 vs. 2.7 events/30 days,  $p < 0.001$ ), suggesting a need for dosage modification in future studies.

A metered-dose inhaler formulation of short-acting human insulin by Kos was compared with bedtime SC insulin glargine as add-on therapy in 24 patients with Type 2 insulin poorly controlled with metformin and/or sulfonylureas (mean age 56 years, BMI 33 kg/m<sup>2</sup>, HbA1c 8.4%) (417-P). Inhaled insulin was administered up to 15 minutes before main meals with SC glargine administered at bedtime for 28 days. Patients treated with either formulation showed similar and significant ( $p < 0.01$ ) improvements from baseline in HbA1c (-1.23% with inhaled vs. -1.05% with SC) and in mean and fasting blood glucose levels. The change in serum triglycerides showed a statistically significant difference in favor of the inhaled dosage formulation (-35.8% vs. -11.5%,  $p = 0.011$ ). No differences

in hypoglycemic events or pulmonary adverse events were observed.

## An Insulin Pill? How About a Nasal Spray?

A new technology is being studied that uses a delivery agent (carrier) to facilitate intestinal insulin absorption by transiently altering the hydrophobicity of the hormone via modification of the hydration shell and/or the tertiary structure of the polypeptide. The carrier interacts non-covalently with the insulin such that it is unaltered chemically. The interaction is weak and enables the carrier to dissociate rapidly after absorption. In a poster presentation, Heise and associates of the US and Germany presented promising findings of a study designed to optimize the insulin:carrier ratio for oral insulin using this technology (418-P). Eight subjects with diet-treated Type 2 diabetes received a single dose of either four 75 IU insulin tablets with 100 mg carrier each or two 150 IU insulin tablets with 80 mg carrier each. Both formulations produced significant increases in plasma insulin concentration and decreases in fasting blood glucose when administered with a meal. The formulations displayed rapid absorption (within 20 minutes) and a short duration of activity, with plasma insulin levels returning to basal levels within one hour.

In another exploratory study, Leary and American and Irish colleagues found a nasal formulation of insulin administered to seven patients with Type 1 diabetes produced a prompt and sustained reduction in serum glucose (430-P).

## I've Got You Under My Skin

Given the size of the insulin molecule and the effectiveness of skin as a barrier, the development of a transdermal delivery system for insulin has been unsuccessful thus far. At this

**Table 2. Long-Term Effects of Inhaled Insulin in Type 2 Diabetic Patients**

	Studies 1 + 2 Combined		Study 3
	Exubera <sup>®</sup> (n = 158)	Comparator (n = 146)	Exubera <sup>®</sup> (n = 384)
HbA1c (%), baseline	9.6	9.6	8.6
HbA1c (%), endpoint	7.7	8.1	7.2
Hypoglycemia rate (events/subject-mo)	0.120	0.148	0.793
Change in FEV <sub>1</sub> (l/yr)	-0.077	-0.067	-0.074
[95% CI]	[-0.092, -0.062]	[-0.087, -0.047]	[-0.084, -0.063]
Change in DL <sub>CO</sub> (ml/min/mm Hg/yr) [95% CI]	-0.703	-0.735	-0.634
	[-0.940, -0.466]	[-0.960, -0.510]	[-0.816, -0.452]

FEV<sub>1</sub>=forced expiratory volume in 1 second; DO<sub>CO</sub>=carbon monoxide diffusing capacity.

*Continued on page 5*

## Insulin Administration..

Continued from page 4

week's meeting, Heinemann and multinational colleagues presented data suggesting that the transdermal delivery of insulin may be feasible (362-OR).

Using short radio-frequency electrical energy pretreatment of the skin, which creates microchannels in the upper layers, the investiga-

tors then applied a drug patch containing insulin (150 U) in a dry form to five healthy subjects. Subjects were crossed over to SC regular human insulin (10 U). Although the relative bioavailability of the transdermal insulin was low (9.6%, corresponding to a delivery of 10 to 15 U), the mean area under the curve values were similar between the administration routes (5393 and 5933  $\mu\text{U}/\text{ml}/600$  minutes for the transdermal and SC routes, respectively). Further studies of this as

well as the other promising noninvasive forms of insulin delivery are anxiously awaited.

For the past five years, we've been describing a series of novel insulin delivery systems as reported at international diabetes meetings. It is interesting to note that none has yet made it to market. While several inhaled formulations appear to be close, particularly Exubera<sup>®</sup>, their ultimate exact role in the management of diabetes remains to be defined.



## On the Horizon



The annual ADA meeting is an excellent venue to peer into the future of diabetes care. Dozens of abstracts are typically presented unveiling novel pharmacological approaches to combating hyperglycemia and obesity. Some of these are thoughtfully based on a growing understanding of the molecular underpinnings of metabolic diseases; others appear to have occurred simply through happenstance! Here are some highlights from this week's meeting:

Pinitol (3-O-methyl-D-chiro-inositol) has hypoglycemic activity and appears to act downstream of the insulin signaling pathway to mimic insulin's effects. The agent was studied in 22 Type 2 diabetic patients by Kim *et al.* of Korea over 12 weeks (385-P). HbA1c and fasting and post-prandial glucose all fell significantly in this non-randomized study. A Japanese group, led by Shin-Ichiro, presented data on SGL0010, a novel orally active inhibitor of the renal sodium-dependent glucose transporter (473-P). Its activity is based on a marked (50-fold) induction of glucose excretion through the urine. In their animal models, the Zucker diabetic fatty (ZDF) rat and non-diabetic beagle dogs, the drug significantly lowered glucose concentrations after oral glucose challenges. From the UK, Bartlett and colleagues (492-P) described the *in vitro* and *in vivo* profile

of Gpi688, a glycogen phosphorylase inhibitor. This agent dramatically reduces glucose output (>80%) in rat hepatocyte cell lines. In live rats, the agent prominently decreased glucagon-stimulated hyperglycemia. Van Poelje and US collaborators presented data on MB06322, an oral selective fructose 1,6-biphosphatase inhibitor, which attenuates gluconeogenesis (503-P). The drug was tested in the ZDF rat and significantly lowered glucose levels, with less prominent effects on triglycerides and insulin levels. Two glucokinase activators (PSN101 and PSN010) were presented by Fyfe *et al.* from England (522-P). This class of medication attenuates hyperglycemia by simultaneously decreasing hepatic glucose production and increasing glucose-dependent pancreatic insulin secretion. A significant glucose lowering effect was demonstrated in the ob/ob mouse, an accepted model of Type 2 diabetes. Gene therapy is another potential approach for the future treatment of diabetes. Parsons and American colleagues have developed glucagon-like peptide 1 (GLP-1, an incretin—see tomorrow's edition) chimeric expression vectors. They've administered it systemically in rodent diabetic models and demonstrated long-term lowering of blood glucose. At this week's meeting, this group reported their initial experi-

ence in administering this vector locally, to the quadriceps muscle of the ZDF rat. (This approach would be expected to mitigate any potential adverse effects involved in systemic administration of viral vectors.) In these latest experiments, plasma GLP-1 levels increased and glucose levels were maintained near the normal range. Finally, Australian investigators (Wittert *et al.*, 1835-P) displayed a poster describing an orally active modified fragment of the human growth hormone (hGH). This peptide has lipolytic and anti-lipogenic activity in animal models, but without the usual anabolic effects of hGH. In a 12-week study involving 300 obese patients a daily 1 mg dose was associated with a weight loss of 2.8 kg, with some benefits also on glucose and lipid parameters. There were no reported serious adverse effects.

Of course, as seen in the prior article on insulin formulations, only a fraction of products in development ever make it to market. We'd also point out that effects in rodent models do not necessarily predict ultimate results in man. Accordingly, while interesting, it remains to be seen which of these agents, if any, will ever become part of our therapeutic armamentarium for diabetes and/or obesity.



## So Many Posters, So Little Time...



Cukierman and Canadian colleagues (162-OR) this week presented a meta-analysis to assess the magnitude of the risk of cognitive functional decline associated with diabetes. A comprehensive literature review was conducted and 25 studies were found that met rigid, evidence-based medicine inclusion and exclusion criteria. In these, overall, patients with diabetes had a 1.2-1.5 fold greater change over time in measures of cognitive function than those without diabetes. Specifically, the risk of dementia was increased by a factor of 1.59 (95% confidence interval, 1.37-1.84) in diabetic patients. We suspect this

observation is due to small-vessel cerebrovascular disease, although the possibility that recurrent hypoglycemia plays some role should also be considered.

Fan *et al.* from Baltimore compared treatment patterns and glycemic control rates (HbA1c <7%) in diabetes patients in the NHANES database during 1988-1994 and 1999-2002 (1000-P). The proportion of patients using only diet to control glycemia decreased between survey periods

(27.4% vs. 18.7%, respectively), as did the use of insulin (24.2% vs. 14.0%). In contrast, treatment with oral anti-hyperglycemic agents without (45.4% vs. 57.4%) and with insulin (3.1% vs. 10.0%) increased. Despite this, the investigators found that the overall age-adjusted glycemic control rates decreased significantly over time (from 44.5% to 38.5%,  $p < 0.0001$ ), suggesting that earlier and more aggressive therapy is needed to achieve proper glucose targets.

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