

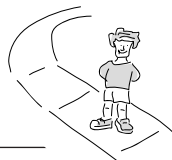
Diabetes 2006

From the 66th Annual Scientific Sessions of the American Diabetes Association ■ Washington, DC

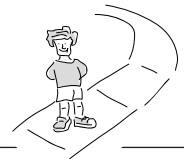
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DPP-4 Inhibitors: New Kid on the Block



Important data on diabetes presented at the 66th Annual Scientific Sessions of the American Diabetes Association come to you in **Diabetes 2006**, a newsletter CME program that is being offered to you by Yale University School of Medicine with the support of Takeda Pharmaceuticals North America, Inc. E-mail or fax delivery to your office of **Diabetes 2006** will be followed by a **Diabetes 2006** booklet (ACC and ADA newsletters) in the mail. After successfully completing the quiz and evaluation therein contained and remitting a \$25 processing 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 2006 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 interrelationship between insulin resistance, hyperglycemia, and atherosclerosis in patients with Type 2 diabetes.
- Identify evolving and emerging management strategies for diabetes (e.g., combination therapies, 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.

Supported through an unrestricted educational grant from Takeda Pharmaceuticals North America, Inc.

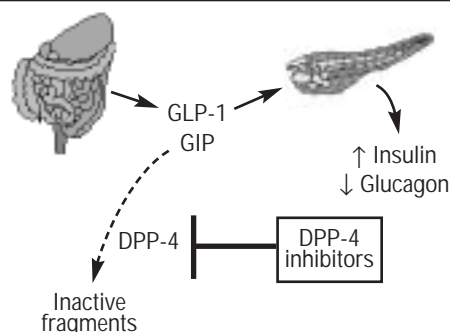
Incretin-based therapy is a new treatment option for our patients with Type 2 diabetes. The GLP-1 (glucagon-like peptide 1) mimetic, exenatide, is the only drug currently available in this category. This product is based on an active compound found in the saliva of the Gila monster and activates GLP-1 receptors in a variety of tissues, most notably the endocrine pancreas. It stimulates insulin secretion from the β -cell in a glucose-dependent fashion, while also reducing glucagon output from the α -cell. The result is increased glucose disposal by peripheral tissues and a reduction in hepatic glucose output. Exenatide also slows gastric emptying and possibly has a central effect on satiety through hypothalamic centers. The net result is a lowering of glucose levels, particularly in the postprandial setting. Exenatide and other GLP-1 analogues under investigation also lead to weight loss. Since the stimulation of insulin secretion is glucose-dependent, these agents are not associated with hypoglycemia, at least when used alone or with insulin sensitizers. Side effects are mainly gastrointestinal. To date, published studies with exenatide show a reduction in HbA1c of nearly 1%. Exenatide is now approved for use with metformin and/or sulfonylureas. Other GLP-1 analogues, such as liraglutide, are also under investigation. To date, all these GLP-1-based therapies need to be administered by subcutaneous injection.

The endogenous incretins are derived from the L-cells of the small and large bowel, namely GLP-1 and GIP (glucose dependent insulinotropic peptide, formerly gastric inhibitory peptide), and are rapidly metabolized by the enzyme dipeptidyl peptidase 4 (DPP-4) (Figure 1). DPP-4 inhibitors have the net effect of increasing endogenous incretin levels. In addition to being available in oral formulations, the DPP-4 inhibitors have the additional benefit of less (or no) nausea, which is the most common side effect of the injectable GLP-1 mimetics/analogues. On the other hand, their efficacy on HbA1c may be slightly less than that of the GLP-1 analogues, and the DPP-4 inhibitors are weight neutral.

The two DPP-4 inhibitors in the late stages of development are sitagliptin and vildagliptin, applications for which have already been submitted to the US Food and Drug Administration (FDA). Given their likely approval later this year, there was a significant degree of interest in their role within the diabetes pharmacopeia at this week's meeting.

Rosenstock and international colleagues (557-P) presented the results of a randomized, double-blind, 24-week study in 697 drug-naive patients with Type 2 diabetes, comparing the effects of vildagliptin 50 mg bid to rosiglitazone 8 mg qd. The two groups were balanced at baseline, with a mean age of 54 years, BMI 32.4 kg/m², diabetes duration 2.4 years, and HbA1c 8.7%. The vildagliptin group experienced a 1.1 ± 0.1% decline in HbA1c, which was equal to that seen in rosiglitazone patients. Of note, in patients with higher HbA1c (baseline >9%, n=254), the drug effect was greater, as reported in many antihyperglycemic drug trials: -1.8 ± 0.1% with vildagliptin and -1.9 ± 0.2% with rosiglitazone. The investigators reported that vildagliptin-treated patients experienced reductions in triglycerides, total cholesterol, and LDL-cholesterol as compared to rosiglitazone, but the actual changes with the DPP-4 inhibitor were minimal—the difference was primarily driven by increases in the rosiglitazone group. Rosiglitazone, however, had a more prominent beneficial effect on

Figure 1. Incretin Secretion and Degradation



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DPP-4 Inhibitors..

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HDL-cholesterol levels. There was no significant hypoglycemia with either treatment. The incidence of edema was greater with rosiglitazone (4.9% vs. 2.5%). The investigators concluded that in monotherapy, vildagliptin is as efficacious as rosiglitazone. We wonder what the data might have shown if rosiglitazone were dosed at 4 mg bid, which has been shown to be more efficacious in some studies.

Fonseca *et al.* (467-P) conducted their own randomized, double-blind, placebo-controlled 24-week study with vildagliptin in 256 patients with more advanced Type 2 diabetes—those inadequately controlled on insulin (HbA1c 7.5%-11.0% taking >30 units per day). Baseline characteristics included a mean age of 59 years, BMI 33.0 kg/m², duration of diabetes 15 years (on insulin for 6 years; average dose 82 units/day), and HbA1c 8.5%. The adjusted mean change in HbA1c from baseline was -0.5% in the vildagliptin group vs. -0.2% in the placebo group ($p=0.02$). The insulin dose was decreased by just 3 units in the active therapy group, increasing by 5 units with placebo. In older patients (≥ 65 years), the difference between groups was more prominent (-0.7% HbA1c with vildagliptin, 0.0% with placebo). Hypoglycemic events were less common and less severe with vildagliptin (113 events [0 severe] vs. 185 events [6 severe] with placebo). Although the research group concluded that vildagliptin reduced HbA1c when added to insulin, we question the clinical significance of their findings. Admittedly, the data in older individuals appear more interesting, but may be the result of less aggressive insulin titration in these patients, who were perhaps perceived to be at greater risk of hypoglycemic sequelae. The hypoglycemic event data are provocative, especially since the change in insulin dosing was minimal, but the mechanism is unexplained.

Dejager and international colleagues (120-OR) presented the results of a head-to-head vildagliptin-metformin trial. 780 patients with Type 2 diabetes (mean age 53 years, BMI 32.4 kg/m²,

diabetes duration 2.4 years, and HbA1c 8.7%) were randomized in a 2:1 ratio to vildagliptin 50 mg bid vs. metformin 1,000 mg bid. The adjusted mean change in HbA1c was $-1.0 \pm 0.1\%$ with vildagliptin and $-1.4 \pm 0.1\%$ with metformin, statistically favoring the latter. Gastrointestinal side effects were more common with metformin. In combination, these drugs, which have different mechanisms of action, would be expected to have added benefit. Garber *et al.* (121-OR) reported from such a combination study. 416 patients with Type 2 diabetes on stable metformin therapy were randomly assigned to receive the addition of either vildagliptin 50 mg qd, 50 mg bid, or placebo. Their mean age was 56 years, BMI 32.8 kg/m², diabetes duration 6 years, and baseline HbA1c 8.4%. The between-group difference in the adjusted mean change in HbA1c was $-0.7 \pm 0.1\%$ in the low-dose group ($p < 0.001$ vs. placebo) and $-1.1 \pm 0.1\%$ with the higher dose ($p < 0.001$). It was also suggested that vildagliptin may have mitigated metformin-associated gastrointestinal side effects ($p=0.022$), although the mean doses of metformin in the three groups was not reported.

Sitagliptin or placebo was added to ongoing metformin therapy in 701 patients with Type 2 diabetes by Karasik and international colleagues (501-P). The mean age was 54 years, BMI 31 kg/m², diabetes duration 7 years, and baseline HbA1c 8.0%. After a metformin titration/stabilization period, sitagliptin 100 mg qd was administered for 24 weeks. Active therapy patients experienced a 0.65% reduction in HbA1c (placebo-subtracted), the result of a mean 25 mg/dl reduction in fasting glucose and 51 mg/dl reduction in post-prandial glucose. Sitagliptin also increased insulin, C-peptide levels, and HOMA- β as well as decreased the proinsulin:insulin ratio, reflecting improved β -cell function. Active therapy resulted in no significant hypoglycemia.

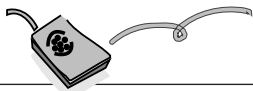
Using an identical experimental design, Rosenstock and US colleagues assessed the efficacy of sitagliptin 100 mg qd added to stable pioglitazone therapy in 353 patients with inadequately controlled Type 2 diabetes (556-P). In this study,

the mean age was 56 years, BMI 31.5 kg/m², diabetes duration 6 years, and baseline HbA1c 8.0%, with no differences between active therapy and placebo groups. Placebo-subtracted HbA1c reduction with sitagliptin was 0.65%. No hypoglycemia and no significant mean weight gain occurred in the trial.

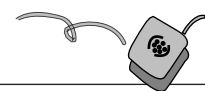
These trials, and others, suggest that the DPP-4 inhibitor class of medications may provide benefit to patients with Type 2 diabetes, although the HbA1c reductions appear less than with conventional therapies (usually in the 1%-2% range). However, we'd point out that the absolute HbA1c reduction in clinical trials is in part dependent on the baseline HbA1c level. Less reduction is to be expected when baseline HbA1c is 8.0% or less. In this light, we find the comparison study vs. rosiglitazone of significant interest. Also, although there was some initial concern that these drugs might have significant side effects (through their inhibition of other peptidases), that has not emerged from the clinical trials to date.

How the DPP-4 inhibitors will fit into our therapeutic armamentarium for Type 2 diabetes remains unclear. They will most likely have a role in our more mildly hyperglycemic patients, probably most commonly used in combination with other agents. Their relative value vis-à-vis the injectable GLP-1 analogues remains controversial—they appear to be better tolerated, although probably less efficacious, at least as body weight gain is concerned. We look forward to additional scientific studies on this interesting new class, particularly as related to long-term efficacy, given their purported effects on β -cell survival.

The similarities and differences between the GLP-1 mimetics/analogues and the DPP-4 inhibitors were reviewed by Dr. Michael Nauck of Germany during an incretin symposium on Sunday. He suggested that while glucose lowering effects of these classes were similar, the GLP-1 drugs likely have a more robust effect on β -cell function. Ultimately, comparative trials will be needed to further elucidate these differences.



Glucose Monitoring in the 21st Century



After being discussed in this newsletter for years, the indwelling continuous glucose monitoring sensors are now commercially available for home use by selected patients with diabetes. These devices are small, disposable, and subcutaneously inserted. They measure the glucose concentration within interstitial fluid, which correlates reasonably well with plasma

glucose. Information is transmitted to a receiver, typically the size of a pager, which displays the glucose data in live time, including recent trends. The devices also have alarm systems that warn the user about impending hypoglycemia or hyperglycemia. Certain issues remain in terms of precision, reliability, convenience, and cost, but the devices will likely represent an important aspect

of diabetes care over the coming years. Several presentations were devoted to this topic at the 66th Scientific Sessions.

The recently FDA approved short-term, continuous glucose monitoring (CGM) device, DexCom™ STS™ System, was the subject of an oral presentation by Zisser and colleagues (69-OR) who reported their experience with the device as

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a means to direct diabetes self-management. Three different periods were compared in 21 study sessions of patients with Type 1 diabetes: Period 1 (24-hour, self-monitoring of blood glucose [SMBG] with blinded CGM); Period 2 (12-hour, clinic, staff supervised, self-management with CGM); and Period 3 (36-hour home use, self-management with CGM). SMBG decisions were deemed appropriate if sensor glucose was within target (80-200 mg/dl) 3-hours post-decision. Two groups of decisions were analyzed: bolus doses of rapid-acting insulin and correction of hypoglycemia with carbohydrates. Results strongly favored CGM whether supervised or in the home setting (Table 1).

Choudhary and colleagues (388-P) correlated pairings of capillary blood glucose measurements via SMBG and CGM (Medtronic Minimed CGMS®) in 381 diabetes patients during symptomatic hypoglycemia. Previous data had suggested that sensor readings may overestimate hypoglycemia. Corresponding readings were available for 238 episodes. Mean glucose values were 54.6 ± 11.8 mg/dl and 56.8 ± 17.7 mg/dl for SMBG and CGM, respectively. During the six episodes of severe hypoglycemia, the mean was 36.9 ± 4.1 mg/dl for SMBG. For five of these, the CGM was at the lower limit of detection (40 mg/dl) and at 45 mg/dl for the other. There were significantly lower capillary blood glucose values for symptomatic hypoglycemic episodes associated with CGM readings < 40 mg/dl (capillary glucose 46.7 ± 10.3 mg/dl) versus values > 40 mg/dl (capillary glucose 57.4 ± 11.0 mg/dl) ($p < 0.0001$). Type 1 patients ($n = 107$) had lower capillary glucose values (52 ± 25 mg/dl) than Type 2 patients (59 ± 12.6 mg/dl; $p = 0.001$) during symptomatic events, but not with sensor values. The authors identified the sensitivity and specificity of CGM at various glucose levels (Table 2) to detect capillary blood glucose < 65 mg/dl. From these data, the researchers suggest that the CGMS is very specific for hypoglycemia at the lower detection level, 40 mg/dl, but that the optimal "cut-off" value for hypoglycemia utilizing this system should be 60 mg/dl. (The version of the CGMS that is available for patients, known as the Guardian™, was recently approved in the US.)

Whether use of continuous sensors by patients will translate into better long-term control remains unclear. Garg *et al.* from Colorado and California addressed this point (393-P). Data pairings from the DexCom™ STS™ System and SMBG were used to analyze glycemic profiles in 86 patients for three consecutive seven-day periods. Sensors were blinded in the first period

Table 1. Comparison of CGM vs. SMBG for Self-Management Decisions

Period 1 (SMBG, home)	Period 2 (CGM, supervised)	p-value
53.1% appropriate decisions	70.6% appropriate decisions	0.0052
40% increase in time spent in target range (80-200 mg/dl) in Period 2 vs. Period 1		0.0018
76.4% decrease in time spent in hypoglycemia range (< 55 mg/dl) in Period 2 vs. Period 1		0.0431
Period 1 (SMBG, home)	Period 3 (CGM, home)	p-value
31.0% increase in time spent in target range (80-200 mg/dl) in Period 3 vs. Period 1		0.0266
84.0% decrease in time spent in hypoglycemia range (< 55 mg/dl) in Period 3 vs. Period 1		0.0550

SMBG=self-monitored blood glucose; CGM=continuous glucose monitoring.

and displayed in periods 2 and 3. For 6,357 pairings, the mean absolute relative difference in glucose measures was 15.7%. Patients entering the study with an HbA1c > 9% demonstrated a 94.6% increase in euglycemia (81-140 mg/dl) during periods 2 and 3 without increases in hypoglycemia. Those with HbA1c values ≤ 7% maintained euglycemia in the blinded state, but experienced a 46.6% decrease in hypoglycemic time (< 55 mg/dl). The overall conclusion was that the use of the STS device for seven-day periods improves glycemic control in the poorly controlled patient and maintains control and minimizes exposure to hypoglycemia in the well-controlled patient. Bailey and colleagues from Texas and California (1-LB) made a similar determination in their "late-breaking" abstract involving this same device. The investigators reported that after 12 weeks, HbA1c was reduced by 0.49% ($p < 0.001$) in 60 patients with diabetes (37 Type 1, 23 Type 2) who used the STS System, without any increased risk of hypoglycemia. Those with the highest HbA1c at baseline (>8%) experienced a reduction of 1.03% ($p = 0.004$). These data are difficult to interpret given the uncontrolled study design. A third sensor, the FreeStyle Navigator™ was also the subject of several abstracts (391-P, 2-LB).

Table 2. Sensitivity and Specificity of the MiniMed CGMS to Detect Capillary Blood Glucose of < 65 mg/dl

CGMS Value	Sensitivity	Specificity
40 mg/dl	0.33	0.94
50 mg/dl	0.52	0.88
60 mg/dl	0.73	0.73
70 mg/dl	0.92	0.38

How these devices will ultimately be employed in practice remains unclear, particularly given their expected high price. At the very least, they will assist our most labile patients in detecting severe glycemic excursions. We feel that eventually they may become a routine aspect of diabetes care.

Down the Road a Bit...

Two novel approaches were investigated as alternatives to standard glucose monitors. Galassetti *et al.* (392-P) investigated exhaled aromatic volatile organic compounds (VOCs) as a marker of intravenously-induced hyperglycemia. The sophistication of VOC analysis has improved such that exhaled gas patterns can be identified that correlate to hyperglycemic conditions. Analysis of 10 healthy subjects exposed to an intravenous glucose tolerance test revealed three gases with aromatic rings with early peaks mimicking glucose profiles in plasma. The compounds accurately tracked plasma glucose under the conditions of acute hyperglycemia (~300 mg/dl). The investigators concluded that this preliminary research may assist in the development of non-invasive, portable devices for glucose monitoring. Another non-invasive approach involves the device, OneLook®. Mitchell and colleagues from the UK (401-P) reported that the analysis of reflections gained from shining low-power light into the eye might someday provide an alternative to SMBG. Correlations between two fingerstick devices and the OneLook® were conducted in 17 subjects (10 with diabetes and 7 controls) providing 150 data points. Values were obtained during euglycemia, 70-180 mg/dl ($n = 127$), hypoglycemia ($n = 1$), and hyperglycemia ($n = 22$). The correlation coefficient was $r = 0.93$ ($p < 0.001$), and the mean absolute

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percentage error was 15%. Of the 150 paired data elements, the Clark Error Grid analysis demonstrated 81.3% and 17.3% of measurements in Zones A and B, respectively. This indicates



The symposium, *Cause or Consequence? Novel Complications Associated with Diabetes* addressed several "chicken vs. egg" questions on disease states associated with diabetes. Dr. Jeanne Clark of Johns Hopkins University, initiated the session with a discussion on "Fatty Liver Disease and Diabetes." Non-alcoholic fatty liver disease (NAFLD) is histologically identical to alcoholic steatosis, with the absence of ethanol as the culprit. Epidemiologic data have demonstrated an association between diabetes and NAFLD, and increases in hepatic enzymes are associated with an increased prevalence of impaired glucose tolerance and diabetes. It has not yet been elucidated whether (1) diabetes induces NAFLD; (2) NAFLD causes diabetes; or (3) a common source is responsible for both. Dr. Clark reviewed the evidence in support of each theory, recognizing that none is definitive at the present time. Based on current evidence, she commented that it is most likely that diabetes and NAFLD are derived from a common origin. Insulin resistance and metabolic syndrome have both been linked to an increased risk for NAFLD and may be to blame. Therefore, patients with either condition should be screened for the other disease.

The second presenter, Dr. Naresh Punjabi also of Johns Hopkins, proposed a bidirectional relationship between pulmonary disease and diabetes. Similar to hepatic dysfunction, it is not known whether pulmonary disease induces diabetes or vice versa. Cross sectional data from the Framingham Offspring Cohort demonstrated lower than predicted pulmonary function in patients with diabetes or high fasting plasma glucose levels, particularly in smokers. Conversely, impaired lung function has been shown to confer a greater risk of diabetes. Patients with lower forced expiratory volume (FEV) and forced vital capacity (FVC) have a higher incidence of developing diabetes. However, an impaired FEV/FVC ratio ends up not being predictive. Punjabi hypothesized that the mechanism may be related to microangiopathy and decreased capillary blood volume in the lung, since the FEV/FVC ratio is indicative of obstructive lung disease, while, alone, low FEV and FVC are measures of restrictive physiology.

very good correlation.

One of the "holy grails" for patients with diabetes (and for clinicians who care for them) has been reliable, non-invasive monitoring of blood glucose. The field has been fraught with many delays and disappointments to date.

Whether either of these novel approaches will pan out is unclear. We do feel, however, that continuous monitoring is here to stay, but we need to learn how to most efficiently implement these new systems into our clinical practice.



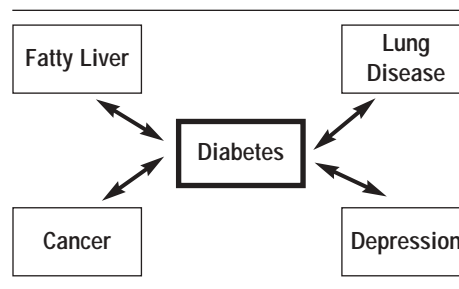
Which Came First?

Lastly, independent of obesity as a risk factor, patients with obstructive sleep apnea have a higher incidence of glucose intolerance and insulin resistance, further underscoring the relationship between pulmonary disease and metabolic abnormalities. This issue is becoming increasingly important with pulmonary insulin having been recently approved by the FDA and soon to be released.

Cancer and its association with diabetes was the topic of the third presentation delivered by Dr. Tim Byers of the University of Colorado. Byers portrayed the relationship between various cancers and diabetes mediated by both behavioral and metabolic factors. He shared the World Health Organization estimate that 20% of all cancers are caused by obesity and lack of physical activity. Data also demonstrate that the risk of cancer mortality increases with larger body mass index. Byers noted that diabetes is commonplace following an oncologic diagnosis primarily due to: (1) a decrease in physical activity; (2) an increase in "sarcopenic adiposity", and (3) behavioral and physiological changes. (We would add that glucocorticoids are a frequent component of various chemotherapeutic regimens and have a major diabetogenic effect in many patients.) Lastly, Byers identified the convergence of evidence for prevention of cancer, heart disease, and diabetes that encourages proper diet, physical activity, and weight management. He emphasized the importance of a common and shared message by all disciplines to optimize public health, commending the collaboration between the American Diabetes Association, American Heart Association, and American Cancer Society in delivering that common theme.

Finally, Dr. Sherita Goldman from Johns Hopkins, made a case for her presentation entitled, "Psychological Stress, Depression, and Diabetes: the Neuroendocrine Link." She identified that patients with diabetes have a two-fold increase in the incidence of depression, previously considered the result of stress from dealing with a chronic illness. Paralleling the previous talks, Goldman also proposed the reverse scenario of depression-induced diabetes, providing three hypotheses: (1) Depression affects behavioral

Figure 2. Association Between Diabetes and Other Diseases



factors that lead to diabetes such as decreased physical activity and change in eating patterns. (2) Treatment of depression and related illnesses can induce diabetes. For example, the association between atypical antipsychotics and weight gain and hyperglycemia is well documented. (3) Neurohormonal changes associated with depression may increase the incidence of diabetes. This may evolve from stress-induced catecholamine and cortisol release, impacting glucose metabolism and regulatory hormones and leading to insulin resistance and Type 2 diabetes. In line with this discussion by Goldman, Skaff *et al.* presented results of a study in which they assessed the impact of "negative affect" on next morning fasting glucose in 210 Type 2 diabetes patients (59% female, mean age 58 years) (213-OR). Over the 21-day observation period, blood glucose was higher in those with higher mean levels of self-reported negative affect. On an individual basis, blood glucose was significantly higher on days when the previous day's negative affect was rated as worse than the individual's mean. This association was stronger in males than females, but was not influenced by other factors (i.e., age, education, duration of diabetes, type of diabetes medication). These findings suggest a biological/behavioral basis between mood and glycemia.

Learning more about each of these conditions and how they relate to diabetes (Figure 2) will lead to a better understanding of the complex interplay between metabolism and disease expression.



Focus on Science



The medial hypothalamus is a major integrator of nutritional and hormonal signals, which may play a pivotal role in the regulation of energy balance and modulation of liver glucose and lipid production. Numerous studies were presented this week highlighting the central role of the brain in the regulation of intermediary metabolism.

It is well established that an acute bout of exercise lowers circulating levels of triglycerides (TG) and TG-enriched very low density lipoprotein (VLDL) particles, but the precise mechanism has never been fully elucidated. In rat models, increased central lactate conversion to pyruvate via lactate dehydrogenase (LDH) has also been shown to suppress TG levels by 50% and hepatic VLDL production by 40%. Camacho *et al.* (60-OR) from New York used lactate infusion to

simulate the physiological increase in lactate levels after a bout of exercise in male Sprague-Dawley rats. This elevation in plasma lactate was sufficient to reproduce a similar reduction in TG levels (-50%) and hepatic VLDL production (-31%) as seen after exercise. The effects were then blunted by administration of the LDH inhibitor, oxamate, within the mediobasal hypothalamus, thus highlighting the important sensing role of the hypothalamus for circulating lactate levels. After central conversion to pyruvate, a "brain-liver circuit" is activated, curtailing hepatic synthesis of VLDL and resulting in a marked drop in circulating triglycerides.

Hypothalamic centers may also play a key role in the regulation of hepatic glucose output by monitoring the availability of various nutrients from the circulation. Gutierrez-Juarez *et al.*

(198-OR), also from New York, showed marked (47 ± 4%) suppression of endogenous glucose output by infusion of the ketogenic amino acid leucine within the mediobasal hypothalamus. Ross *et al.* (197-OR) used infusion of the monounsaturated fatty acid, oleic acid, in the same region of the rat hypothalamus to show inhibition of endogenous glucose production by 61%, an effect so powerful that exogenous glucose had to be infused to avoid hypoglycemia. Hypothalamic infusion of the saturated fatty acid palmitate had slightly less effect, whereas the polyunsaturated fatty acid linoleic acid had none.

Growing scientific understanding of this previously unrecognized "brain-liver circuit" is rapidly advancing our understanding of the central regulation of metabolism.



So Many Posters, So Little Time...



In EDIC (Epidemiology of Diabetes Interventions and Complications), a long-term observational study as a follow-up to the DCCT (Diabetes Control and Complications Trial), a 42% reduction in cardiovascular events ($p=0.02$) and a 57% reduction in risk of non-fatal MI, stroke, or death from cardiovascular disease ($p=0.02$) were observed among those who received intensive insulin therapy during the DCCT (Nathan *et al.*, *NEJM* 2005). These benefits were observed despite convergence of HbA1c values between the original intensive and conventional treatment groups at year five of EDIC. Exploring possible reasons for these benefits, Prince *et al.* presented 16-year follow-up data from the childhood-onset (diagnosis < age 17 years) Type 1 diabetes cohort of the Pittsburgh Epidemiology of Diabetes Complications (EDC) study ($n=408$) (2-OR). Those who experienced a decline (of >1 SD) in HbA1c were less likely to develop CAD (RR per one unit decrease = 0.73, 95% CI 0.62-0.86), independent of baseline HbA1c or diabetes duration. Furthermore, HbA1c volatility (SD of all HbA1c measures during follow-up, adjusted for baseline HbA1c and duration of illness) appeared to predict CAD (RR 1.63, 95% CI 1.08-2.45). These findings suggest that lower overall glycemic exposure and change in HbA1c may be important factors that predict CAD risk in patients with Type 1 diabetes.

Reports of a tighter association between cardiovascular risk and postprandial (as opposed to fasting) glucose have increased interest in

controlling glycemia after meals. Two research groups presented data this week addressing the optimal timing of postprandial glucose testing. Daenen and French coworkers analyzed glucose profile (by the continuous glucose monitor, CGMS[®]) in 99 consecutive diabetic patients (66 with Type 1) who followed their usual diet and were treated with either basal-bolus insulin using a rapid insulin analogue and either glargine or NPH, or an insulin pump (70-OR). The time to peak glucose following breakfast was 72 ± 23 minutes, with 80% of patients reaching their peak glucose level in less than 90 minutes. The day-to-day coefficient of variation was 49%. Time to peak level was related to glucose increment ($r^2=0.14$, $p=0.015$), but not to peak level, and was not different between those with Type 1 and Type 2 disease. The times to peak postprandial level were similar after all meals. Based on measurements of mean glucose increment and decrement, the investigators determined that a variation of ± 5 minutes in time post-prandial glucose is measured will lead to an error of ± 18 mg/dl. The investigators concluded that current ADA recommendations to measure postprandial glucose 1 to 2 hours after the start of a meal likely underestimate peak glucose levels for many diabetes patients treated with short-acting insulin analogues. In a related abstract, with a different finding, Sakharova *et al.* assessed timing of postprandial

glucose testing in 19 Type 2 diabetes patients failing oral antihyperglycemic therapy (HbA1c $\geq 7\%$; mean 2.6 ± 0.5 oral agents) and referred for insulin initiation (1953-PO). Patients underwent a 12-hour mixed-meal tolerance test (isocaloric meals at 8 am, 12 pm, and 4 pm), with glucose levels measured every hour. In contrast to the report in Type 1 patients, the highest postprandial glucose levels and largest glucose excursions occurred 2 to 3 hours after breakfast, with mean and peak levels ~ 20 -30 mg/dl higher and peak excursions ~ 2 - to 6-fold greater than after other meals (Table 3). Taken together, these data may indicate that the optimal time for measuring postprandial glucose may depend on the type and severity of diabetes, the meal schedule, and the type of agents (e.g., oral, short-acting insulin) used for its treatment.

Table 3. Postprandial Glucose (mg/dl) Following Isocaloric Meals

Meal	Peak Glucose	Peak Glucose Excursion*
Breakfast	283 ± 84	88 ± 40
Lunch	253 ± 88 [†]	13 ± 23 [‡]
Dinner	256 ± 90 [†]	41 ± 25 [‡]

* peak postprandial glucose - pre-meal glucose.

[†] $p < 0.05$ vs. breakfast.

[‡] $p < 0.001$ vs. breakfast.

Silvio E. Inzucchi, MD
Robert S. Sherwin, MD

Editors, Yale University,
New Haven, Connecticut