

Diabetes 2009

From the 45th Annual Meeting of the European Association
for the Study of Diabetes ■ Vienna, Austria

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Drugs for Diabetes: The Old and the New



Important data on diabetes presented at the 45th Annual Meeting of the European Association for the Study of Diabetes comes to you in **Diabetes 2009**, 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 2009** will be followed by a **Diabetes 2009** 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 2009 is being offered to physicians practicing in the United States. After successfully completing this program, participants will be able to:

- Describe the mechanisms of β -cell failure, the progression of diabetes, and its complications.
- Implement strategies for the early diagnosis and treatment of diabetes.
- Recognize the manifestations of the macrovascular and microvascular complications of diabetes and describe appropriate therapies.
- Understand the interrelationship between insulin resistance, hyperglycemia, and atherosclerosis in patients with Type 2 diabetes.
- Compare the mechanisms of action of diabetes therapies, their risks, benefits, and proper roles in disease management.
- Identify evolving and emerging therapeutic strategies in diabetes care.
- Describe the approach to managing dyslipidemia, hypertension, and cardiovascular risk factors in patients with diabetes.

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Pharmacologic therapy for Type 2 diabetes is astonishingly different in 2009 than it was in the early 1990's, when the sole treatment regimens involved either sulfonylureas or insulin. As of this year, 11 classes of anti-hyperglycemic agents are available for clinical use in the US. Table 1 lists these and reviews their individual mechanisms of action. When one considers the various types of insulin formulations also available, literally

dozens of individualized treatment regimens can now be designed for our patients. The goal is always safe glycemic control as close to target as feasible, within the capacities of each patient. At this week's EASD meeting in Vienna, investigators presented data on both established medications and emerging compounds and how they might be effectively used to lower glucose in patients with Type 2 diabetes.

Table 1. Currently Available Anti-Hyperglycemic Agents for Type 2 Diabetes

<i>Agent</i>	<i>Examples</i>	<i>Mechanism</i>	<i>Action</i>
Sulfonylureas	Glyburide, Glipizide, Glimpiride	Closes KATP channels on beta cells	↑ Pancreatic insulin secretion
'Glinides	Repaglinide, Nateglinide	Closes KATP channels on beta cells	↑ Pancreatic insulin secretion
Biguanides	Metformin	Activates AMP-kinase in the liver	↓ Hepatic glucose production
α -Glucosidase inhibitors	Acarbose, Miglitol	Blocks small bowel alpha-glucosidase	↓ Intestinal carbohydrate absorption
Thiazolidinediones	Rosiglitazone, Pioglitazone	Activates PPAR- γ , mainly in adipocytes	↑ Peripheral insulin sensitivity
GLP-1 agonists	Exenatide	Activates GLP-1 receptors	↑ Pancreatic insulin secretion; ↓ pancreatic glucagon secretion; delays gastric emptying; ↑ satiety
Amylinomimetics	Pramlintide	Activates amylin receptors	↓ Pancreatic glucagon secretion; delays gastric emptying; ↑ satiety
DPP-4 inhibitors	Sitagliptin, Saxagliptin	Inhibits dipeptidyl peptidase-4, endogenous incretin levels	↑ Pancreatic insulin secretion; ↓ pancreatic glucagon secretion
Bile acid sequestrants	Colesevelam	Binds bile acid cholesterol	?
D2 agonists	Bromocriptine	Activates dopaminergic receptors	Resets hypothalamic circadian organization; ↑ insulin sensitivity
Insulin	NPH, Regular, Glargine, Detemir, Lispro, Aspart, Glulisine	Activates insulin receptors	↑ Glucose disposal; ↓ hepatic glucose production; ↓ proteolysis, lipolysis, ketogenesis

Continued on page 2

Drugs for Diabetes...

Continued from page 1

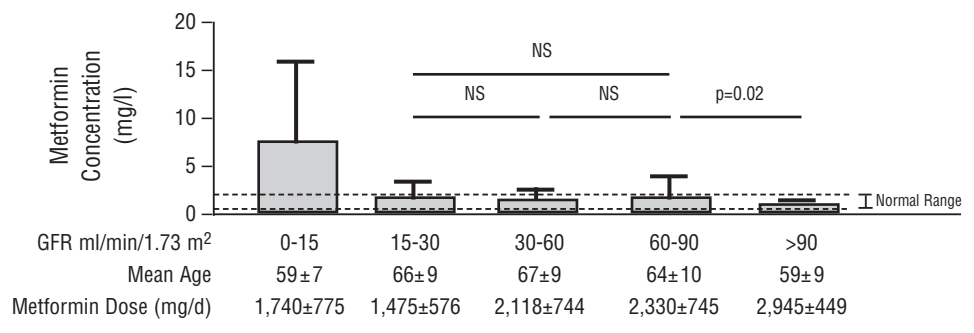
Metformin Safety in CKD

Metformin continues to be considered the 'cornerstone' therapy for Type 2 diabetes. This reputation has been forged over several decades of clinical use, during which time the benefits of this unique drug have been revealed. Sometimes referred to as an 'insulin sensitizer', metformin's effect is mainly to reduce hepatic glucose production, likely through activation of the enzyme AMP-kinase. In addition to modest weight loss in the near-term, and weight neutrality in the long-term, metformin's main advantage is the lack of hypoglycemia associated with its use. Unlike sulfonylureas, metformin does not stimulate insulin secretion. Improvements in various cardiovascular (CV) risk markers have also been demonstrated in small clinical trials, including small reductions in LDL-cholesterol and triglycerides as well as in C-reactive protein. Additionally, in the United Kingdom Prospective Diabetes Study (UKPDS), metformin monotherapy was associated with a reduction in myocardial infarction events as compared to diet therapy, and stroke events as compared to the group who received sulfonylureas or insulin. Accordingly, metformin is now widely used as first-line therapy in most patients. Indeed, it is often referred to when clinicians consider anti-hyperglycemic therapy beyond lifestyle change for the prevention of diabetes in at-risk individuals, such as those with impaired glucose tolerance. (This agent is not FDA-approved for this indication, however.)

The main downside to metformin therapy is its contraindication in patients with renal failure. While use of the drug does not portend any detrimental effects on renal function, because metformin is almost entirely renally cleared, its systemic concentrations build up when glomerular filtration is reduced. This increases the risk of the drug's only serious adverse effect, lactic acidosis. Accordingly, the US prescribing guidelines for metformin stipulate that it should not be used in men with creatinine levels at or above 1.5 mg/dl. The corresponding threshold in women is 1.4 mg/dl. Both were somewhat arbitrarily chosen when metformin was made available in this country in 1995. However, neither has been updated in recent years as new data have become available suggesting that metformin may be safer than originally suspected in this setting. In addition, prescribing guidelines have not been modified to the recently available estimated (e)GFR levels on routine chemistry reports.

Briet and French colleagues explored erythrocyte concentrations of metformin in patients

Figure 1. Erythrocyte Metformin Concentration by CKD Stage



with altered renal function (abstract 858). In Europe, prescribing guidelines advise avoiding metformin in patients with eGFR <60 ml/min/1.73 m². However, since metformin clearance is actually 4-5 times that of creatinine, the actual degree of renal dysfunction associated with significant metformin accumulation is unknown. The investigators used erythrocyte metformin concentration because it is known to be a better marker of chronic accumulation than concentration in plasma. In all, erythrocyte metformin levels were available in 126 patients. eGFR was calculated using the MDRD (Modification of the Diet in Renal Disease) equation. Patients were divided into 5 groups, based on their eGFR-determined stage of chronic kidney disease (CKD), stages 1-5 (>90, 60-90, 30-60, 15-30, and <15.) The mean age of the patients was 65±9 years and the gender ratio was approximately 2:1 male:female. The mean eGFR was 47.8±24.1 ml/min/1.73m², with nearly three-quarter of patients having a value <60.

Erythrocyte metformin concentrations in the different CKD groups are shown in Figure 1. Metformin concentrations were slightly higher in mild-moderate renal failure (stage 2-4) as compared to stage 1, but remained within the 'normal' therapeutic range. Actually, levels did not climb substantially until a GFR of <15 was reached. The researchers proposed that their data suggested that metformin could be safely used in patients with CKD stages 1-4, if the dose was adequately adjusted. Note that in this study population, metformin dose was reduced by approximately one-half once CKD stage 4 was reached. While we find this report of significant interest, larger prospective data sets across the spectrum of CKD will be necessary to further substantiate the safety of this important compound in this commonly encountered clinical scenario.

Redefining the Bolus in 'Basal-Bolus'

Pramlintide is an injectable agent predom-

inately used in Type 1 diabetes patients. It is an analogue of naturally occurring amylin, a beta-cell product that is co-secreted with insulin. The physiological effects of amylin include the suppression of alpha-cell glucagon secretion, a delay in gastric emptying, and the enhancement of satiety due to a central nervous system effect. It has been shown to reduce HbA1c by approximately 0.5% mainly by attenuating post-prandial glucose (PPG) excursions, and its use is also associated with some weight loss. While approved in insulin-treated patients with Type 2 diabetes, the use of pramlintide has been extremely limited in this setting due to cost and its method and frequency (3 times daily) of administration.

Karounos *et al.* from the US presented data on a relatively new concept—the use of mealtime pramlintide in combination with basal insulin in Type 2 diabetes (abstract 912). They observed that mealtime rapid-acting insulin, while effective in controlling PPG, is associated with hypoglycemia and weight gain. Since pramlintide has been shown to lower PPG without these adverse effects, it might offer an advantage to the more conventional 'basal-bolus' insulin strategy. The investigators randomized 112 patients in an open-label fashion to either pramlintide 120 µg three times daily or a rapid-acting insulin analogue (lispro, aspart, or glulisine). Their baseline characteristics included a mean age of 54 ±11 years, HbA1c 8.2±0.8%, fasting plasma glucose (FPG) 160±45 mg/dl, and BMI 36±6 kg/m².

Phase 1 of the study was 24 weeks in duration and compared pramlintide to rapid insulin analogue when added to basal insulin. Phase 2 lasted 12 weeks and explored additional prandial therapy for patients failing to achieve an aggressive HbA1c target of 6.5% at the end of phase 1. In phase 2, such patients initially assigned to pramlintide added rapid mealtime insulin (n=31) and vice versa (n=36).

See Figure 2 for the results. At the end of phase 1, both mealtime protocols had resulted

Continued on page 3

Drugs for Diabetes...

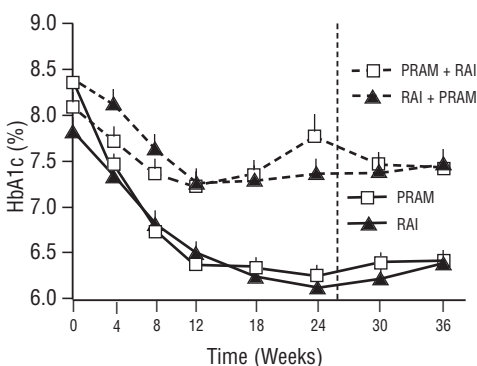
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in similar HbA1c reductions (pramlintide: $-0.9 \pm 0.2\%$ vs. rapid insulin: $-1.1 \pm 0.2\%$; $p=NS$) and had achieved a nearly identical FPG (121 ± 7 vs. 122 ± 5 mg/dl, respectively; $p=NS$). However significant weight gain was seen with insulin (4.2 ± 0.6 kg, $p < 0.001$), whereas weight remained stable with pramlintide (-0.3 ± 0.7 kg). Hypoglycemia occurred less commonly with pramlintide (55% vs. 82%). Those patients achieving the HbA1c target had stable glycemic control during phase 2 (pramlintide: $6.3 \pm 0.1\%$ at week 24 vs. $6.4 \pm 0.1\%$ at week 36; insulin: $6.1 \pm 0.1\%$ vs. $6.4 \pm 0.1\%$).

In phase 2, patients adding the opposing agent to their mealtime regimen experienced little to no improvement in HbA1c (pramlintide + rapid insulin: $7.7 \pm 0.2\%$ at week 24 vs. $7.4 \pm 0.2\%$ at week 36; rapid insulin + pramlintide: $7.3 \pm 0.2\%$ vs. $7.4 \pm 0.2\%$). There were also no differences in these two groups as far as hypoglycemia was concerned (58% and 53%, respectively). Addition of pramlintide in patients using rapid insulin did allow for a reduction in the insulin dose (38.6 ± 3.8 units/day at week 24 vs. 19.4 ± 3.2 units/day at week 36). The main side effect of amylin analogues, nausea, was observed in 21% of patients on pramlintide.

The investigators concluded that mealtime pramlintide resulted in similar improvements in glycemic control as compared to rapid acting insulin analogues, with less hypoglycemia and no weight gain. They also argued that the addition of the alternate prandial agent in phase 2 resulted in "maintenance of HbA1c and weight." We wonder, however, why HbA1c wasn't actually reduced during this phase of the trial. Nonetheless, we find the phase 1 results provocative and worthy of

Figure 2. HbA1c—Phase 1 and 2



Phase 2 ITT population, $n=98$, mean \pm SE.
PRAM=Pramlintide.
RAI=rapid-acting insulin.

Table 2. Effects of Dapagliflozin ± Metformin on HbA1c, FPG, and Weight

	PBO + MET (n=137)	DAPA 2.5 mg + MET (n=137)	DAPA 5 mg + MET (n=137)	DAPA 10 mg + MET (n=135)
HbA1c, baseline (%), mean (SD)	8.11 (0.96)	7.99 (0.90)	8.17 (0.96)	7.92 (0.82)
Week 24 change from baseline in HbA1c (%), adjusted mean (SE)	-0.30 (0.072)	-0.67 (0.072)*	-0.70 (0.072)*	-0.84 (0.072)*
FPG, baseline (mg/dl), mean (SD)	165.6 (46.4)	161.5 (43.1)	169.2 (49.0)	156.0 (38.7)
Week 24 (LOCF) change from baseline in FPG (mg/dl), adjusted mean (SE)	-6.0 (2.7)	-17.8 (2.7)*	-21.5 (2.7)*	-23.5 (2.7)*
Weight, baseline (kg), mean (SD)	87.7 (19.2)	84.9 (17.8)	84.7 (16.3)	86.3 (17.5)
Week 24 (LOCF) percent change from baseline in weight, adjusted mean (SE)	-1.02 (0.29)	-2.66 (0.28)	-3.66 (0.28)	-3.43 (0.28)

* Statistically significant compared to placebo.

DAPA=dapagliflozin, FPG=fasting plasma glucose, LOCF=last observation carried forward, MET=metformin, PBO=placebo.

consideration in advanced patients with Type 2 diabetes. However, the relative cost implications of this novel strategy were not mentioned in the poster.

Bile Acids, Incretins, and Glucose

One drug recently approved as an anti-hyperglycemic agent in Type 2 diabetes is the bile acid sequestrant, colesevelam. It has been on the market for years as a cholesterol-lowering drug, although its use has been limited generally to patients who are statin-intolerant. Modest reductions in HbA1c, on the order of 0.5%, have been demonstrated in clinical trials and the drug is now approved mainly as a second- or third-line agent in those patients needing better glucose control than they get from conventional agents. Colesevelam's specific mechanism of action has been poorly understood, however. Carbohydrate malabsorption is clearly not playing a major role.

Beysen and American colleagues studied 55 patients with Type 2 diabetes with HbA1c 6.7-10.0% (abstract 171). They were randomized to either 3.75 g/day colesevelam or placebo for 12 weeks. Fasting endogenous glucose production (EGP), gluconeogenesis, glycogenolysis, and plasma glucose clearance were measured in each patient at baseline and the end of the treatment course using standard stable isotope techniques. In addition, plasma glucose, insulin, glucagon-like peptide 1 (GLP-1), glucose-dependent insulinotropic polypeptide (GIP), and glucagon levels were also measured while fasting and after a meal tolerance test.

Significant treatment differences in HbA1C ($-0.62 \pm 0.23\%$, $p < 0.01$) and FPG (-23 ± 11 mg/dl, $p < 0.05$) were seen at 12 weeks in the active therapy group. Compared to placebo, colesevelam also increased fasting GLP-1 ($+10 \pm 4$ pmol/l, $p = 0.01$), postprandial GLP-1 area under the curve (AUC) ($+2,267 \pm 750$ pmol/l/300 min, $p < 0.01$), and postprandial GIP AUC ($+3,859 \pm 857$ pmol/l/300 min, $p < 0.0001$) compared to placebo. Plasma glucose clearance increased significantly with colesevelam but was unchanged with placebo ($+0.26 \pm 0.42$ and -0.06 ± 0.39 ml/kg fat free mass/minute, respectively, $p < 0.01$). EGP and glycogenolysis were unchanged with colesevelam and increased significantly with placebo ($p < 0.05$), but the changes from baseline were not different between groups. Other parameters, including insulin and glucagon levels, fasting GIP, and gluconeogenesis rates were unchanged.

These data suggest that the bile acid sequestrants may improve glycemic control through effects on the incretin axis, but further investigations will be required to confirm the findings. We were somewhat puzzled by the apparent incretin effect without any changes in downstream hormones, such as insulin and glucagon, although the data were presented on absolute values and not adjusted by glucose.

Still Investigational

The EASD meeting has traditionally been a venue to display emerging information on new anti-hyperglycemic agents. This week in Vienna, two oral classes under development received

Continued on page 4

Drugs for Diabetes...

Continued from page 3

some attention, the SGLT-2 inhibitors and the 11-beta HSD1 inhibitors. SGLT (sodium-glucose transporter)-2 inhibitors block glucose reuptake in the nephron, essentially allowing for glycosuria to attenuate glucose levels, particularly in the post-prandial setting. While not an immediately attractive mechanism of action, the agents are already in phase 3 development and early clinical trials have demonstrated modest efficacy, with some weight loss and a generally mild side effect profile. One concern has been the possibility of increased urinary tract infections as well as vaginal candidiasis with SGLT blockade. The 11-beta HSD (hydroxysteroid dehydrogenase)-1 inhibitors, now in phase 2 development, block the conversion of cortisone to cortisol mainly in adipocytes, resulting in reduced insulin resistance and perhaps some CV benefits.

Bailey and international colleagues presented data on 546 Type 2 diabetes patients with suboptimal glycemic control on metformin monotherapy (abstract 169). They were randomized to the SGLT-2 inhibitor, dapagliflozin, vs. placebo over 24 weeks. Eligible patients were between 18-77 years with a HbA1c of 7.0-10.0% on a stable dose of at least 1500 mg/day of metformin. Patients were assigned to one of four treatment groups: dapagliflozin 2.5, 5, or 10 mg once daily,

or placebo, along with open-label metformin. At 24 weeks, the dapagliflozin groups experienced mean reductions from baseline HbA1c, FPG, and weight (Table 2). Greater proportions of patients in all dapagliflozin groups achieved HbA1c <7.0% at week 24 than patients on placebo (40.6% at highest dose vs. 25.9% on placebo [$p<0.05$]). More patients treated with dapagliflozin achieved weight decreases $\geq 5\%$ compared to placebo (28.0% vs. 5.9%). Rates of urinary tract infections were similar in dapagliflozin-treated patients (placebo 8.0%; 2.5 mg, 4.4%; 5 mg, 7.3%; 10 mg, 8.1%), although rates of genital infections were higher with active therapy (placebo, 5.1%; 2.5 mg, 8.0%; 5 mg, 13.1%; 10 mg, 8.9%). No deterioration in renal function was demonstrated during the study, and blood pressure parameters appeared stable as well.

Finally, Huber and US colleagues presented new data on the 11-beta-HSD1 inhibitor currently referred to as INCB13739 (abstract 172). 159 patients with Type 2 diabetes inadequately controlled with metformin were randomized to one of four doses of the active compound or placebo for 12 weeks. Metformin therapy was continued. Statistically significant reductions in HbA1c were demonstrated in the two highest doses (100 mg, -0.6% and 200 mg, -0.5%) vs. placebo (0.0%) at week 12 ($p<0.01$). In addition, these doses resulted in modest improvements in LDL-cholesterol, with

the 100 mg dose leading to a 16 mg/dl decrease vs. 3 mg/dl increase with placebo ($p=0.03$). Side effect profile appeared to be similar to placebo in this small trial. Of particular interest, INCB13739 did not affect gonadal steroid levels or the renin-aldosterone axis. A dose-dependent increase in morning plasma ACTH occurred by week 4 and then plateaued (mean 48 pg/ml in the highest dose group at week 12; normal range <63 pg/ml). Plasma DHEA-S levels increased in a dose-dependent manner along with ACTH, reaching a maximum at week 4 with the 200 mg dose (mean, 198 $\mu\text{g/dl}$), also remaining within age- and gender-based normative ranges. Plasma morning cortisol, late-night salivary cortisol, and response to cosyntropin stimulation were unchanged from baseline. Larger and longer-term studies will be needed with this compound. The increases in ACTH and DHEA-S will need to be fleshed out further—just because they remain within normal range does not necessarily mean that these changes will have no clinical consequences.

If and where these two investigational agents will ultimately fit into an increasingly complex diabetes pharmacopoeia remains to be seen. It is quite likely, however, that within a few short years, the number of classes of anti-hyperglycemic agents will exceed one dozen—surpassing the number of unique drug classes currently available for the treatment of hypertension.



Haste Makes Waist



Obesity, a major risk factor for diabetes, is an increasingly common problem in most Westernized societies. It is also becoming an emerging issue in the developing world. International diabetes meetings have recently devoted a large proportion of their programs to discuss a growing body of research in this area. These span the spectrum from basic epidemiological investigations, to physiological inquiries into the underlying mechanisms of appetite control and weight regulation, and to studies involving novel management strategies. In Vienna, we found several obesity-related abstract presentations that were noteworthy.

Where's the Fat?

Distribution of body fat varies from individual to individual, and this topography likely carries with it significant implications for CV risk. This notion was further explored by Czernichow and colleagues from France, the UK, and the Netherlands (abstract 135). The investigators

remarked that, while the relative importance of anthropometric markers reflecting total vs. central obesity were reasonably well established for the general population, there was less certainty within the group of patients with known Type 2 diabetes. They evaluated which baseline markers—BMI, waist circumference (WC), and waist-to-hip ratio (WHR)—best predicted CV events in the recently concluded ADVANCE (Action in Diabetes and Vascular Disease: PreterAx and DiamicroN MR Controlled Evaluation) Study. This large, international trial was designed to assess the CV impact of a more intensive glucose control strategy, targeting an HbA1c of <6.5% vs. conventional care. The study reported its primary results at the 2008 American Diabetes Association Scientific Sessions in San Francisco (*Diabetes 2008*, Volume 18, pg 11) as one of a trio of important clinical trials (including ACCORD and VADT), essentially concluding that, in the near term, tighter glycemic control does not translate into better CV outcomes.

In this week's presentation, data from 11,140 ADVANCE participants, followed over 5 years, were analyzed. Cox proportional hazard models, adjusting for age, gender, ethnicity, current smoking, and antihyperglycemic and antihypertensive treatments, were used to determine the hazard ratios (HR) and 95% confidence intervals (95% CI) for a one standard deviation (SD) change in baseline BMI, WC, and WHR.

The mean age of the study subjects was 66 ± 6 years; 43% were women, and nearly one-third had established CV disease (CVD) at baseline. The mean BMI was 28 ± 5 kg/m^2 , mean WC 98 ± 13 cm (38.6 ± 5 inches), and mean WHR 0.93 ± 0.8 . During follow-up, 1147 major CV, 647 major coronary, and 484 major cerebrovascular events had occurred. 542 of these had fatal outcomes and were categorized as CV deaths. Positive linear trends were observed for WC with CV and coronary events (both $p\leq 0.05$) and CV death ($p=0.07$), as well as for WHR with CV and coronary events, CV death (all $p\leq 0.001$), and cerebrovascular events

Continued on page 5

Haste Makes Waist*Continued from page 4*

($p=0.07$). Multivariate HRs (95% CI) associated with one higher SD for CV events, coronary events, and CV death were 1.10 (1.03-1.18), 1.13 (1.03-1.24), and 1.08 (0.98-1.19) for WC, respectively. The corresponding HRs for WHR were 1.12 (1.05-1.19), 1.17 (1.08-1.28), and 1.19 (1.09-1.31). In contradistinction, BMI was not linearly related to any CV outcome. Indeed, there was actually some suggestion of an *inverse* association with cerebrovascular events (each SD increment in BMI associated with stroke risk of 0.92 [0.83-1.02]; $p=0.04$). The relationships proved similar when the data were assessed in patients with vs. without overt CVD at baseline.

The authors concluded that measures of central adiposity are strongly related to CV risk, whereas overall obesity is not. This concept, well established in the general population, has now been confirmed in a large, well-characterized cohort of diabetic patients, followed prospectively. These data may need to be considered as we further refine our secondary prevention strategies for the increasing population of patients with Type 2 diabetes. The question of an inverse relationship of BMI and stroke risk will need further exploration.

Obesity: A Surgical Disease?

The early metabolic effect of Roux-en-Y gastric bypass (RYGB) on insulin-resistance in obese diabetic patients was the subject of an oral presentation by Camastra and Italian collaborators (abstract 95). As a group, bariatric procedures (gastric banding, RYGB, and ileal bypass) are now some of the most common major surgical procedures performed in the US. They clearly result in substantial weight loss, not generally achievable with lifestyle counseling or with our limited array of anti-obesity drugs alone. They also commonly lead to, if not a complete 'cure' of diabetes, at least a marked improvement in glycemic control, which can prompt major reductions in anti-hyperglycemic drug therapy. Moreover, recent studies using weight-matched control patients who have not undergone bariatric surgery suggest a possible benefit on overall mortality.

The rapidity of the improvement in glycemic parameters following these procedures has stimulated intense interest in their immediate metabolic sequelae, especially on the incretin system, which is known to be directly stimulated by the delivery of food to the proximal gastrointestinal tract. Several small investigations suggest

that some component of the improvement in diabetes status post RYGB, for example, may result from enhanced GLP-1 and GIP levels. These may lead to downstream augmentation in post-prandial insulin levels as well as decreases in glucagon secretion. In fact, one side-effect of RYGB, namely post-prandial hypoglycemia, has been ascribed by some to this phenomenon that may hypothetically lead to increased beta-cell mass.

Camastra *et al.* studied insulin sensitivity and insulin secretory capacity in 11 (3 male, 8 female) morbidly obese patients with Type 2 diabetes undergoing RYGB, a predominantly restrictive surgery that has been associated with metabolic hormonal changes and improved insulin sensitivity before substantial weight can occur. The mean age of the subjects was 49 ± 2 years—a number that was precisely matched by their BMI, 49 ± 2 kg/m² (!) They underwent baseline euglycemic hyperinsulinemic clamp studies in combination with glucose and glycerol tracer infusions to measure insulin sensitivity, EGP (mainly hepatic), and whole-body lipolysis. The subjects also underwent assessment of beta-cell function using the acute insulin response (AIR) to an intravenous glucose bolus. Investigations were repeated at 19 ± 1 days post procedure.

After RYGB, body weight fell by 7% (133 ± 9 vs. 123 ± 8 kg, $p=0.003$), and both FPG (142 ± 11 vs. 122 ± 7 mg/dl, $p=0.01$) and insulin levels (162 ± 26 vs. 92 ± 13 pmol/l, $p=0.003$) were significantly reduced. During the clamp, peripheral insulin sensitivity was increased by 39% post RYGB ($p=0.03$), but EGP was not changed. The hepatic insulin resistance index (EGP \times basal plasma insulin), however, was significantly reduced by 47% ($p=0.04$) and whole-body lipolysis (as measured by the rate of systemic glycerol appearance) by 46% ($p=0.02$). AIR, in contrast, was unchanged.

The investigators concluded that in morbidly obese patients with Type 2 diabetes, RYGB, a mostly restrictive bariatric procedure (as opposed to a more malabsorptive procedure such as ileal bypass) is associated with an early improvement in glycemia due to increased peripheral, hepatic, and adipose insulin sensitivity, but that beta-cell function appears unchanged. Since weight loss at this juncture was comparatively modest, these metabolic changes were felt likely to be the result of caloric restriction alone. We would point out that while the AIR result suggests no early effect on the incretin system, GLP-1 and GIP levels were

not reported. Altered incretin physiology may still play a role in the more long-term metabolic effects from this form of bariatric surgery.

**It's Not What You Eat,
It's How Fast You Eat It!**

Kokkinos and colleagues from Greece and the UK conducted an interesting study to examine the effects of the rate or speed of calorie consumption on the levels of gut hormones that regulate appetite (abstract 567). The speed with which people consume a meal has been associated by some with obesity, but there have been no studies examining how the rate of eating affects appetite regulation specifically via the postprandial orexigenic (hunger) and anorexigenic (satiety) gut peptide responses. Seventeen healthy adult male volunteers (age: 29.7 ± 1.2 years, BMI: 26.1 ± 0.9 kg/m²) were studied in a cross-over fashion, consuming a test meal (300 ml ice cream: 675 kcal, 59% from fat, 33% carbohydrates, 8% protein) at two different rates. In one session, the meal was consumed within 5 minutes, while in the other, over 30 minutes. Blood levels of glucose, insulin, plasma lipids, the orexigenic hormone ghrelin, and the anorexigenic hormones PYY and GLP-1 were measured before the meal and at 30 minute intervals after the beginning of the meal and extending an additional 3.5 hours. Visual analogue scales to assess subjective feelings of hunger and fullness were also completed by the subjects during and after the meal challenge.

The investigators found that, overall, the PYY AUC concentration was approximately 20% higher after the 30-minute meal than after the 5-minute meal (mean [\pm SEM] AUC-5 minute meal: 4133 ± 324 vs. AUC-30 minute meal: 5250 ± 330 pmol/l \cdot min, $p=0.004$). The differences in GLP-1 AUC were even greater at nearly 30% (6219 ± 256 vs. 8794 ± 656 pmol/l \cdot min, $p=0.001$). There were no differences in the responses of ghrelin, insulin, or glucose between the sessions. A trend for higher visual analogue scale fullness ratings immediately at the end of the 30-minute meal compared to the 5-minute meal was noted ($p=0.09$), despite an equal number and mix of calories eaten.

These findings suggest that consuming food at a more leisurely pace may result in a more pronounced satiety sensation than eating quickly and that this may have an underlying physiological basis in the form of altered gut peptide responses. The term "fast food" now takes on a whole new meaning!