

Diabetes 2007

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Incretins...That Gut Feeling



Important data on diabetes presented at the 43rd Annual Meeting of the European Association for the Study of Diabetes comes to you in **Diabetes 2007**, a newsletter CME program that is being offered to you by Yale University School of Medicine with the support of Takeda Pharmaceuticals North America, Inc., Merck & Co., Inc., Novo Nordisk Inc., and Amylin Pharmaceuticals, Inc./Eli Lilly and Company. Fax or e-mail delivery to your office of **Diabetes 2007** will be followed by a **Diabetes 2007** booklet (EASD and AHA newsletters) in the mail. After successfully completing the quiz and evaluation therein contained, you will qualify for up to 5.5 Category 1 credits towards the Physician's Recognition Award of the American Medical Association to be issued by Yale University School of Medicine.

Diabetes 2007 is being offered to physicians practicing in the United States. After successfully completing this program, participants will be able to:

- Explain the pathogenesis of Type 2 diabetes, especially the coexisting roles of insulin resistance and insulin secretion.
- Recognize the clinical manifestations of the macrovascular and microvascular complications of diabetes and describe appropriate therapeutic interventions.
- Recognize the important association between insulin resistance/metabolic syndrome and atherosclerosis in patients with Type 2 diabetes.
- Identify evolving and emerging management strategies for diabetes (e.g., combination antihyperglycemic therapy, new insulin delivery systems, new glucose monitoring techniques, novel drugs).
- Describe the approach to managing dyslipidemia, hypertension, and cardiovascular risk factors in patients with diabetes.

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Several sessions at the 43rd EASD Annual Meeting were devoted to further exploration of the incretin system and anti-hyperglycemic drugs that modulate it. Topics ranged from investigation of the physiology of the incretin effect in humans to comparative pharmacology and outcomes of incretin-based drugs.

The two major incretins, glucagon-like peptide (GLP)-1 and glucose-dependent insulinotropic peptide (GIP), are released from the intestine in response to meals. They exert a systemic effect at multiple sites, particularly at the level of the endocrine pancreas. Both GLP-1 and GIP increase insulin secretion, in a glucose-dependent fashion. GLP-1 suppresses glucagon secretion from the pancreas, which, in turn, reduces hepatic glucose production. GLP-1 also delays gastric emptying and may have a central effect to enhance satiety. The incretin system mainly functions as a regulator of post-prandial glucose metabolism. The incretins are metabolized through an enzyme known as dipeptidyl peptidase (DPP)-4. Development of therapeutics in this area has involved finding GLP-1 analogues or mimetics, or inhibitors of DPP-4, the latter augmenting endogenous incretin levels. The two incretin-based drugs currently available to treat patients with Type 2 diabetes are exenatide, a GLP-1 mimetic, and sitagliptin, a DPP-4 inhibitor.

Muscelli *et al.* evaluated the relationship between obesity and hyperglycemia on the "incretin effect," defined as the ratio of insulin secretory response to oral glucose vs. intravenous (IV) glucose (abstract 580). (Incretins result in a greater response when glucose is given orally.) Oral and IV glucose were administered to 50 subjects (25 with normal glucose tolerance, 16 with impaired glucose tolerance, and nine with Type 2 diabetes) on separate days. The range in BMI was quite large, 19.6 to 61.2 kg/m² (mean of 35.4). Insulin secretion rates, β -cell function, and β -cell glucose sensitivity were determined by mathematical modeling of glucose, C-peptide, and insulin levels in response to the glucose challenges. In the entire group, insulin secretion and β -cell glucose sensitivity were significantly higher following oral vs. IV glucose ($p < 0.0001$). The

incretin effect was inversely related to BMI and the glucose area under the curve (AUC_G) (all $p < 0.01$). The researchers concluded that obesity and ambient hyperglycemia independently down-regulate insulin secretion and β -cell glucose sensitivity mediated by incretin hormones.

The precise mechanism of action of exenatide, a GLP-1 mimetic, was the subject of investigation by Ionut and US colleagues (abstract 590). While it is established that exenatide exerts some of its anti-hyperglycemic effect via effects on pancreatic hormones, the investigators postulated that additional glucose lowering might occur through islet-independent mechanisms. Utilizing eight male mongrel conscious dogs, a series of three experiments were conducted. (1) Meal time exenatide (vs. no exenatide) demonstrated lower post-prandial glucose mainly through significant glucagon suppression ($p < 0.001$). (2) Intraportal glucose infusion was then utilized to investigate whether exenatide's action on glucose levels might occur in the absence of already recognized delayed intestinal absorption. In this experiment, the exenatide-treated dogs displayed significantly lower glycemia without either compensatory hyperinsulinemia or glucagon suppression. The drug therefore displayed extrapancreatic glucose lowering effect, likely related to increased hepatic glucose clearance. (3) In the final experiments, the portal infusion study was repeated with an intraportal exenatide antagonist, exendin 9-39. Glucose levels following antagonist infusion were significantly increased in comparison to those values in the exenatide only experiment—suggesting that the effect was indeed mediated through hepatic GLP-1 receptors. From these experiments, the investigators concluded that exenatide has a pancreatic hormone-independent effect on glucose, mediated by porto-hepatic GLP-1 receptors.

The impact of exenatide on hypoglycemia was compared to that of insulin glargine in Type 2 diabetes patients (144 completers) receiving concomitant metformin or sulfonylurea by Trautmann *et al.* (abstract 819). In an open-label, two-period crossover trial, patients received exenatide 5 mcg BID x 4 weeks followed by 10 mcg

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BID x 12 weeks and insulin glargine QD targeting a fasting blood glucose of ≤ 100 mg/dl for 16 weeks. The incidences of overall and nocturnal hypoglycemia in patients treated with exenatide were greater in the concomitant sulfonylurea group, however, insulin glargine was associated with an increased risk regardless of which oral agent it was combined with (Table 1). Episodes of severe hypoglycemia occurred only in the insulin glargine group (seven episodes in three patients) and were associated with poorer glycemic control (mean endpoint HbA1c in sulfonylurea-treated patients: exenatide [n=18] = $7.01 \pm 0.97\%$ versus insulin glargine [n=20] = $7.58 \pm 1.07\%$). From this investigation, the authors concluded that addition of exenatide (versus insulin glargine) to an oral agent, especially metformin, is likely to result in improvements in glycemia (HbA1c) and body weight, while decreasing the risk of hypoglycemia.

In another study comparing exenatide and insulin, Brodows and US colleagues examined predictors of achieving glycemic targets (abstract 853). Data were pooled from two comparative trials (n=1050) of exenatide 10 mcg twice daily vs. insulin glargine or biphasic insulin aspart 70/30 to identify baseline characteristics associated with achieving an endpoint HbA1c of $\leq 6.5\%$ or $\leq 7\%$. Both groups had similar mean baseline HbA1c. The exenatide-treated group was more likely to achieve the target $\leq 6.5\%$ than those managed with insulin (odds ratio [OR] 1.69, 95% CI 1.21-2.35, $p=0.002$). There was no difference between groups in achieving the higher HbA1c target of $\leq 7\%$. In both groups, baseline HbA1c, not surprisingly, was the strongest predictor for achieving the HbA1c targets. Exenatide was associated with a greater percentage of patients achieving the lower target with no overall increase in hypoglycemia and a reduction in weight. We would point out, however, that because of exenatide's mechanism of action, hypoglycemia is not associated with its use. Accordingly, lower glucose targets may be easier to achieve with drugs in this class, especially when compared to insulin, which obviously becomes trickier to adjust in patients approaching the euglycemic range.

Clinical data were also reported with the DPP-4 inhibitors, both as monotherapy and in combination with other oral agents. In a study by Xu and Williams-Herman, US, β -cell function was assessed in subjects receiving sitagliptin or metformin or in combination (abstract 884). Patients

Table 1. Effect of Exenatide vs. Insulin Glargine on Body Weight and Hypoglycemia

	HbA1c	Body Weight (kg)	% with Hypoglycemia	% with Nocturnal Hypoglycemia
Exenatide	-1.43%	-2.0†		
Insulin glargine	-1.41%	+0.5		
Exenatide + sulfonylurea	-1.38%	-0.5	30%	7%
Insulin glargine + sulfonylurea	-1.29%	+0.9	34%	16%
Exenatide + metformin	-1.48%	-3.1†	2.6%*	1.3%*
Insulin glargine + metformin	-1.50%	-0.1	17.4%	13%

* $p < 0.05$ for exenatide vs. insulin glargine.

† $p < 0.001$ vs. baseline.

were randomized to receive one of six treatments in a 24-week controlled trial: metformin 1000 mg, metformin 2000 mg, sitagliptin 100 mg, sitagliptin 100 mg + metformin 1000 mg, sitagliptin 100 mg + metformin 2000 mg, and placebo. Beta-cell function was measured using the C-peptide model. Beta-cell responsiveness and insulin secretion rates were estimated using standardized plasma parameters of β -cell function. At 24 weeks, β -cell responsiveness and insulin secretion rates were increased with all treatments in comparison with placebo. It also appeared that beta-cell function was further improved (approximately additive) with concomitant sitagliptin and high-dose metformin in comparison with monotherapies of either agent.

In a related trial, monotherapy with sitagliptin or metformin was compared with combination therapy to assess the potential for effects on GLP-1 physiology (Migoya *et al.*, 111-OR). This randomized, double-blind, placebo-controlled trial (n=16 healthy adults) compared four treatment groups: sitagliptin 100 mg QD, metformin 500 mg BID, sitagliptin 100 mg QD + metformin 500 mg BID, and placebo in a two-day, four-period crossover design. Following the morning dose of study medication on day 2, each subject ate a standard meal (765 calories: 25% fat, 55% carbohydrate, 20% protein). Baseline and post-meal blood samples of GLP-1 and GIP were collected. Each treatment resulted in a significant increase in active GLP-1 relative to placebo (monotherapy 1.5-2-fold increase and combination therapy >4-fold increase; each $p < 0.001$). However, sitagliptin monotherapy decreased total GLP-1; both metformin-treated groups, in contrast, demonstrated an increase in total GLP-1 (each, $p < 0.001$). Additionally, active GIP concentrations

increased with sitagliptin but remained unchanged with metformin. Based on these findings, the investigators concluded that combination therapy with sitagliptin and metformin provides a complementary effect on the incretin axis. Metformin likely increases intestinal release of GLP-1 (given increased active and total GLP-1 concentrations), whereas sitagliptin inhibits degradation of the active hormone (given increased active, but decreased total GLP-1.) Metformin appears to have no effects on GIP, while sitagliptin also impairs its degradation.

The efficacy and safety of the investigational DPP-4 inhibitor, vildagliptin, was assessed in the elderly (age ≥ 65 years) by Pratley *et al.* (abstract 887). Data from five clinical trials were pooled to examine age-related differences in efficacy and tolerability of vildagliptin. The mean HbA1c lowering effect of vildagliptin was slightly better at $-1.2\% \pm 0.1\%$ in those aged 65 years or older, as compared with a reduction of $1.0\% \pm 0.0\%$ in those younger than 65. There were no episodes of serious hypoglycemia and the drug appeared to be equally well tolerated in older and younger patients. The DPP-4 inhibitors may be particularly suited to elderly diabetic patients given their safety profile to date. Sulfonylureas may be challenging in this group, especially those who are tightly controlled, due to the risk of hypoglycemia. Moreover, metformin is often contraindicated due to impaired renal function.

While the definitive role of the incretin mimetics continues to evolve, it is clear that these compounds have a significant place in the management of Type 2 diabetes. There is active investigation in both the GLP-1 and DPP-4 arenas and we expect significant new developments in this field over the coming years.



A Decade of TZDs



Controversy continues regarding the thiazolidinedione (TZD) class of medications. These drugs, which have been available since 1997, now constitute about one in four to five of all prescriptions for oral anti-hyperglycemics in the US. They activate the nuclear receptor known as PPAR- γ , thereby exerting their effect on improving insulin sensitivity in muscle, liver, and adipocytes. As a result, their use is associated with reduced glucose and insulin levels. Given the association of insulin resistance and cardiovascular disease, their popularity has been enhanced by the notion that they might reduce cardiovascular event rates over time in Type 2 diabetic patients.

Over the past several months the effects of these drugs on cardiovascular risk have been extensively discussed, at times with great passion. The recent meta-analysis by Nissen and Wolski published in the *New England Journal of Medicine* (356:2457, 2007) suggested that rosiglitazone may, if anything, increase the risk of myocardial infarction. This meta-analysis has been criticized on several fronts, including both methodological and statistical. Despite these limitations, the company that produces rosiglitazone as well as the FDA itself have conducted their own analyses of the same data set and found point estimates of risk in approximately the same range. Just last week, another meta-analysis was published by Singh *et al.* in *JAMA* (298:1189, 2007), focusing solely on rosiglitazone trials of at least 12 months duration. Understandably, this paper involved many of the same trials included in the original meta-analysis. Singh found that rosiglitazone was associated with an increased relative risk (RR) for myocardial infarction of 1.42 (95% CI, 1.06-1.91, $p=0.02$) and heart failure of 2.09 (1.52-2.88, $p<0.001$). There was no increase, however, in cardiovascular mortality (RR 0.90 [0.63-1.26], $p=0.53$). The overall event rates in all these studies are relatively small, however. Nonetheless, the puzzling question at this point is: Why doesn't rosiglitazone decrease cardiovascular events? This is especially perplexing given the extensive pre-clinical and surrogate marker data that uniformly indicated a potential benefit of this entire drug class on atherosclerosis.

The story appears to be different as far as the other TZD, namely pioglitazone, is concerned. First, this agent has already been assessed in the largest diabetes cardiovascular trial, the PROactive study. In this three-year investigation, pioglitazone added to baseline anti-hyperglycemic therapy in high-risk patients with diabetes and established

macrovascular disease resulted in a 16% relative risk reduction in the composite endpoint of death, myocardial infarction, and stroke ($p=0.03$). Because the study's primary endpoint was not achieved (a broader cardiovascular composite), PROactive cannot be viewed overall as a positive study. In addition, more heart failure events, including hospitalizations, were reported in patients taking pioglitazone—partially offsetting the benefits on ischemic events. *JAMA* also recently published a pioglitazone meta-analysis, put together by the same Cleveland Clinic group responsible for the original meta-analysis on rosiglitazone (Lincoff *et al.*, *JAMA* 298:1180, 2007). In all, 19 studies were included, with a length varying from four months to 3.5 years with a total of almost 17,000 patients. The primary endpoint of the analysis—composite of death, MI, or stroke—was significantly lower in pioglitazone patients (pioglitazone, 4.4% vs. control comparators, 5.7%; hazard ratio [HR]=0.82 [0.72-0.94]; $p=0.005$). Serious heart failure was, again, more frequent in pioglitazone-treated patients (2.3% vs. 1.8%; HR=1.41 [1.14-1.76]; $p=0.002$).

Why these two agents appear to have potentially opposite effects on ischemic cardiovascular outcomes remains unclear. Pioglitazone has better effects on plasma lipids, including a reduction in triglycerides, and perhaps less effect on raising LDL-cholesterol and more effect on raising HDL-cholesterol than does rosiglitazone (Goldberg *et al.*, *Diabetes Care* 28:1547, 2005). Recently, a small study showed that pioglitazone, but not rosiglitazone, lowered Lp(a) concentrations (DeRosa *et al.*, *Clin Therap* 28:679, 2006). We

suspect that any differences may lie beyond these lipid effects—and may speak somehow to the pharmacogenomic differences between the drugs.

Not surprisingly, this week's meeting included many TZD-related presentations, as there continues to be great interest in the glycemic and non-glycemic effects of these insulin sensitizers. De Flines and Scheen from Belgium conducted a meta-analysis of published, randomized pioglitazone studies consisting of at least 50 patients to assess the effects on edema and heart failure (abstract 75). They excluded the large PROactive trial due to its distinct study design. A total of 25 randomized clinical trials were found (10 vs. placebo, 14 vs. another oral agent, and 1 vs. insulin.) The total patient cohort included 5,121 patients treated with pioglitazone and 4,567 patients treated with placebo or another agent. For the three subclasses of trials (monotherapy, combination therapy, and insulin-treated groups), the OR for edema were 2.37 (1.85-3.02), 3.13 (2.29-4.27), and 2.73 (1.77-4.23) (all $p<0.00001$). For heart failure the rates were low. In all, 21 cases were reported in the pioglitazone group and 5 in the comparator group—confirming the heart failure findings of PROactive. Clearly, caution is advised when using any TZD in a patient at risk for heart failure or who has pre-existing edema. Notably, this drug class is now considered contraindicated in patients with NYHA Class III-IV heart failure and not recommended in those with Class II symptoms. The mechanism of heart failure is not fully understood with the TZDs, but likely reflects their known effect on renal sodium handling, resulting in fluid retention.

Table 2. Impact of Adding Pioglitazone to Atorvastatin in Non-Diabetic High-Cardiovascular Risk Patients

Parameter	Atorvastatin+Placebo		Atorvastatin+Pioglitazone	
	Baseline	6 months	Baseline	6 months
HOMA-IR	2.9±2.2	2.9±1.6	3.0±2.3	2.5±2.1*
Intact proinsulin (pmol/l)	6.4±7.3	5.9±4.5	6.3±6.3	5.3±4.3*
Adiponectin (µg/ml)	14.8±11.0	14.3±11.5	15.7±9.6	32.0±19.0*†
IL-6 (pg/ml)	3.23±0.2	3.20±0.0	3.37±1.0	3.63±2.9
MCP-1 (pg/ml)	435±120	432±119	431±119	409±107*
MMP-9 (ng/ml)	277±126	291±160	291±117	279±154
P-Selectin (ng/ml)	98.1±26.7	96.6±28.5	100.9±28.3	95.3±25.9*
t-PA (ng/ml)	13.6±6.4	13.6±6.0	12.9±5.3	10.1±4.4*†

Data reported as mean±SD.

* $p<0.05$ vs. baseline; † $p<0.05$ between treatments.

IL=interleukin, MCP=monocyte chemotactic protein, MMP=matrix metalloproteinase, t-PA=tissue Plasminogen Activator.

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Importantly, there is no evidence of any deleterious effect of pioglitazone on ventricular function *per se*.

Forst and German collaborators studied 148 non-diabetic patients at increased cardiovascular risk (age 61.4 ± 6.5 years, BMI 29.2 ± 4.2 kg/m²) (abstract 1256). Patients were randomized to 40 mg of atorvastatin and placebo or 40 mg of atorvastatin + 45 mg pioglitazone. At baseline and six months, laboratory studies, including markers of insulin sensitivity (HOMA-IR, proinsulin), vascular inflammation (IL-6, MCP-1, MMP-9), endothelial function (P-selectin), and coagulation (t-PA) were obtained, as shown in Table 2. The investigators concluded that the addition of pioglitazone to atorvastatin exerted multiple pleiotrophic effects on cardiovascular risk in non-diabetic patients. It remains unclear whether the risk reduction reported

in PROactive and the Lincoff meta-analysis is related to these changes, however.

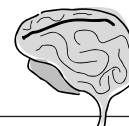
Finally, Xu *et al.* from the US conducted a retrospective study involving a large healthcare database to explore the possible effect of pioglitazone on stroke and myocardial infarction risk (abstract 1257). The analysis included patients enrolled in US healthcare plans affiliated with i3 Innovus, a database manager that has access to patient demographics, medical claims, and pharmacy information. Patients were included in the analysis if they had a diagnosis of Type 2 diabetes, were at least 45 years old, had continuous enrollment data for at least six months, and no record of prior stroke or myocardial infarction for six months prior to their index date of enrollment. Two groups were compared: those who were prescribed an anti-hyperglycemic regimen that included pioglitazone vs. those who were being treated with a non-TZD-

based regimen. The adjusted RR for stroke was 0.80 (0.72-0.89) for the pioglitazone group ($n=11,433$) vs. non-TZD patients ($n=55,273$), after adjustments for age, gender, status of hypertension, hyperlipidemia, heart failure, edema, the use of other anti-diabetic medications, as well as those medications that might impact cardiovascular risk (statins, clopidogrel, aspirin, warfarin). In this group, the adjusted RR for myocardial infarction was 0.62 (0.50-0.77). These data would appear to support the findings of PROactive and the Lincoff analysis. However, we would caution that such pharmacoepidemiological data sets are fraught with potential biases that render them useful only to generate hypotheses.

Several large cardiovascular trials with both TZDs are currently underway which will hopefully further elucidate their precise role in managing our patients with Type 2 diabetes. Stay tuned!



Metabolic Concerns in Psychiatric Disease



Chairpersons, Dr. Holt, UK and Dr. Hermanns, Germany hosted a Tuesday afternoon symposium addressing issues related to diabetes and severe mental illness, including schizophrenia and bipolar illness. The initial lecture, presented by Dr. Gough, UK, provided an overview of the relationship between diabetes and psychiatric disease. While it is commonly assumed the association is medication-induced, Dr. Gough urged the audience to think beyond diabetes and antipsychotic drug therapy. He proceeded to share data identifying an increased prevalence of diabetes and impaired glucose tolerance in severe mental illness, schizophrenia in particular, which is greater than in the general population. Additionally, the incidence of undiagnosed diabetes is quite high in this patient group. To date, it appears that the majority of data support an association with Type 2 diabetes, versus with Type 1. Several factors contribute to an increased risk including genetics, low birth weight, lifestyle, and drug therapy. In his concluding remarks, Gough stated that there is a clear link between psychiatric diseases and diabetes that is unexplained by solely the weight gain associated with most antipsychotic medications. It is likely to be multi-factorial related to both genetic and environmental factors.

Dr. Thakore, Ireland, next described biological mechanisms underlying the association. He expounded on many of the factors suggested by Dr. Gough. Lifestyle contributes to the development of disease as many schizophrenic patients tend to eat poorly (with diets rich in

saturated fat and decreased fiber), smoke, and avoid exercise. There are several studies evaluating first episode drug-naïve schizophrenia patients in which multiple factors related to diabetes and/or metabolic syndrome have been identified. These patients have visceral obesity with a three-fold increase in intra-abdominal fat compared to BMI-matched controls. There is also evidence of increased cortisol secretion with basal overactivity of the hypothalamic-pituitary-adrenal axis. First-episode schizophrenia drug-naïve patients possess increased intimal medial thickness and increased risk of thrombosis. Accordingly, as with diabetes, the risks of coronary heart disease and stroke are higher in patients with severe mental illness. Dr. Thakore urged that all patients with schizophrenia as well as their first-degree relatives be screened for both diabetes and cardiovascular disease.

The third presenter, Dr. Citrome, US, discussed findings from a recent review of 15 pharmacoepidemiological studies (published in *Annals of Pharmacotherapy*, Sept. 2007) in which attributable risk of diabetes from antipsychotic treatment was estimated. Based on the currently available data, he determined there is insufficient evidence to support the choice of a given antipsychotic to avoid the development of diabetes (i.e., second-generation agents are not preferable to first-generation agents). No one specific agent can be specifically implicated. There is a great need for prospective, long-term trials that account for the multi-factorial nature of the development of diabetes in the mentally ill.

Dr. Holt concluded the session with guidance for the practical management of metabolic issues in patients with psychiatric disease. He reiterated several points made in the three previous presentations. Clinicians must be aware that severe mental illness is associated with diabetes and the metabolic syndrome. These individuals should be screened for diabetes prior to starting therapy with an antipsychotic as well as when treatment is changed. A random blood glucose is the most practical measure. Repeat measures should occur after three to four months, and if normal, annually thereafter. Diabetes screening in those with severe mental illness is recommended in position statements/guidelines from the UK, US (ADA), Canadian, and Australian diabetes organizations. Holt continued with a case presentation illustrating the importance of managing mental illness first and foremost. Antipsychotics should not be discontinued or altered unless it is thought to be a major contributor to diabetes and only when first discussed with a psychiatrist. Although it is commonly believed that modifiable risk factors (e.g., diet, exercise, smoking status) are difficult to manage in this population, he shared the success story of the Pendlebury Clinic that utilizes group therapy and patient negotiation. Lastly, Dr. Holt urged practitioners to employ aggressive pharmacologic management to prevent cardiovascular disease. Upon the close of the symposium it was clear that diabetes and mental illness are linked and successful patient management requires a multi-disciplinary approach.



So Many Posters, So Little Time....



Shimizu *et al.* from Japan assessed the correlation between self-monitored fasting and post-prandial glucose concentrations and HbA1c levels in 57 insulin-treated patients (abstract 965). As presented in Table 3, postprandial blood glucose levels, especially those after breakfast and dinner, were more important determinants of HbA1c levels than were pre-meal glucose levels. As has been suggested by other investigators, therefore, targeting post-prandial hyperglycemia, particularly after breakfast and dinner, may improve HbA1c levels in insulin-treated diabetic patients.

The value of metabolic syndrome as a predictor of diabetes risk was the subject of several presentations made this week. Saumell and Spanish coworkers compared the utility of using the NCEP ATP III's metabolic syndrome criteria to that of the Framingham risk score for the prediction of cardiovascular disease (CVD) and Type 2 diabetes (abstract 338). Incident events were determined in a large cohort (n=43,000) over an eight-year follow-up period. The results confirmed that metabolic syndrome is a good predictor of diabetes and showed comparability to the Framingham risk engine as a predictor of CVD. In a related study by Bonora *et al.* from Italy and Austria, the sex- and age-adjusted OR for the development of Type 2 diabetes was 4.4 (95% CI 2.7-7.2, p<0.001) among patients who fulfilled the (ATP III) criteria for metabolic syndrome (abstract 370). More specifically, as compared to subjects without any metabolic components, the OR for diabetes in those with 1, 2, 3, and 4/5 components were impressively elevated: 6.4 (0.8-49.6, p=0.08), 18.5 (2.5-139, p=0.005), 22.2 (2.9-172, p=0.003), and 119 (15.1-942, p<0.001), respectively (overall p<0.001). Among metabolic syndrome components, impaired fasting glucose (IFG) was the strongest risk factor for diabetes risk (sex- and age-adjusted OR 12.2, 7.1-20.5, p<0.001), followed by high waist circumference (5.4, 3.0-9.5, p<0.001), hypertension (4.4, 2.1-9.0, p<0.001), high triglycerides (1.7, 1.1-2.8, p=0.03), and low HDL-cholesterol (1.8, 1.0-3.1, p=0.05). Even in subjects with normal insulin sensitivity, the risk of diabetes was significantly increased in subjects with the metabolic syndrome (quartiles 1-3 of HOMA-IR) (OR=12.3 in those with 3 and OR=38.0 in those with 4/5 abnormalities vs. those with no abnormality). Although there's been some controversy recently regarding the clinical use of the term "metabolic syndrome", based on these data, it appears to be an excellent discriminator of diabetes risk.

Abstainer patients (n=109) randomized to receive moderate alcohol (150 ml wine daily)

Table 3. Correlation of Blood Glucose and HbA1c Levels

	Conventional Treatment* (n=24)		Intensive Treatment† (n=33)		Total (n=57)	
	Correlation	p-value	Correlation	p-value	Correlation	p-value
Before Breakfast	0.044	ns	0.359	0.05	0.238	ns
PP - Breakfast	0.669	0.001	0.525	0.01	0.576	0.001
Before Lunch	0.559	0.01	0.504	0.01	0.513	0.001
PP - Lunch	0.480	0.05	0.319	n.s.	0.389	0.05
Before Dinner	0.413	ns	0.183	n.s.	0.273	ns
PP - Dinner	0.707	0.001	0.602	0.01	0.646	0.001

*bid treatment. †basal-bolus treatment. ns=not significant, PP=post-prandial.

versus non-alcoholic diet beer experienced a decrease in fasting glucose (-21.6 mg/dl, p=0.02), but not post-prandial glucose, when compared with controls in a three-month study conducted by Shai *et al.* from Israel and the US (abstract 147). There was no impact on hepatic enzymes or adverse effects. While most cardiologists already recognize the benefit of moderate alcohol intake on cardiovascular risk factors, particularly HDL-cholesterol, there is not much published data regarding glucose control. This will certainly need to be tracked in longer-term studies. Importantly, any diabetic patient incorporating moderate amounts of alcohol into the diet should maintain calorie intake stable. In addition, because of a negative effect on gluconeogenesis, patients should be reminded to not drink on an empty stomach, for fear of inducing hypoglycemia during the overnight hours.

Adler *et al.* from the UK expanded our understanding of the epidemiology of diabetes in patients with cystic fibrosis (CF) (abstract 67). The study population included 8,029 CF patients (54% male, mean age 12 years, BMI 17.9 kg/m²), of whom 5,196 had no diabetes at baseline (1996-2004) and had at least one annual follow-up visit. A total of 526 patients developed diabetes during a follow-up period of more than 15,000 person-years (median 2.8 years). The annual incidence was 3.5%. Patients who developed diabetes were more likely to have a low BMI, pulmonary infections, required antibiotic treatment, liver and pulmonary function test abnormalities, had an organ transplant, and been using pancreatic enzyme replacement. In multivariate analysis controlling for age, BMI, and history of organ transplantation, female sex (HR 1.59, 95% CI 1.32-1.90), pulmonary infection with *Pseudomonas aeruginosa* (1.28, 1.06-1.56), FEV₁ (1.02 per 1% decrement, 1.02-1.03), and portal hypertension (2.0, 1.2-3.1) were independently associated

with incident diabetes.

The safety of extremely low cholesterol levels has recently been in question, particularly as regards to adrenal and gonadal steroids, for which cholesterol serves as a metabolic precursor. In an open-label study, Demirag and associates from Turkey randomized 120 patients (high-risk males and post-menopausal females) to simvastatin or atorvastatin, with doses titrated to 40 mg and 80 mg, respectively, as required for LDL-cholesterol (LDL-C) reduction (abstract 1234). After 12 weeks of treatment, there were no statistically significant changes from baseline in cortisol, androstenedione, or total testosterone, even among those who achieved an LDL-C <70 mg/dl. For DHEA-S, there was a significant reduction from baseline for subjects who reached that LDL-C lower threshold (by 17% and 21% after simvastatin and atorvastatin administration, respectively), but not among those who were treated to simply <100 mg/dl. These results indicate that achieving an LDL-C <70 mg/dl has little impact on adrenocortical and gonadal steroidogenesis in diabetic patients, except for perhaps a modest reduction in DHEA-S, the clinical consequence of which is unknown. Additional study is necessary to determine if there is an LDL-C level below which steroidogenic capacity is threatened.

Utilizing magnetic resonance imaging (MRI), Swamy *et al.* from the UK and Australia evaluated the influence of a small oral glucose load on patterns of brain activity in seven volunteers following exposure to pictures of non-food items or foods of differing palatabilities (abstract 42). In the fasting state, brain activation in response to bland and appetizing foods was indistinguishable; however, after glucose load, there was significantly greater activation in the insula and the putamen when subjects were presented with appetizing foods. These data suggest a possible important influence from ambient glucose status on feeding behaviors.

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