Diabetes2008

From the 44th Annual Meeting of the European Association for the Study of Diabetes ▪ Rome, Italy

2004 2005 2006 2007 **2008** 2009 2010

Sponsored by **Yale University School of Medicine**,
Department of Internal Medicine, Section of Endocrinology

Volume **18** ▪ September 10, 2008 ▪ Issue **3**

Important data on diabetes presented at the 44th Annual Meeting of the European Association for the Study of Diabetes comes to you in **Diabetes 2008**, a newsletter CME program that is being offered to you by Yale University School of Medicine. Fax or e-mail delivery to your office of **Diabetes 2008** will be followed by a **Diabetes 2008** 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 AMA PRA Category 1 Credits™ to be issued by Yale University School of Medicine.

Diabetes 2008 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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The Legacy of the UKPDS

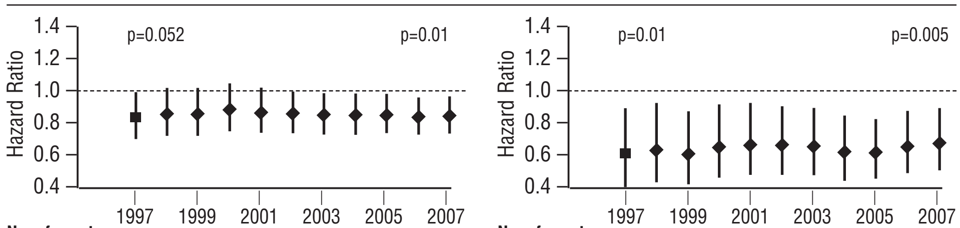
The DCCT/EDIC (Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications) study of patients with Type 1 diabetes showed that the earlier benefits of intensive insulin therapy (IIT) on microvascular disease persisted, and a beneficial effect of IIT on macrovascular risk reduction emerged, in an 8-year post-study follow-up period. This occurred despite the fact that differences in glucose control between IIT and conventionally-treated groups were not maintained over time. Similarly, in the Steno-2 study of patients with Type 2 diabetes, a similar persisting benefit of intensive glucose control was seen over a 5.5-year post-trial follow-up despite differences in glucose-control not being maintained. More recently, the Veterans Administration Diabetes Trial (VADT), while not showing an overall benefit for macrovascular complications with intensive glucose control in Type 2 diabetes, did demonstrate a benefit from intensive glucose control in those with short disease duration. Taken together it might be inferred from these trials that early intensive therapy designed to reduce prevailing glucose levels to near normal in Type 2 diabetes will have long-term benefits even if initial levels of glucose control cannot be maintained. With that in mind, many participants at the EASD in Rome were eager to hear the results of a 10-year follow-up study presented yesterday by Drs. Holman and Matthews on behalf of the UKPDS and available on-line at: *N Engl J Med* 2008;359.DOI: 10.1056/NEJMoa0806470.

The UKPDS, whose results were published in 1998, showed that, in patients with newly-diagnosed Type 2 diabetes, intensive therapy was associated with a reduced risk of microvascular complications and a non-significant reduction (16%; $p=0.052$) in the relative risk of myocardial infarction (MI). On completion of the UKPDS all surviving patients were entered into a post-trial monitoring program, with a 10-year follow-up planned. Patients were advised on the basis of the UKPDS findings to lower blood glucose and blood pressure as much as possible and discharged to community-based diabetes care. Subsequently, they were reviewed annually for 5 years in UKPDS clinics then followed-up through a mixture of clinic assessments and mailed questionnaires.

Of the 4,209 patients randomized into the initial UKPDS, 3,277 (78%) entered post-trial monitoring, and the majority attended UKPDS clinics for the first 5 years. The median follow-up periods in the sulfonylurea (SU)-insulin and metformin groups were respectively, 16.8 and 17.7 years, with 8.5 and 8.8 years of post-trial follow-up. Overall mortality was 44% and the leading causes of death were cardiovascular (52%) and cancer (24%). Baseline differences in the combinations of glucose therapy used at post-trial onset disappeared by 5 years, with 50% of all patients receiving insulin with or without oral therapy. Moreover, baseline differences in HbA1c disappeared by 1-year post-trial and subsequently showed a similar improvement in both groups.

Dr. Holman then reported the clinical outcome data. At 10 years, the risk reductions in the SU-insulin group were 9% for any diabetes-related endpoint ($p=0.04$), 24% for microvascular disease

Figure 1. Hazards Ratios for Myocardial Infarction



No. of events	1997	1999	2001	2003	2005	2007
Conventional therapy	186	212	239	271	296	319
SU-insulin	387	450	513	573	636	678

No. of events	1997	1999	2001	2003	2005	2007
Conventional therapy	73	83	92	106	118	126
Metformin	39	45	55	64	68	81

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(p=0.001), 17% for any diabetes-related death (p=0.01), 15% for MI (p=0.01 [Figure 1]), and 13% for death from any cause (p=0.007).

For overweight patients on metformin therapy, as compared to overweight patients in the conventional-therapy group, the relative risk reduction for any diabetes-related end-point was 21% (p=0.01), 30% for diabetes-related death (p=0.01), 33% for MI (p=0.005 [Figure 1]), and 27% for death from any cause (p=0.002). In both groups, no significant risk reductions were observed during or after the trial for peripheral vascular disease and stroke.

This major intervention trial in newly-diagnosed patients with Type 2 diabetes with follow-up for almost 20 years suggests that early intensive intervention has a long-term benefit for patients. This data underscore the findings from DCCT/EDIC and Steno-2 and buttress some of the implications of the VADT. What the trials do not tell us is how aggressively we should treat our patients, i.e. what are our HbA1c goals. The recent ACCORD and ADVANCE trials have cast some doubt on the overall benefit of near-normal (HbA1c <6% to 6.5%) control, particularly with the identification of severe hypoglycemia as a risk factor for mortality. Future studies will be needed to address this issue. In the meantime, early aggressive intervention with glucose-lowering strategies designed to avoid hypoglycemia appears appropriate.

Mimicking Incretins

Intensive research efforts continue on incretin mimetics—drugs that activate the glucagon-like peptide (GLP)-1 receptor. The current formulation of exenatide—dosed twice daily—was the subject of several abstracts, while new data concerning investigational GLP-1 compounds were also presented. Endogenous GLP-1, a gut-derived peptide, serves to modulate post-prandial glucose (PPG) excursions, through enhanced glucose-dependent stimulation of pancreatic insulin secretion, suppression of pancreatic glucagon output, the slowing of gastric emptying, and the suppression of appetite. (Another incretin, glucose-dependent insulinotropic peptide [GIP], acts mainly through the stimulation of insulin secretion.)

In a post-hoc analysis, Kendall and US colleagues evaluated metabolic parameters in patients who had received 2 years of continuous exenatide therapy (abstract 886). Patients were stratified into 3 weight status groups: (1) early weight loss (>3% body weight loss by week 12 that was not regained); (2) late weight loss (>3% body weight loss after week 12); and, (3) neutral (<3% body weight loss). In all, weight loss occurred in 80% of patients (34% in the early group and 46% in the late group). All 3 groups experienced significant lowering of HbA1c; however, the early and late weight loss groups demonstrated greater reductions. The investigators noted that exenatide therapy was also associated with improvements in cholesterol (HDL and LDL) and triglycerides, with a greater reduction in triglycerides experienced in the early weight loss group.

The failure of oral agents to control hyperglycemia in patients with Type 2 diabetes is a common clinical scenario. Injectable therapy is often considered the next step, with current options including insulin and exenatide. Malone *et al.* from the US evaluated the impact of exenatide (n=232) versus aspart mix 70/30 (n=231) on PPG in patients with Type 2 diabetes in another post-hoc analysis (abstract 874). Hyperglycemia due to PPG excursions was calculated for each treatment group by measuring area under the curves for both PPG (AUC_{PPG}), total glucose above 110 mg/dl (AUC_{total}), and the percentage contribution of PPG to overall hyperglycemia using the following formula: ($AUC_{PPG} \div AUC_{total}$) x 100. After one year, both groups experienced a significant reduction in fasting glucose (FG) as well as total hyperglycemia, yet PPG excursions were significantly lower in the exenatide group compared with the premixed insulin analogue (Table 1).

Table 1. Contribution of Exenatide vs. Aspart Mix to PPG Excursions after 1 Year

	Mean ± SE			*% Contribution of PPG to Overall Hyperglycemia*
	Overall Hyperglycemia (AUC_{Total};mg/dl•h)	*FG (mg/dl)*	*PPG Excursions (mg/dl•h)*	
Aspart mix 70/30	-455.4±37.8	-28.8±8.6	-84.6±18	42
Exenatide	-397.8±36.0	-28.8±8.6	-147.6±18	37
p value	0.70	0.54	0.002	0.04

AUC=area under the curve; FG=fasting glucose; PPG=post-prandial glucose.

In another exenatide vs. aspart mix comparison, Glass and American co-investigators assessed glucose variability in patients managed with either regimen (abstract 873). The investigators suggested that variability in glucose concentrations may lead to reactive oxygen species production, and, as a result, vascular complications. Patients who were not well controlled on metformin and sulfonylurea were randomized to received exenatide 5 mcg bid x 4 weeks, then 10 mcg bid (n=239) or aspart mix 70/30 titrated to a fasting plasma glucose (FPG) <126 mg/dl and PPG <180 mg/dl in an open-label, 1-year study. Post-hoc analysis was used to evaluate intra-patient glucose variability. After one year, both treatment groups experienced similar reductions in HbA1c, which were statistically significant when compared to baseline (each p<0.001). However, the exenatide-treated group demonstrated a significant reduction in within-day plasma glucose variation (32.0 mg/dl [exenatide] vs. 37.6 mg/dl [aspart mix], p<0.001) and between-day plasma glucose variation (20.7 mg/dl vs. 23.8 mg/dl, p=0.004) (based on 7-point fingerstick glucose profiles), as compared with the premixed insulin. The overall incidence of hypoglycemia was similar between groups, yet exenatide was associated with a significantly lower incidence of nocturnal hypoglycemia (6.3% vs. 0.8%, p=0.002). Whether the improved glucose variability will translate into lower oxidative stress and a decrease in vascular complications remains to be determined. It should also be stressed that while the GLP-1 mimetic and the insulin formulations appeared to be equally effective on HbA1c in these studies, overall, insulin is clearly a more potent therapy, particularly when used in patients with greater degrees of baseline hyperglycemia. That is, insulin therapy has, essentially, no 'ceiling' to its effectiveness, whereas exenatide's absolute effect on HbA1c averages approximately 1% and is likely to be not greater than 1.5 to 2% in selected patients.

The dipeptidyl peptidase-4 (DPP-4) inhibitors prevent the inactivation of endogenous GLP-1. The choice between GLP-1 agonists and DPP-4 inhibitors is often based on practical issues such as patient acceptance of injectable vs. oral therapy, third-party payment, etc. Limited data are available examining comparative efficacy of the two classes of incretin-modulating drugs. Thus, MacConell and US colleagues evaluated the effect of exenatide versus sitagliptin on PPG and gastric emptying in a double-blind, cross-over trial of 61 Type 2 diabetes patients on metformin (abstract 872). Patients received either exenatide 5 mcg twice daily for 1 week, then 10 mcg twice daily for another week, or sitagliptin 100 mg once daily for 2 weeks. Patients were crossed over at the 2-week mark. In addition to PPG and gastric emptying (as measured by an acetaminophen absorption test), fasting glucose and *ad libitum* food intake were

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monitored. When compared with sitagliptin, exenatide significantly decreased 2-hour PPG in both the evaluable and the intent-to-treat populations (Table 2), as well as when patients were switched to exenatide from sitagliptin. Exenatide decreased gastric emptying whereas sitagliptin did not. Each drug demonstrated similar reductions in FPG, however. Food intake decreased in patients receiving exenatide and increased in those receiving sitagliptin. The overall clinical impact on patient outcomes of these differences requires further study.

Exenatide has also been studied alone or in combination with metformin in insulin-resistant, obese women with polycystic ovary syndrome (PCOS). Bhushan and American researchers randomized 60 patients to receive twice daily metformin 1,000 mg, exenatide 10 mcg, or their combination for a total of 24 weeks in obese patients with PCOS (abstract 147). Metabolic parameters and body composition were assessed at baseline and post-treatment. The exenatide treatment groups (monotherapy and combination) demonstrated significantly greater weight loss and reduced androgen excess than metformin alone (p=0.003). Combination therapy had a greater impact than either agent alone on improving ovulatory response, androgen excess, weight loss, abdominal girth, and insulin sensitivity. The investigators suggest that the improvements in metabolic profiles and other measures of PCOS with combination therapy warrant a full scale, prospective trial.

Finally, a number of presentations addressed two GLP-1 agonists not yet commercially available: a once-weekly formulation of exenatide and daily administered liraglutide. Buse and colleagues reported on 22-week follow-up data from the DURATION-1 trial (abstract 146). Glycemic control was measured in the patients originally randomized to weekly exenatide (n=120) as well as in those who switched from twice daily regular exenatide to the weekly product after week 30 (n=121). Similar glycemic control was achieved in both groups by week 52 (weekly: HbA1c -2.0±0.1%; FPG -46.8±3.6 mg/dl; twice daily converted to weekly: HbA1c -2.0±0.1%, FPG -43.2±3.6 mg/dl). Overall, 72% and 54% of patients achieved a HbA1c ≤7.0 % and ≤6.5%, respectively. Both groups attained clinically significant reductions in blood pressure and lipid profiles (greater in the weekly group at week 30, comparable by week 52 [twice daily group had converted to weekly]). The cumulative incidence of patients reporting nausea was lower in the weekly versus the twice daily groups (26% vs. 35%), and neither group experienced major hypoglycemic events. At the 52-week mark, patients receiving the weekly formulation of exenatide demonstrated sustained glucose control and weight loss. Long-term safety data will be important with this new compound, which results in sustained elevation of plasma exenatide levels.

Liraglutide, a once daily GLP-1 analogue, was the subject of an investigation by Matthews and international colleagues (abstract 892). Trial data from four 26-week and one 52-week Liraglutide Effect and Action in Diabetes (LEAD) studies were pooled to evaluate the influence of liraglutide 1.8 mg once daily on 2 measures of ß-cell function—the homeostasis model assessment (HOMA)-ß and the proinsulin:insulin ratio. A significant improvement in these measures vs. comparator agents was observed: an increase in HOMA-ß (28 to 34% from baseline) and a decrease in proinsulin:insulin ratio (between -0.05 and -0.12 from baseline). Whether the improvement in ß-cell function documented in this study will lead to a delay in disease progression—as has been suggested in rodent studies—will obviously require further study.

Table 2. Impact of Exenatide vs. Sitagliptin on 2-hour Post-prandial Glucose

	Exenatide	*Sitagliptin*	*p value*
2-h PPG (mg/dl)			
Evaluable population (n=61)	133.2±6.1	207.0±6.3	<0.0001
ITT population (n=95)	165.6±7.4	210.6±7.6	<0.0001
2-h PPG excursion (Δ from pre-prandial glucose) (mg/dl)	-30.6±5.2	+46.8±5.4	<0.0001

ITT = intent-to-treat, PPG = post-prandial glucose. Data presented as mean ± SD.

The utility of liraglutide as add-on therapy to metformin and a sulfonylurea in comparison with insulin glargine (also as add-on therapy) was investigated by Russell-Jones and international colleagues (abstract 148). In this 26-week trial, 581 patients were randomized to 1 of 3 groups: placebo, liraglutide 1.8 mg daily, or insulin glargine (titrated via a patient-driven algorithm), each in combination with metformin plus glimepiride. The liraglutide group achieved a greater reduction in HbA1c (-1.33%) when compared to placebo (-0.24%, p<0.0001) and to glargine (-1.09, p=0.0015). Similarly, a higher percentage of patients in the liraglutide group achieved HbA1c values ≤6.5% (p<0.0001). Weight loss was also more favorable in the liraglutide group as compared with glargine (-3.4 kg, p<0.0001) and placebo (-1.4 kg, p=0.0001). Minor hypoglycemia occurred with similar frequency in both active treatment groups and was actually increased in the placebo group (for unclear reason). Major hypoglycemic events were reported by 5 subjects, however, on liraglutide. Transient nausea occurred with liraglutide in 15% of subjects. Based on the results of this short-term study, and similar to that described above with exenatide, it appears that liraglutide may offer advantages relative to glycemic control and weight loss when compared with insulin glargine in patients not achieving glucose targets despite two oral agents. For the reasons previously stated, we would again emphasize that the baseline glycemic status of the patient is an important piece of information when one contrasts the success of insulin to any other therapy.

We would also remind our readers that the Food and Drug Administration (FDA) issued a safety alert in October 2007 describing cases of pancreatitis associated with exenatide. More recently, in August 2008, the alert was updated describing 6 cases of hemorrhagic or necrotizing pancreatitis requiring hospitalization, 2 resulting in death. It is unclear if exenatide was causally related to the pancreatic injury in these cases, since otherwise idiopathic pancreatitis can occur in patients with diabetes. It is currently recommended, however, that exenatide be promptly discontinued if signs and symptoms suggestive of pancreatitis occur. As with all new classes medications, large numbers of patient exposures are needed to fully understand the overall risk/benefit ratio.

Comparing Insulin Strategies

With this summer's results from the ADVANCE, ACCORD, and VADT trials now being digested, safe insulin therapy for patients with Type 2 diabetes is becoming a topic area of increasing interest. While basal-bolus therapy or an insulin pump are clearly ideal management strategies in Type 1 diabetes, there is still no consensus as to the optimal insulin regimen for our Type 2 patients. At the EASD meeting this week, several groups of investigators reported their analyses and subanalyses from large prospective clinical trials in an attempt to identify the best regimen to employ.

Fonseca and colleagues observed that different patient types respond differently to two

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popular starting insulin regimens: basal insulin analogues or a pre-mixed preparation (abstract 994). This observation was derived from their meta-analysis of 6 trials (n=1,101 treated with basal analogues and n=288 treated with pre-mixed insulin) that met certain criteria (insulin-naïve, Type 2 diabetes patients; "treat-to-target" study design; and, treatment with either insulin aspart 70/30 mix once/twice daily or basal insulin analogue [insulins glargine or detemir], each with oral agents). The data from the studies were pooled and factors of age, diabetes duration, gender, BMI, HbA1c, FBG, mean PPG, and bedtime plasma glucose at baseline were investigated for predictors of improvement in glycemic parameters with either strategy. The analyses revealed that baseline age and bedtime plasma glucose were interrelated predictors of HbA1c: at higher age or higher plasma glucose, aspart mix was more beneficial, and at lower age and plasma glucose, basal insulin was better (Figure 2).

In a subanalysis of the 24-week initiation phase of the DURABLE trial, Wolffenbuttel and US colleagues evaluated glycemic outcomes in a total of 2,091 patients between the ages of 30 and 80 years with HbA1c >7.0% on at least two oral anti-hyperglycemic agents (minimum doses: 1,500 mg/day metformin, ½ maximum dose sulfonylurea, and/or either 30 mg/day pioglitazone or 4 mg/day rosiglitazone). These patients were randomized to either lispro mix 75/25 twice daily or glargine once daily, added to their current oral regimen (abstract 959). Results 24 weeks after initiation of insulin revealed that those given lispro mix had significantly lower HbA1c values, lower 2-hour PPG values after the morning and evening meals, and lower mid-day premeal glucose levels as compared to those treated with glargine (Table 3). Patients treated with lispro mix exhibited a significant decrease from baseline in HbA1c (-1.8, p<0.01) with a significantly higher percentage attaining HbA1c <7% compared to those treated with glargine (47 vs. 40%, p<0.001). Lispro mix-treated patients also had higher rates of hypoglycemia (defined as symptoms or self-monitored plasma glucose ≤70 mg/dl) but *lower* rates of nocturnal hypoglycemia. Rates of severe hypoglycemia were low and comparable between the two groups. Higher insulin doses at endpoint and greater weight gain were noted in lispro-treated patients compared to those given glargine.

Figure 2. Treatment Difference in Predicted HbA1c % (Aspart Mix-Basal) by Age and Bedtime Plasma Glucose

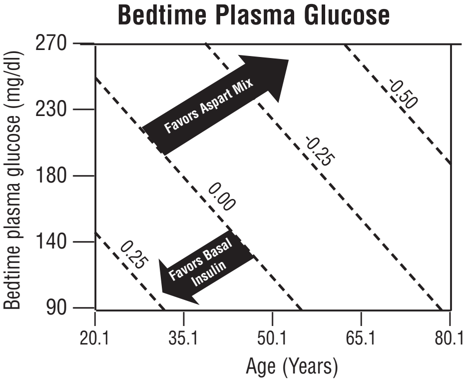

Table 3. 24-Week Outcomes in Type 2 Diabetes Patients Given Lispro Mix vs. Glargine in Addition to Oral Hypoglycemic Agents

	Lispro Mix 75/25 (n=1,045)	*Glargine (n=1,046)*	*p-value*
HbA1c (%), mean ± SD	7.2 ± 1.1	7.3 ± 1.1	0.005
2-h PPG (after morning meal), mg/dl	167 ± 50	171 ± 49	0.016
2-h PPG (after evening meal), mg/dl	164 ± 47	176 ± 49	<0.001
Pre-meal mid-day, glucose, mg/dl	130 ± 43	137 ± 43	<0.001
Hypoglycemic events,* episodes/patient/year	28.0 ± 41.6	23.1 ± 40.7	0.007
Nocturnal hypoglycemic events,† episodes/patient/year	8.9 ± 19.3	11.4 ± 25.3	0.009
Rate of severe hypoglycemic events, episodes/patient/year	0.10 ± 1.6	0.03 ± 0.3	0.167
Weight gain, in kg	3.6 ± 4.0	2.5 ± 4.0	<0.001
Insulin dose at endpoint, U/kg/day	0.47 ± 0.23	0.40 ± 0.23	<0.001

*median event rate of 8.7 in those treated with lispro and 7.0 in those treated with glargine.
†median event rate of 0 in each insulin group.
Data presented as mean (±SD).
PPG=post-prandial glucose.

The PREDICTIVE trial was a prospective, multinational observational study of the use of the basal insulin analogue, detemir, in a variety of treatment regimens that included oral agents. In a subanalysis of 1,964 insulin-naïve patients with Type 2 diabetes enrolled in this trial, Hanaire and European colleagues noted that 12 weeks of treatment with detemir was associated with weight reduction of 0.6±3.4 kg (p<0.0001) (abstract 976). The amount of weight loss was significantly greater among those with higher vs. lower BMI at baseline (mean changes of +0.69, -0.40, -1.02, and -1.52 kg in BMI groups of <25, 25 to <30, 30 to <35, and >35 kg/m^2, respectively). After 26 and 52 weeks of treatment with detemir, weight loss stabilized overall although greater losses in weight were observed among those with higher BMIs (i.e., >30 kg/m^2). This lack of weight gain with insulin therapy is unusual—but a consistent finding in most detemir trials. The exact explanation for this observation is still not clear.

Basal-Bolus vs. Pre-Mixed

Other groups of investigators also reported the glycemic outcomes among patients who required intensification of their initial basal insulin regimen. The GINGER study was a 52-week, open, randomized, multinational clinical trial that compared the efficacy and safety of mealtime rapid-acting glulisine plus glargine once daily (n=153) with an optimized regimen of two daily sc injections of either pre-mixed NPH/regular 70/30 or pre-mixed aspart 70/30 (n=157) (abstract 186). Patients enrolled in the trial were inadequately controlled on a previously prescribed regimen of pre-mixed insulins. Fritsche and German colleagues evaluated the effects on HbA1c (adjusted for country, metformin use, and baseline) and found that a significantly higher percentage of glargine/glulisine-treated patients attained HbA1c ≤7.0% at endpoint compared to those treated with pre-mixed insulin (47% [n=68] vs. 28% [n=43], p=0.0004). Glargine/glulisine as compared to pre-mixed insulin also provided significantly better mean daytime blood glucose control (136±30 vs. 148±38 mg/dl, p=0.0033) and PPG control (141±32 vs. 161±42 mg/dl, p<0.0001). On the other hand, those treated with glargine/glulisine also had higher mean daily insulin doses at endpoint (98.0±48.7 vs. 91.3±44.3 U, p=0.0003) compared to pre-mixed insulin and also experienced greater weight gain (3.6±4.0 vs. 2.2±4.5 kg, p=0.0073). However, the number of on-treatment hypoglycemic events was similar between the treatment groups (14.0 and 18.5 events/patient-year with glargine-glulisine and pre-mixed, respectively; p=0.24).

Timing of Rapid Acting Insulin

While several studies indicate that rapid acting insulin analogs work best when administered 10 to 15 minutes prior to a meal, post-prandial injections may also provide acceptable glucose control. Gelber and Israeli colleagues studied 12 patients (age range of 23-71 years) with Type 1

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diabetes (6 on multiple daily injections [MDI] and 6 on insulin pumps, with HbA1c values ranging from 5.7 to 7.6%) and compared the effects when the patients injected the rapid-acting insulin bolus within 15 minutes before the meal (for 3 days) to that when they injected the bolus immediately after the meal (for 3 days) (abstract 1073). Patients were followed with continuous glucose monitoring during each 3-day time period. Pre-prandial vs. post-prandial glycemic control parameters were similar. With two exceptions, the use of an insulin pump was comparable to that of MDI. Patients on pump therapy compared to those receiving MDI spent a significant greater percentage of time above the recommended upper glucose limit of 180 mg/dl (26.5±13.4% vs. 11.0±8.5%, p=0.037) and had significantly higher maximal glucose values 2 hours post-prandial (140±26 vs. 120±18 mg/dl; p=0.038). In the post-prandial injection period, there was a greater percentage of time during which glucose levels exceeded 180 mg/dl and higher maximal 2-hour glucose values in patients using insulin pumps vs. those on MDI. The investigators concluded that, in MDI patients, the ability to administer insulin following a meal may be more convenient and should be considered a reasonable treatment option. Those on pumps may need to increase their mealtime bolus if they switch from pre- to post-prandial administration.

These abstracts and others presented this week underscore the myriad options available for our insulin-requiring patients. Optimal regimens will vary based on the patient, especially in Type 2 diabetes, where there is significant heterogeneity in endogenous insulin secretory capacity. Traditionally, patients begin with a once daily basal insulin, which minimizes the risk of hypoglycemia. As more intensive regimens are required, patients may be graduated to self-mixed or pre-mixed twice daily regimens, or, eventually, a 'basal-bolus' strategy. Importantly, the prescribed regimen must take into account the capacities of the patient and should be implemented cautiously with an educational program in order to avoid hypoglycemia.

New Insights into Type 2 Diabetes Pathogenesis

Pancreatic ß-cell dysfunction plays a key role in the pathogenesis of Type 2 diabetes. Multiple studies this week examined the sequence of ß-cell decline in subjects as they transition from normal glucose tolerance to Type 2 diabetes. Related studies postulated contributing events that underlie the complex biological underpinnings of pancreatic insulin secretory failure, including its link to the incretin system.

Bonora and colleagues from Italy evaluated the frequency of insulin resistance and ß-cell dysfunction in 451 patients with newly-diagnosed, untreated Type 2 diabetes (abstract 652). Insulin resistance was measured using the gold-standard hyperinsulinemic euglycemic clamp, and ß-cell dysfunction was estimated using the 'minimal model' analysis of C-peptide and glucose levels during an oral glucose tolerance test (OGTT). 81.2% of the patients had both insulin resistance (i.e., decreased insulin sensitivity) and ß-cell dysfunction, defined as within the lowest quartile of measurements for non-obese, healthy controls. Of the remaining patients, 8.2% had isolated insulin resistance and 10.6% had isolated ß-cell dysfunction. In another part of the study, no difference in insulin resistance or ß-cell dysfunction was found between patients with and without microangiopathy or with and without macroangiopathy.

Lingvay *et al.* from the University of Texas Southwestern Medical Center postulated that ß-cell dysfunction in subjects with insulin resistance or Type 2 diabetes is associated with pancreatic steatosis (abstract 747). They measured pancreatic triglyceride (TG) content *in vivo* using magnetic resonance imaging and spectroscopy in 64 subjects. Pancreatic TG content was 4.7 times higher in overweight/obese subjects compared with those of normal weight (6.2% vs. 1.3%; p<0.01). Pancreatic TG content was even higher in subjects with a comparable BMI but abnormal glucose tolerance. The mean pancreatic TG content for the IFG/IGT group was 9.6%. These results suggest that ectopic fat accumulation in the pancreas may be related to ß-cell dysfunction.

The incretins GLP-1 and GIP, are important augmenters of the ß-cell response in the post-prandial phase. Incretin physiology in Type 2 diabetes was a major topic of interest at this year's conference. Lindgren *et al.* from Denmark examined whether there is a diurnal variation in the release of incretins that may explain why glucose tolerance tends to be better in the morning than in the evening (abstract 611). They looked at 12 healthy, lean young men, comparing the incretin response to a standardized meal consumed in the morning (8 am) and in the late afternoon (5 pm). Glucose, insulin, and total and intact GLP-1 and GIP were measured before and after the meals. In the morning, glucose levels peaked earlier (26±3 vs. 56±2 minutes, p<0.0001) and were lower (110±4 vs. 133±5 mg/dl, p=0.0015) when compared to the evening meal. A similar trend was observed for insulin levels, which peaked earlier in the morning than in the evening (30±2 vs. 61±5 minutes, p=0.0005). Total GLP-1 levels also peaked higher (35±4 vs. 28±2 pmol/l, p=0.03) and earlier (24±3 vs. 46±3 minutes, p=0.0005) in the morning than in the evening. While both total and intact GIP levels peaked earlier in the morning, there was no difference in peak levels between morning and evening. The results indicate that a morning meal elicits a faster and greater ß-cell response than the same meal in the evening. This newly discovered twist to incretin physiology may explain the typically lower post-prandial glucose peaks following the morning vs. evening meal.

Knop and collaborators, also from Denmark, reported results of a study comparing the incretin effect in obese versus lean subjects with normal glucose tolerance (NGT) or with Type 2 diabetes (abstract 637). The incretin effect was calculated from the comparative insulin levels measured during both an oral and an IV glucose tolerance test in each subject. Insulin resistance was calculated according to the homeostasis model assessment (HOMA). As expected, the incretin effect was significantly (p<0.05) reduced in patients with Type 2 diabetes (obese: 7±7%; lean: 29±8%; p<0.06) as compared to subjects with NGT (obese: 41±4%; lean: 53±4%; p<0.05). Also, obese NGT subjects had greater insulin resistance by HOMA (3.2±0.6 vs. 1.1±0.2) and lower incretin effect than lean NGT subjects, suggesting that the incretin effect declines along with the development of obesity-related insulin resistance.

The pathogenesis behind declining ß-cell function in patients with Type 2 diabetes is likely multifactorial, with many contributing factors having been proposed, including ß-cell apoptosis, the effects of islet amyloid polypeptide, and inflammatory cytokines as well as both gluco- and lipotoxicity. Studies this week suggest additional contributions from ectopic fat as well as impaired incretin hormone physiology. No matter the specific causes and their relative degrees, it is clear that, by the time of Type 2 diabetes diagnosis, the majority of patients exhibit significant derangements in both insulin sensitivity and ß-cell function.

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