

Diabetes2007

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for the Study of Diabetes ■ Amsterdam, The Netherlands

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HbA1c

Sharpening the Tool

HbA1c

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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The HbA1c is an invaluable and convenient tool to monitor glycemia. Current national guidelines advise a target of <6.5-7.0% in order to minimize the risk of long-term diabetic complications. Although most of us have become increasingly dependent on the HbA1c to manage our patients, the intricacies and shortcomings of this test are not as well known. An international working group has been collaborating since 2004 to ensure world-wide standardization of the HbA1c test as a valid, reproducible marker of average glucose control. As a result, HbA1c result reporting will soon be modified by laboratories world-wide. A symposium was held today to address these anticipated changes.

Glycated hemoglobin was originally discovered in the 1950's during research on hemoglobinopathies. In a substrate-dependent non-enzymatic reaction, glucose irreversibly binds to the hemoglobin (Hb) molecule, with three species created: HbA1a, HbA1b, and HbA1c. The HbA1c molecule is formed when glucose binds the amino terminus of valine on the β -chain, and is most highly reflective of ambient glucose concentrations during the preceding three months. Unfortunately, there are many different methods to determine glycated hemoglobin, each of which have varying abilities to detect HbA1c alone and avoid interference by other contaminants. HbA1c levels can also be affected by variables that have nothing to do with glucose (Table 1).

For this reason in the 1990's, the National Glycohemoglobin Standardization Program (NGSP) endorsed a reference method that directly and specifically measures HbA1c and developed a conversion algorithm for each commercially available assay to ensure that results were reported in a standardized fashion in the US. The group chose the same method used in the Diabetes Control and Complications Trial (DCCT) and United Kingdom Prospective Diabetes Study (UKPDS), which are the landmark human trials correlating HbA1c values to risk of vascular complications. Our current HbA1c tests employ this NGSP

standardization and report the results as a percentage of HbA1c to non-glycated Hb.

Dr. Sacks from Harvard Medical School discussed a new standardization method proposed by the International Federation of Clinical Chemistry (IFCC) to replace the NGSP method. The IFCC method is more sophisticated and accurate, as well as being much more labor intensive and expensive. Importantly, this is not meant for routine HbA1c measurement, but would instead serve as a standard that reports the values in more accurate scientific terms, mmol/mol Hb. Routinely measured HbA1c levels using the conventional technique could then be converted to these more scientific IFCC units. It should be noted, however, that the % HbA1c derived from the IFCC standardization are generally lower than those of the NGSP method. This proposal created controversy on a number of fronts.

As Dr. Home from the UK pointed out, the purpose of the HbA1c is to serve as a marker of average blood glucose to aid in diabetes management. Glycated hemoglobin is not a pathological entity in diabetes *per se*, so having a more accurate measurement does not necessarily improve patient care. The NGSP standard reporting system is more important because its values immediately correlate with the outcome data generated by long-term clinical trials.

Another concern about current HbA1c measurements is that it does not accurately reflect the mean blood glucose over the previous three months, a time course whose major influence is the 120-day lifespan of the red blood cell. A small amount of data from the DCCT was used to estimate average blood glucose with HbA1c.

Table 1. Non-Glycemic Factors That May Alter HbA1c Levels

- Hemoglobinopathies
- Anemia
- Pregnancy

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To develop an improved regression equation correlating HbA1c and “estimated average glucose” (EAG), an international trial involving 630 patients (with and without diabetes) was conducted to establish a conversion formula. Dr. Kuenen, the Netherlands, presented the study’s results. Daily glucose measurements over a four-month period were performed using a variety of methods, including continuous glucose monitoring. All these were then correlated to monthly HbA1c. Dr. Borg, Denmark, highlighted how this relationship was not affected by type of diabetes, gender, age,

or smoking status.

In a statement made three months ago, the American and European diabetes associations (ADA, EASD), the IFCC, and the International Diabetes Federation (IDF) recommended that all HbA1c results be reported in three forms, as shown in the Table 2. However, individual labs will decide how to report their own results.

With the increasing prevalence of diabetes world-wide, optimizing and coordinating our diagnostic tools is a top priority. These new developments are generating a lot of debate, although the changes to how we view HbA1c values are unlikely to change significantly.

Table 2. Revised HbA1C Reporting Recommendations

- “% HbA1c”—as currently reported, using NGSP standardized methodology and calculated from the ratio of HbA1c to non-glycated hemoglobin
- “Estimated Average Glucose (EAG)” —directly calculated from the NGSP % HbA1c using a more accurate equation, based on updated correlation data
- HbA1c concentration (mmol/mol Hb), calculated from the IFCC standardized technique

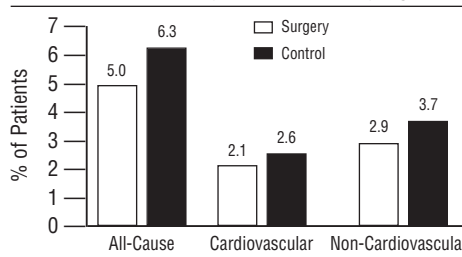


Is Obesity a Surgical Disease?



Two recently published studies in the *New England Journal of Medicine* concerning the long-term outcomes of bariatric surgery provided provocative results. Sjostrom *et al.* reported mortality findings from the multicenter Swedish Obese Subjects study of 4,047 severely obese patients (BMI ≥ 34 and 38 kg/m² in men and women, respectively; 11% with diabetes), approximately half of whom underwent a bariatric surgical procedure (gastric bypass, vertical banded gastroplasty, or nonadjustable/adjustable gastric banding) (*New Engl J Med* 2007;357:741-52). Outcomes in the surgical patients were compared to those of matched (for 18 variables) controls who either received no therapy or lifestyle intervention (conventional treatment group). Weight reduction with the three procedures was greatest in the two-year period following surgery (-20 to -32% from baseline). Over a mean follow-up period of ~11 years, cumulative all-cause mortality was reduced by 24% (HR 0.76, 95% CI 0.59-0.99,

Figure 1. Mortality Over an 11-Year Period Following Bariatric Surgery



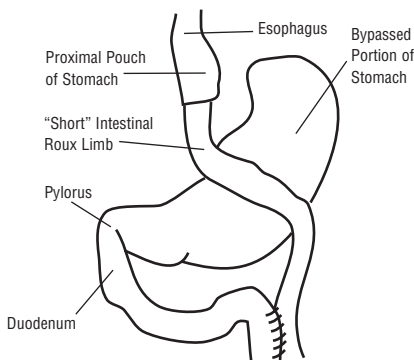
$p=0.04$) in the bariatric surgery group compared to the control group, including lower mortality rates due to cardiovascular as well as non-cardiovascular causes (Figure 1). In stepwise multivariate analyses, diabetes (HR 1.61), previous myocardial infarction (HR 2.17), and previous stroke (HR 3.19) were strong predictors of mortality.

In a related paper, Adams *et al.* reported outcomes of 7,925 consecutive obese patients

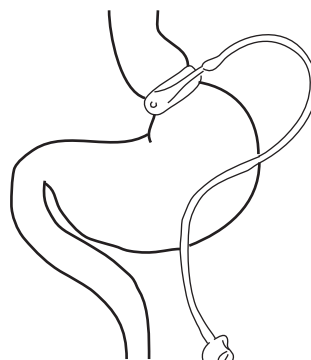
(BMI >35 kg/m²) who underwent a Roux-en-Y gastroplasty at the University of Utah (*New Engl J Med* 2007;357:753-61). Over a ~7-year follow-up period, there was a 40% reduction in all-cause mortality (HR 0.60, 95% CI 0.45-0.67, $p<0.001$) compared to sex-, BMI-, age-, and year-matched controls. In addition, mortality attributable to diabetes (HR=0.08, $p=0.005$) and coronary artery disease (HR=0.41, $p=0.006$) were significantly reduced in the surgery patients compared to controls. These findings were off-set however, in part, by a higher mortality rate (HR=1.58, $p=0.04$) from non-diabetes causes (e.g., accident, suicide, poisoning) among the gastric bypass patients. Although these trials did not have a randomized design, which would be very difficult to conduct, their data clearly support a long-term mortality benefit in properly selected obese patients.

Adding to our understanding of the metabolic effects of such procedures are the results of

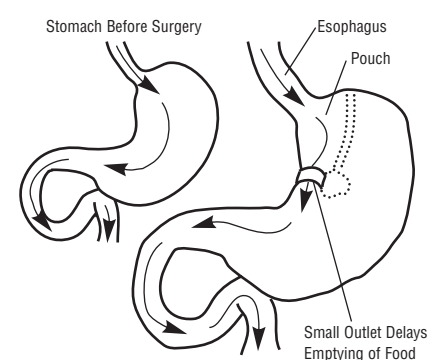
Three Most Common Procedures of Gastric Bypass



Roux-en-Y Gastroplasty



Gastric Banding



Vertical Banded Gastroplasty

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Is Obesity a Surgical Disease?

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two studies presented this week in Amsterdam at the EASD meeting. Thompson *et al.* from Australia related regional adiposity with insulin sensitivity before and up to 12 months after laparoscopic adjustable gastric banding in a group of 18 non-diabetic females (BMI 39 ± 5 kg/m²) (abstract 633). Liver fat was assessed by magnetic resonance spectroscopy and visceral and subcutaneous abdominal adipose tissue, by magnetic resonance imaging. As can be seen in Table 3, there was progressive fat loss from both visceral sites (-11% at three months, -29% at 12 months) and subcutaneous sites (-13% at three months, -28% at 12 months) over the year following bariatric surgery, with similar relative changes at both timepoints. Interestingly, liver fat was unchanged overall, although it did decrease from 12% to 8% ($p=0.015$) at three months and no further thereafter in the eight patients with pre-operative hepatic steatosis (defined as percent liver fat >5%). Insulin resistance was improved at 12 months ($p=0.04$). The pre-operative degree of hepatic steatosis correlated with the post-operative loss of visceral adiposity ($r=0.51$ at 12 months, $p<0.05$) and improvement in insulin resistance ($r=0.48$, $p<0.05$ at three months and $r=0.47$, $p<0.05$ at 12 months). Relative to visceral fat loss, subcutaneous fat loss at 12 months was greatest in the most insulin sensitive patients at baseline ($r=0.70$; $p<0.01$).

In a separate abstract from Promintzer *et al.* of Austria and Italy, surprising results were reported in a group of morbidly obese (BMI 48.8 ± 1.5 kg/m²), non-diabetic patients undergoing bariatric surgery (abstract 895).

Table 3. Mean (\pm SD) BMI, Liver, Visceral, and Subcutaneous Abdominal Fat, and Insulin Resistance Before and After Bariatric Surgery

Parameter	Following Surgery		
	Prior to Surgery	3 months	12 months
BMI (kg/m ²)	39 \pm 5	35 \pm 4*	32 \pm 5†
Liver fat (%)	12 \pm 13	7.5 \pm 7.5	9.3 \pm 14.9
Abdominal visceral fat (ml)	175 \pm 89	142 \pm 71*	111 \pm 54†
Abdominal subcutaneous fat (ml)	596 \pm 127	506 \pm 108*	421 \pm 124†
HOMA-IR	3.6 \pm 3.5	2.7 \pm 1.5	1.8 \pm 1.3*

HOMA-IR = homeostasis model assessment insulin resistance index.

* $p<0.05$ vs. baseline; † $p<0.01$ vs. three months post-surgery.

Compared to pre-surgery, fasting and early post-prandial glucose concentrations as well as fasting insulin were unchanged. However, late post-prandial glucose concentrations were lower at ~6 months, and postprandial insulin and C-peptide concentrations were higher following surgery vs. pre-surgery and vs. controls (each $p<0.001$). The insulin-stimulated glucose infusion rate (GIR), a marker of insulin sensitivity, was reduced before surgery and failed to increase after weight loss. The investigators suggested that improved insulin secretion rather than changes in insulin resistance may be responsible for the reported improvements in glycemic control in their patients after bariatric surgery. One might speculate that this finding could be explained by changes in the secretion of incretin hormones by the gut.

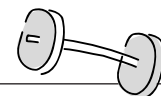
In the US, bariatric procedures are approved for use in patients with severe obesity, i.e., BMI >40 kg/m². In our patients with diabetes, considered a "medical complication" of obesity, the threshold is conventionally lowered to 35 kg/m². When performed, such procedures must be conducted

in specialized centers so as to minimize post-operative complication rates. Patients receiving these procedures must also undergo a rigorous pre-operative evaluation, including an assessment of cardiovascular risk. Post-operatively, special attention should be placed on rapid modification of the presurgical antihyperglycemic and antihypertensive regimens. In addition, the patient's nutritional status must be carefully tracked, with supplements provided to prevent the anticipated deficiencies in several vitamins and minerals, including calcium, iron, folate, vitamin B12, and vitamin D.

Despite these reported successes from bariatric surgery, we continue to feel that lifestyle modification is still "first-line" therapy in most patients with obesity. These surgical procedures should be restricted to the severely obese patient with medical sequelae who simply cannot lose weight despite his or her best efforts. Once we better understand the neurochemistry of appetite and body weight control, it is expected that targeted drug therapies may, at some point in the future, obviate the need for such invasive procedures.



Healthy Habits



Long-term adherence to commercial medical fitness programs is poor and correlates inversely with their cost. Praet *et al.* of The Netherlands sought to determine whether patients with Type 2 diabetes might be more persistent with a regimen of simple, brisk walking instead (abstract 809). They randomized Type 2 diabetes patients (59.9 \pm 0.9 years) to structured exercise, consisting of 45-60 minutes three times a week of either walking ($n=43$) or a medical fitness program ($n=49$) and monitored changes in metabolic profile, blood pressure, physical fitness, and BMI. It was discouraging to hear that, after one year, less than 40% of the participants in either group were still actively participating; moreover, only

25% of the participants adhered to >70% of the exercise sessions. Besides motivational problems, various co-morbidities, such as overuse injuries and subclinical osteoarthritis, appeared an important reason for the relatively high drop-out rate. Intention-to-treat analysis showed significant improvements in blood pressure, HbA1c, total cholesterol/HDL-cholesterol ratio, LDL-cholesterol, and BMI, while fasting glucose tended to improve as well ($p=0.09$). There were no statistically significant differences between the two groups (ANOVA, $p>0.05$) based on metabolic or cardiovascular improvements. These data suggest that simpler recommendations regarding brisk walking may result in a benefit comparable to a more expensive

and structured exercise program. However, compliance with any exercise regimen remains the major hurdle. We should point out that Holland is flat and it rarely snows, so success rates with brisk walking may be even lower than in some parts of the US.

Papakonstantinou *et al.* (abstract 792) Athens, Greece, compared the effects of two isocaloric, hypoenergetic diets that differed in protein and fat content on indices of glycemic control, body composition, blood pressure, and lipids. They studied 17 obese volunteers, age 46 \pm 3 years, with mild Type 2 diabetes in a random, blinded, and cross-over design study. The subjects followed two diets: (a) a high protein, low fat diet (protein:carbohydrate:

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Healthy Habits

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fat=30:15:20%) and (b) a low protein, high fat diet (protein:carbohydrate:fat=15:50:35%), for four weeks each with a three-week washout in between during which no specific diet was advised. The investigators found that the high protein, low fat diet caused a significantly higher reduction in blood pressure ($p=0.013$) and triglyceride levels ($p=0.042$), compared to the low protein diet. High protein diet also caused a significant reduction in HbA1c ($p < 0.001$), whereas the low protein diet did not. Both diets reduced glucose, insulin, LDL- and HDL-cholesterol levels as well as BMI, waist, body fat, and fat-free mass to the same extent. The investigators concluded that a high protein, low fat diet might improve cardiovascular risk by lowering blood pressure and triglyceride levels.

In a similar study, Tripp *et al.* (abstract 793) from Austria, investigated the metabolic effects of a high-protein diet (protein:carbohydrate:fat=30:40:30%), predominantly from vegetables,

Table 4. Impact of High-Protein Diet on Cardiovascular Risk in Type 2 Diabetes Patients

Indice	Baseline	3 Months*
Body weight (kg)	94.1 ± 15.6	91.0 ± 15.7
Insulin dose (U/day)	57.3 ± 26.6	48.2 ± 30.8
HbA1c (%)	7.8 ± 1.4	7.5 ± 1.4
Fasting plasma glucose (mg/dl)	203.2 ± 56.9	160.0 ± 47.7
Diastolic blood pressure (mmHg)	83.2 ± 7.2	76.9 ± 8.7
Triglycerides (mg/dl)	186.9 ± 114.9	140.7 ± 55.6
Fat mass (kg)	29.1 ± 8.2	26.7 ± 6.2

* $p < 0.05$ for each indice at three months vs. baseline.

compared with a standard diet (protein:carbohydrate:fat=15:55:30%), in 44 Type 2 diabetic patients on insulin therapy. After three months, several favorable effects were observed in the high-protein diet group (Table 4), whereas no changes were seen with the standard diet, except for a significant increase in insulin dose.

Taken together, results of the latter two studies suggest that a high-protein diet might have beneficial effects on glycemic parameters and insulin requirements in Type 2 diabetic

patients compared to a low protein or standard diet. These interesting findings require confirmation over longer observation periods. The specific concern would be compliance over time and also potentially deleterious renal effects.

Modern medical care is usually focused on the pharmacotherapy of disease. It is important to realize, however, that there are significant benefits from lifestyle changes for many conditions, particularly those that have fundamental nutritional origins, such as diabetes and obesity.



The Other Beta-Cell Peptide

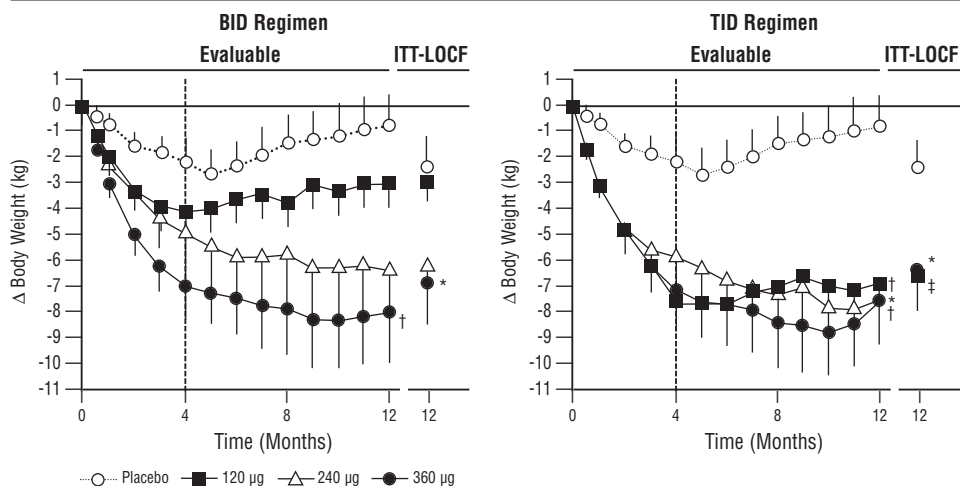


Riddle and US co-workers studied pramlintide as an alternative, rather than an addition, to mealtime insulin in Type 2 diabetes inadequately controlled with basal insulin with or without oral agents (abstract 912). This drug is an analogue of amylin, a peptide secreted by the beta cell along with insulin. It is currently approved for use in diabetic patients on intensive insulin regimens not achieving adequate control. It exerts its antihyperglycemic effect mainly through the suppression of glucagon and a delay in gastric emptying. A central effect on appetite is also likely. 211 patients (mean age 55±9 y, HbA1c 8.5±0.9%, BMI 35±5 kg/m²) using insulin glargine ± oral agents were randomized to pramlintide (60 or 120 µg) or placebo with major meals for 16 weeks. Insulin was titrated weekly, targeting a fasting glucose concentration of 70 to 100 mg/dl, with mean insulin doses of 61±32 units and 70±50 units for the pramlintide and placebo groups, respectively. The addition of pramlintide resulted in improved HbA1c (-0.7±0.1% vs. -0.4±0.1% with placebo, $p < 0.05$) due to a decrease in post-prandial glucose (-24.4±3.6 mg/dl vs. -0.4±3.0 mg/dl with placebo, $p < 0.0001$). Although the change in HbA1c is less than what would be expected with pre-meal insulin, pramlintide was associated with significant weight loss (-1.6±0.3 kg vs. +0.7±0.3 kg with placebo, $p < 0.0001$). There was also no treatment-related severe hypoglycemia.

Based on the results of a study by Halseth *et al.*, weight loss with pramlintide appears sustainable (abstract 838). Of patients completing a four month randomized, placebo-controlled study of lifestyle intervention combined with pramlintide, 75% (n=209; 76% female; mean±SD weight 106.0±18.4 kg) opted to continue treatment with either pramlintide (120, 240, 360 µg, BID/TID) or placebo in an eight-month extension study. During the extension study, lifestyle intervention

was geared towards weight maintenance (not loss). In contrast to recidivism seen in the placebo-treated patients, weight loss was maintained in all but the lower dose pramlintide group (Figure 2), with total effect after one year on the order of 8 kg. Despite the fact that the doses used in this study were much higher than those currently approved, the incidence of nausea was low and similar between pramlintide-treated (0-9%) and placebo-treated patients (7%).

Figure 2. Weight Loss Over 12 Months in Patients Treated With Pramlintide



* $p < 0.05$, † $p < 0.01$, ‡ $p < 0.001$ from baseline to month 12 for each pramlintide treatment group vs. placebo.
Note: Treatment groups ranged between 17-25 evaluable patients and 25-38 ITT patients per group.



So Many Posters, So Little Time....



Ongoing research adds to our understanding of “nutraceuticals” and their possible role in diabetic patients. In a double-blind study, Weitgasser *et al.* from Austria and Germany randomized 109 patients with Type 2 diabetes (62 men, mean age 59±9 years, mean HbA1c 7.8±0.8%) treated with diet and exercise to either cinnamon extract 360 mg or placebo once daily for three months (abstract 919). A treatment benefit was observed based on favorable changes of multiple indices (each presented for cinnamon vs. placebo, respectively): HbA1c -0.6 ±1.0% vs. -0.3±1.0%, $p=0.070$; insulin resistance by HOMA-IR: -0.8±3.1 vs. +0.6±2.5, $p<0.05$; adiponectin +1.1±2.3 vs. +0.1±2.7 mg/l, $p=0.052$; HDL-cholesterol +2±4 vs. 0±5 mg/dl, $p=0.071$; triglycerides -16±64 vs. +27±87 mg/dl, $p<0.005$). Whether these effects of cinnamon result from insulin sensitization, as has been postulated, or through other mechanisms (e.g., appetite regulation) remains in question.

Chevassus and French co-workers conducted two double-blind studies of fenugreek seed extract in which they found concordant results on fat intake (abstract 800). In one study, 12 healthy, male volunteers were randomized to two different doses (588 or 1176 mg/day) of the extract or placebo for 14 days. The three treatment periods were each separated by a 14-day washout. In the second study, 39 overweight male subjects (BMI 27.3±0.2 kg/m²) were randomized to fenugreek seed extract 1,176 mg/day or placebo for six weeks. Spontaneous fat intake was significantly decreased in those patients assigned to active therapy, both for healthy volunteers (-17.3%, $p=0.038$) and for overweight subjects (-9.5%, $p=0.032$), as was basal plasma insulin/glucose ratio (-44%, $p=0.044$) in the overweight subjects.

Using continuous glucose monitoring (CGM) data from 226 patients with insulin-treated diabetes (91 Type 1, mean HbA1c 7.5%), Choudhary *et al.* discovered that nocturnal hypoglycemia (defined as <54 mg/dl) is a common occurrence (28% of nights in Type 1 diabetes and 23% of nights in Type 2) (abstract 812). Fasting blood glucose was significantly lower following nights with hypoglycemia compared to nights with no hypoglycemia (106 mg/dl vs. 157 mg/dl, respectively; ($p<0.001$)). Nadir glucose was significantly correlated with fasting glucose ($r=0.7$, $p<0.001$) but, interestingly, *not* with bedtime capillary glucose ($r=0.25$, $p=0.7$). Taken together, these findings suggest that the so-called Somogyi effect (i.e., asymptomatic nocturnal hypoglycemia causing counterregulatory hormone release leading to fasting hyperglycemia) is uncommon among insulin-treated patients.

After a four-week washout period, 15 Type 2 diabetes patients with albuminuria received the new renin inhibitor, aliskiren 300 mg once daily for 28 days, with antihypertensive and antialbuminuric effects measured during four weeks of treatment (abstract 1118). Urinary albumin excretion was significantly reduced after five to seven days, by 29% (95% CI, 14-41) from a median baseline level of 173 mg/g and further reduced to 44% (32-54) at day 28 ($p=0.001$ vs. baseline). Interestingly, the reduction in urinary albumin was in part sustained four weeks after treatment was discontinued—it remained reduced by 22% (2-37)% from baseline. These values were independent of blood pressure reduction, suggesting the antialbuminuric effect of aliskiren is mediated by both hemodynamic and non-hemodynamic factors, as has been described with other modulators of the renin-angiotensin axis, such as the ACE inhibitors and the angiotensin receptor blockers (ARBs).

Obstructive sleep apnea (OSA) and other sleep disorders are being diagnosed more frequently with the widespread availability of sleep labs. Recently, the association between OSA and various metabolic derangements pertaining to diabetes has emerged. Pallayova *et al.* from Slovakia evaluated nocturnal glycemic variability using CGM and apnea-hypopnea index (AHI) in 29 Type 2 diabetic patients (mean age 55.4 ±7.5 years, BMI 35.6±8.5 kg/m², HbA1c 6.9±0.98%) treated with diet/oral hypoglycemic therapy (abstract 847). Glycemic variability during the night, as measured by overnight glucose standard deviation (SD) and mean of nocturnal glucose differences (Table 5) distinguished those patients

with from those without OSA. While there was no statistically significant difference in mean nocturnal glycemia or in HbA1c between patients with mild-to-moderate vs. severe OSA, CGM demonstrated severity of sleep apnea was directly related to the variability of glucose.

Okuno and Japanese colleagues evaluated the effect of CS-917, a fructose 1,6-bisphosphatase inhibitor, on glucose uptake/release in Goto-Kakizaki rats *in vivo*, and in human cells *in vitro* (i.e., gluconeogenesis in primary human hepatocytes and glycolysis in colon carcinoma cells) (abstract 218). They found that CS-917 suppresses hepatic glucose production by directly inhibiting gluconeogenesis in a dose-dependent manner ($IC_{50s}=0.041-0.061\mu M$), but does not alter glucose utilization. We note that several pharmaceutical companies have active programs in this area.

Mavrogiannaki *et al.* from Greece compared the prevalence of glucose intolerance, as measured by the oral glucose tolerance test (OGTT), in 187 patients with chronic hepatitis B or C to that in control subjects matched for age, sex, and BMI (abstract 380). Interestingly, as compared to controls, the prevalence of abnormal OGTT findings was higher in both the chronic hepatitis groups as compared to controls (B: 23.4% vs. 8.3%, $p=0.013$; C: 30.5% vs. 9.2%, $p<0.001$). Of particular interest is the observation that, despite normal fasting glucose levels, the results of the OGTT were abnormal in 70% and 55% of patients with hepatitis B and C, respectively. This finding confirms the critical role of the liver in the maintenance of glucose homeostasis.

Table 5. Glycemic Variability in Type 2 Diabetes Patients Based on Obstructive Sleep Apnea Status

	Normal* (n=15)	Mild to Moderate OSA* (n=6)	Severe OSA* (n=8)
HbA1c (%)	6.41 ± 0.68	7.4 ± 1.09	7.26 ± 1.1
Mean nocturnal glucose (mg/dl)	105 ± 18.5	153 ± 43.6†	162 ± 31.3†
Overnight glucose standard deviation (SD; mg/dl)	7 ± 2.3	11 ± 3.9†	19 ± 9.5†
Mean of nocturnal glucose differences (mg/dl)	31 ± 10.3	45 ± 13.9†	73 ± 38.2†

Normal: AHI<10/h; mild to moderate OSA: >10/h but < 25/h; severe OSA: >25/h.

NOTE: 86 nocturnal CGM glucose profiles: mean length of sensor wear 83±32 hours; correlation coefficient 0.89 ± 0.15; mean absolute difference 11.96 ± 6.0%.

† $p<0.01$ vs. normal, by ANOVA.

‡ $p<0.001$ vs. normal, by ANOVA.

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