

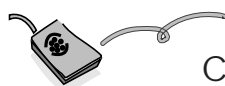
Diabetes 2007

From the 67th Annual Scientific Sessions of the American Diabetes Association ■ Chicago, IL

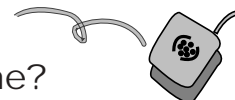
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Sponsored by Yale University School of Medicine, Department of Internal Medicine, Section of Endocrinology

Volume 15 ■ June 24, 2007 ■ Issue 3



CGM—Ready for Prime Time?



Important data on diabetes presented at the 67th Annual Scientific Sessions of the American Diabetes Association come 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 (ACC and ADA 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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Supported in part through educational grants from Takeda Pharmaceuticals North America, Inc., Merck & Co., Inc., Novo Nordisk Inc., and Amylin Pharmaceuticals, Inc./Eli Lilly and Company. It is understood that supporters will in no way control the content of this program.

Clinical issues with continuous glucose monitoring (CGM) was the subject of a symposium chaired by Dr. Satish Garg from the University of Colorado. These "glucose sensors" are inserted into subcutaneous tissue and measure glucose in interstitial fluid consistently over a 24-hour period. The first speaker, Dr. Jay Skyler from the University of Miami, noted that there was initial resistance to CGM when introduced in the 1970s due to poor accuracy and lack of acceptance. CGM has advanced considerably since then, however, with several devices now commercially available (Table 1). Published data on these devices suggest that their use is associated with improved HbA1c, improved time in the normoglycemic range, and decreased hypoglycemic and hyperglycemic excursions.

Dr. Howard Wolpert of the Joslin Clinic in Boston, MA continued the discussion by addressing certain practical issues with CGM. He reiterated the value of real-time glucose readings in daily patient management while identifying some important caveats. Given the lag time between interstitial and blood glucose values, it is critically important that monitor calibration occurs at glucose steady state (as opposed to when glucose is on the rise or decline) to avoid gross inaccuracies. Wolpert provided recommendations to share with patients based on his clinical experience: (1) if the sensor demonstrates increasing/decreasing glucose values, given the physiological lag, check a fingerstick before making any treatment decision; (2) if the sensor reading is normal, the potential for hypoglycemia

exists, therefore check a fingerstick before driving or other risky endeavors; (3) if there is reason to suspect glucose will decrease rapidly (e.g., following vigorous exercise), rely on fingerstick information; and (4) use of sensor readings to assess response to treatment of hypoglycemia may lead to over treatment. As Hirsch *et al.* reported in the STAR 1 trial (90-OR), increased and more severe hypoglycemic events may occur with CGM due to fear of complications from the now readily observed hyperglycemic excursions, with a tendency to administer too much correction insulin. Another patient concern is the individual wishing to avoid weight gain. In lieu of a snack to compensate for low blood glucose, these patients suspend basal dosing and may experience exaggerated hypoglycemia or rebound hyperglycemia. Successful use of CGM clearly depends on patient education and optimal patient selection.

Dr. Geremia Bolli of Italy next provided a synopsis of the strengths and weakness of CGM. In brief, the strengths were identified as "real-time" glucose values, trend analysis, alarms for hypo- and hyperglycemia, and the ability to review trends to provide insight into the interplay between food, insulin, and activity level—which can subsequently evolve into a tool for behavior modification. The lag time and/or discrepancies between monitors/sensors and blood glucose continues to be a major weakness. This lag, which has an actual physiological explanation, occurs with all subcutaneous sensors. It can delay hypoglycemia

Table 1. FDA-Approved Real-Time CGMS Devices

CGMS device	Possible location for sensor wear	Initial calibration time	Calibrations per 72 hour lifespan of sensor	Frequency of glucose readings	Hypo- and hyperglycemic alarms
Guardian® Real-time CGMS	Abdomen, hip, buttock, thigh	2 hours	7	Every 5 minutes	Yes
Dex-Com™ STS®	Abdomen	2 hours	5	Every 5 minutes	Yes
Freestyle Navigator® CGMS	Posterior arm, abdomen, hip, buttock	10 hours	4	Every 1 minute	Yes

CGMS = continuous glucose monitoring system

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CGM—Ready for Prime Time?

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alarms and also affects the calibration of the unit. As Dr. Wolpert proclaimed, the “holy grail” remains the closed loop system—that is, the automated insulin pump linked directly to an accurate and reliable glucose sensor. Some have termed this the “artificial pancreas.” Several groups are working on this project but it may be a number of years before the sensor accuracy and the necessary computer interfaces are at a point where such a system is commercially available.

Many posters and oral presentations this week involved both invasive and non-invasive glucose sensing. With recent evidence of the importance of glucose variability in the development of microvascular complications, Gomez-Peralta *et al.* from Spain quantified these glycemic excursions in 104 patients with Type 1 diabetes using CGM (Minimed) for at least 72 hours (441-P). 92 patients were on multiple daily injections and 12 were on insulin pumps, with a mean HbA1c of $8.3 \pm 1.1\%$. Overall HbA1c was correlated with CGM data, reflecting the glycemic load, but did not inform well concerning glycemic excursions. In patients with HbA1c $< 7\%$, 45% of time was spent out of the 80-180 mg/dl range, with nearly 20% of time spent < 80 mg/dl. This additional information obtained through CGM may be relevant to the overall care of Type 1 diabetic patients, data which may be missed on routine testing with a glucose meter.

Kovatchev and Clarke from Charlottesville, VA examined the use of CGM for patients to rapidly recognize and reduce glycemic extremes (86-OR). 123 patients (Type 1 and Type 2) used the Freestyle Navigator® CGMS for 20 days while masked to real-time data and then an additional 20 unmasked days with the sensor displaying the data with alarm settings functional. There was a highly significant reduction in the risk of hypoglycemia ($p < 0.001$), hyperglycemia ($p < 0.005$) and extreme glycemic excursions ($p < 0.001$) between the masked and unmasked phases. A three-fold reduction was observed in the percent of patients at high risk for hypoglycemia (9.8%

Table 2. Glycemic Profiles of Normal Glucose Tolerance and Type 2 Diabetes Groups

Glycemia Status	N	HbA1c (%)	Glucose			
			Peak (mg/dl)	Max-Min (mg/dl)	SD* (mg/dl)	AUC (mg/dl·24h)
Normal Glucose Tolerance	43	5.6 ± 0.5	140.4 ± 25.2	70.2 ± 28.8	15.1 ± 6.2	95.4 ± 9.3
Type 2 Diabetes	69	8.9 ± 2.1	309.6 ± 59.8	183.1 ± 50.5	43.2 ± 13.9	198.7 ± 50.8

* SD of diurnal glycemic excursions

vs. 2.9%) as well as severe hyperglycemia (7.9% to 2.9%). Overall there was a reduction in glucose variability; time within target range (72-180 mg/dl) increased marginally from 55% to 59% ($p < 0.001$) during the unmasked phase.

Ellis *et al.* from Colorado tried to reduplicate these findings over the long term with a retrospective study of 34 patients (mean HbA1c 7.36%) who used either Dexcom STS or Medtronic Paradigm glucose sensors for three months (449-P). With average sensor use of 17 ± 9 days per month, HbA1c decreased significantly at three months (7.36 vs. 7.06) despite no change in daily insulin dose (43.0 units vs. 42.7 units). There was a 23% reduction in self-reported hypoglycemia and a 41% reduction in nocturnal hypoglycemia. Mean blood glucose was reduced from 164 ± 74.5 to 153.2 ± 69.9 mg/dl at three months. There was a 30% increase in number of patients achieving a HbA1c $< 7\%$ with a sensor usage of at least 15 days/month compared to patients using the sensor less often. Thereby, in this population, sensor usage significantly improved glucose control with sizeable reductions in overall and nocturnal hypoglycemia.

Yu *et al.* from China compared glycemic profiles of 43 normal glucose tolerance (NGT) individuals with 69 newly diagnosed Type 2 diabetes using CGMS for 71 ± 10 hours (see Table 2) (418-P). After treatment for two to three weeks, glycemic values were significantly lowered in 23 patients who were re-examined with the sensor.

Truly non-invasive real-time glucose sensors are at this point investigational. Gabbay *et al.* from Hershey, PA showed the feasibility of using

second-generation optical coherence tomography (OCT) in measuring capillary blood glucose over a four day period in 27 subjects who had a simultaneous capillary glucose measurement (405-P). Based on 446 matched points, Clarke error grid analysis indicated 99% of values in the so-called “A+B zones,” indicating good matches or discrepancies that would not lead to any change in therapy. The correlation coefficient was 0.88 ($p < 0.0001$), comparing OCT vs. capillary blood glucose. However, no conclusions could be made about glucose values < 75 mg/dl as only six values were below this threshold. Amir and Israeli colleagues showed the efficacy of another non-invasive CGM, the NBM device, which is based on near-infrared occlusion spectroscopy technology (442-P). Seven Type 1 diabetes patients participated in a Phase 2 trial consisting of sessions lasting up to 14 hours for three to seven days. The overall reference range for blood glucose was 40-496 mg/dl, with Clarke grid analysis yielding 96.9% of all points in the A+B zones. The correlation coefficient was 0.9 when compared to reference blood glucose by conventional fingerstick method collected every 30 minutes. Further study in broader clinical settings is needed for both of these devices.

We would add that all continuous glucose sensors, while representing a major advance in diabetes technology, remain an expensive and sometimes inaccurate tool that are best used by highly trained patients already on intensive insulin regimens—usually insulin pumps. While some of these preliminary results look promising, the precise role of CGM in diabetes management is currently evolving.



The Lore of Snore



There is a growing and unmet public health challenge with 50-70 million Americans suffering from chronic sleep disorders. Obstructive sleep apnea (OSA) is one of the most important and, unfortunately, one of the most under-diagnosed. Its increasing incidence is directly linked to climbing obesity rates in this country. In a symposium titled “Prevalence of OSA in Type 2 Diabetes”,

various speakers highlighted the need to recognize and treat this condition. Being more common in males, it is estimated that 4% of all men have OSA; in men with diabetes, this figure grows to 25%.

Dr. Klar Yaggi from Yale University examined the pathophysiology of OSA and its related metabolic derangements. We normally spend 80% of our sleep time in non-rapid eye movement (NREM)

sleep, with the remaining 20% in REM sleep. The physiological differences between these two types of sleep are listed in Table 3.

Apnea is defined as cessation of airflow for at least 10 seconds; hypopnea is a decrease in airflow by more than 30%. Severity of OSA is defined by the number of events per hour (apnea-hypopnea index [AHI]): mild, 5-15 events/hour;

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The Lord of Snore

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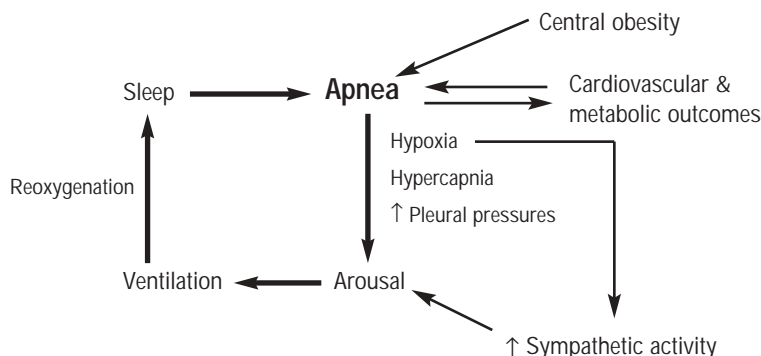
moderate, 15-30 events/hour; and severe, >30 events/hour. As shown in Figure 1, repeated apneic spells lead to increased nocturnal sympathetic activity, intermittent hypoxia, increased pleural pressures, and a decrease in cardiac output, culminating in cardiovascular and metabolic derangements. In addition, there are numerous studies showing increased risk of multiple cardiovascular and metabolic events in patients with OSA (Table 4).

Treatment of OSA with continuous positive airway pressure (CPAP) has been shown to increase not only sleep time and decrease daytime somnolence, but also to decrease blood pressure, improve insulin sensitivity, and even to decrease non-fatal cardiovascular events.

Dr. Esra Tasali from the University of Chicago next highlighted the association between OSA and abnormal glucose metabolism. Intermittent hypoxia leads to sleep fragmentation, reduced slow wave sleep, and increased sympathetic activity. She reviewed a study in which three nights of disordered sleep led to insulin resistance and impaired glucose intolerance (IGT). There were no changes in cortisol levels, but an increase in sympathetic activity was noticed. Dr. Tasali also pointed out that there is a higher prevalence of OSA in patients with polycystic ovarian syndrome (PCOS), a condition associated with insulin resistance. The severity of OSA correlates with degree of glucose intolerance in this population. Potential mechanisms for development of IGT and Type 2 diabetes include increased sympathetic activity, increased inflammatory markers such as IL-6 and TNF- α levels, decreased adiponectin levels, leptin resistance, and sleep debt. Dr. Tasali emphasized the need for more studies to elucidate the interaction between OSA and deranged carbohydrate metabolism.

Dr. Naresh Punjabi from Johns Hopkins talked about the ongoing Sleep Heart Health Study, which is a multicenter, epidemiological NIH-funded 15-year, longitudinal investigation involving more than 6,000 patients. He quoted a famous line by Thomas Deckker, "Sleep is a gold chain that ties our heart and bodies together". Dr.

Figure 1. The Sleep Apnea Cycle



Punjabi showed that there is an increase in the prevalence of IGT as well as Type 2 diabetes with increasing OSA severity. The odds ratio for having a higher fasting blood glucose in patients with severe OSA is 1.46, as compared to someone with a normal AHI index. He postulated that hypoxemia may be one of the pre-disposing factors to these metabolic alterations. Patients with moderate to severe OSA tend to be more insulin resistant (as assessed by HOMA). Triglycerides levels are higher and HDL-cholesterol levels tend to be lower, the more severe the OSA. Sleep duration appears to be integral in this relationship, with subjects sleeping less than five hours each night (or, interestingly, more than nine hours) more likely to have high fasting blood glucose as compared to subjects with a more normal seven to eight hours of sleep. OSA is fairly common in Type 2 diabetes, a relationship that may be mediated primarily by obesity. Use of CPAP has been shown to reduce visceral adiposity and improve insulin sensitivity and HbA1c. Punjabi postulated a syndrome associated with OSA that is analogous to the metabolic syndrome (Figure 2).

Later, Dr. Eve Van Cauter from Chicago examined normal physiological changes during sleep. During slow-wave sleep, there is a surge in growth hormone, prolactin, and vagal tone, with a decrease in cortisol, heart rate, blood pressure, and sympathetic activity. In the modern era, we are spending less time in bed—average nightly

Table 4. Consequences of OSA

- Hypertension
- Pulmonary hypertension
- Increased cardiovascular morbidity and mortality
- Stroke
- Sudden death
- Glucose intolerance and Type 2 diabetes
- Excessive daytime somnolence
- Cognitive dysfunction
- Depression
- Motor vehicle accidents
- Occupational accidents

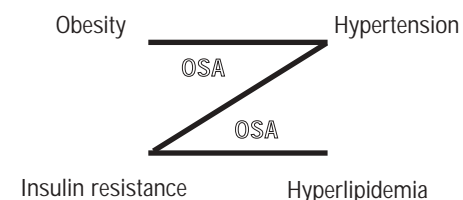
sleep hours have decreased from 8.5 in 1960 to 6.8 in 2000. In the Nurses Health Study, the odds ratio for developing diabetes when sleep duration was less than five hours was 1.4. Also, with advancing age there tends to be more nightly awakenings and decreases in slow-wave and REM sleep. There are studies in diabetic patients showing an increase of 1% in HbA1c with each three hours of nightly sleep debt.

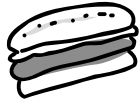
These data are quite provocative and suggest that sleep is important for the maintenance of good metabolic health. We now need well-designed clinical trials to assess whether treatment of OSA will reduce morbidity or even mortality in our diabetic patients.

Table 3. Normal Sleep Patterns

Non-REM Sleep (80%)	REM Sleep (20%)
↓ Sympathetic activity	↑ Sympathetic activity
↓ Heart rate	↑ Heart rate
↓ Blood pressure	↑ Blood pressure
Regular breathing pattern	Irregular breathing pattern (diaphragm dependent)
Decreased muscle tone	Absent muscle tone

Figure 2. Syndrome "Zzz ..."





Food for Thought



Given the obesity epidemic and its link to rising diabetes incidence, there are numerous lines of research in the area of medical nutrition therapy. In this article, we summarize some of the more interesting related studies presented this week at the ADA Scientific Sessions.

The Role of Diet Composition

The optimal macronutrient composition of a diet for patients with Type 2 diabetes remains a matter of controversy. In a one-year trial, 124 moderately well-controlled Type 2 diabetes patients (mean BMI 35.9 kg/m²; mean age 55.7; mean HbA1c 7.3%) were randomly assigned to a high-monounsaturated fat (MUFA) diet (40% of kcal from fat [20% from MUFA; Table 5] and 45% from carbohydrate [CHO]), or a high-CHO diet (60% of kcal from CHO and 25% from fat) (Brehm *et al.*, 64-OR). Modest caloric restriction was prescribed with both diets. The patient retention rate was 69% for high-MUFA and 84% for high-CHO ($p > 0.05$). Weight loss over one year was similar between diet groups (3.93 ± 0.82 kg vs. 3.78 ± 0.64 kg), as were improvements in body fat, diastolic blood pressure, HDL-cholesterol, HbA1c, and fasting glucose and insulin ($p < 0.01$ for each vs. baseline). These results suggest that a high-MUFA diet is a reasonably well-accepted, healthy alternative to a lower fat, high-CHO diet, without negatively impacting anthropometrics, cardiovascular risk factors, or glycemic control.

Tripp *et al.* from Austria randomized 44 insulin-treated Type 2 diabetes patients to either a weight-maintaining high-protein diet predominantly from vegetables (protein:CHO:fat=30:40:30%) or a standard diet (protein:CHO:fat=15:55:30%) (1776-P). The main outcome variables were daily insulin requirements and metabolic control at three months. Body weight decreased in both groups after three months (-3.1 vs. -1.0 kg, respectively; $p < 0.05$). Another difference between the groups at study endpoint was a decrease in insulin dose among patients in the high-protein diet group (57.3 to 48.2 units/day, $p < 0.05$) vs. a

significant increase in insulin dose with standard diet. Other favorable changes observed in the high-protein diet group were mean decreases in HbA1c (7.8 to 7.5%), fasting plasma glucose (203 to 160 mg/dl), triglycerides (187 to 141 mg/dl), diastolic blood pressure (83 to 77 mmHg), and fat mass (29 to 27 kg). As with all dietary studies, these results will require confirmation over a longer observation period.

Barnard and other North American researchers randomly assigned 99 Type 2 diabetes patients to a low-fat, vegan diet or a diet based on ADA guidelines (1774-P). Eighty-seven (42 vegan, 45 ADA) completed the 74-week study. Sustained improvements in glycemia, dyslipidemia, and weight were observed in patients who followed the vegan diet. HbA1c changes from baseline to endpoint were -0.40 and +0.01 for the vegan and ADA diet groups, respectively ($p = 0.03$). Statistically significant differences between treatment groups at endpoint were also observed for total cholesterol (-20.4 vs. -6.8 mg/dl) and LDL-cholesterol (-14.0 vs. -3.4 mg/dl). Patients in both groups lost weight, however: -4.4 kg in the vegan group ($p < 0.0001$) and -3.0 kg in the ADA diet group, ($p = 0.0003$).

Juiced Up

Stanhope and American coworkers investigated the effects of 10 weeks of fructose compared with glucose consumption on lipid parameters in overweight/obese (BMI: 25-35 kg/m²) adults (62-OR). Subjects initially consumed an energy-balanced, moderate fat (30%), high complex carbohydrate (55%) diet for two weeks in a controlled research setting. This was then followed by either fructose- ($n = 13$) or glucose-sweetened ($n = 10$) beverages (at 25% of energy requirements) first with a self-selected, *ad libitum* diet in an outpatient setting and then with an energy-balanced diet for another two weeks back in the research setting. Consumption of fructose in this manner promoted an atherogenic lipid profile within two weeks, whereas glucose did not. At two weeks, increases were observed in 24-hour postprandial triglycerides (212 ± 59%), small dense LDL-cholesterol (27 ± 11%), apoB (28 ± 7%), post-prandial concentrations of atherogenic remnant lipoprotein triglycerides (77 ± 9%) and remnant lipoprotein cholesterol (53 ± 12%) (each $p < 0.01$), as well as in oxidized LDL-cholesterol and intracellular adhesion molecule (ICAM)—all considered risk factors for atherosclerotic cardiovascular disease.

Based on their research findings, the presenters suggested that individuals at risk for developing metabolic syndrome and cardiovascular disease should avoid over-consumption of fructose-containing beverages.

Glycemic Loads

Interested in the association between glycemic index and risk of developing diabetes, Barclay and researchers from Australia conducted a literature search and identified seven relevant, prospective, cohort studies ($n = 297,317$ patients followed for four to nine years) (957-P). There were 5,891 incident cases of diabetes. In pooled data using random effects fully-adjusted models, there were significant positive associations for glycemic index (RR = 1.20, 95% confidence interval [CI], 1.04-1.38) and glycemic load (RR = 1.16, 95% CI 1.01-1.34), which were increased further when three studies with poor validity were excluded from the analysis.

In a related abstract, Lamb *et al.* from Colorado prospectively followed a cohort of 82 with islet autoimmunity (defined as presence of autoantibodies to insulin, GAD65, or IA-2 twice in succession) to determine the impact, if any, of diet on risk of developing Type 1 diabetes (39-OR). Twenty-one children developed Type 1 diabetes, at a mean age of 7.3 years. (Autoimmunity was detected at a mean of 5.1 years.) After adjustments for the at-risk haplotypes HLA-DR and DQ, family history of Type 1 diabetes, age at first islet autoimmunity positivity, and total energy intake in a multivariate survival model, higher reported glycemic index of the childhood diet was associated with more rapid progression to diabetes (HR 1.86; 95% CI, 1.13-3.04). We all recall the "old wife's tale" that sugary sweets will lead to diabetes in children. While these data don't support this myth, they raise the possibility that, in certain individuals at risk for β -cell failure, increased islet demands may hasten the loss of insulin secretory capacity.

Azevedo and Brazilian associates examined the impact of diet on the development of metabolic syndrome (using the International Diabetes Federation criteria) in 214 Type 2 diabetes patients (1769-P). Their findings were based on a three-day weighed-diet record (% of total daily energy intake or g/day-energy adjusted), which was confirmed by 24-hour urinary nitrogen output. In multiple logistic regression models, adjusted for diabetes duration, gender, and physical activity, soluble fibers from whole grains (OR 0.41, 95%

Table 5. Foods High in Monounsaturated Fat

- Avocados
- Most nuts (e.g., macademia, hazelnuts, pecans)
- Nut butters (e.g., peanut butter, almond butter)
- Olive, peanut and canola oils
- Olives

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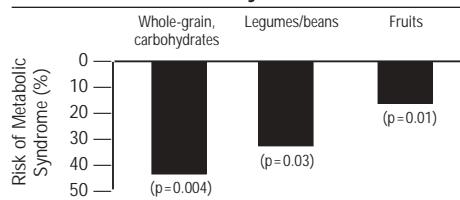
Food for Thought

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CI 0.24-0.70; $p=0.001$) and from fruits (OR 0.76, 95% CI 0.60-0.94; $p=0.01$) were negatively associated with presence of metabolic syndrome. Regarding specific foods, they found whole-grain foods from the carbohydrate group (e.g., wheat or rye breads, brown rice, pasta, oat bran, crackers) legumes/beans, and fruits to be protective for



Figure 3. Foods Protective for Metabolic Syndrome



metabolic syndrome (Figure 3).

Nutritional science often takes a back seat to the more alluring research concerning pharmacologically-based interventions. However, since diet remains intrinsically linked to the obesity and diabetes epidemics, more high quality investigation is needed in this area. Moreover, it is important that, as clinicians, we understand the impact caloric intake and make-up has on our patients' metabolic risk.



Baby and Me

The 'Pedersen hypothesis' dates back 50 years and sheds light upon the link between maternal gestational diabetes (GDM) and adverse fetal outcomes. It has never been clear, however, to what extent milder forms of hyperglycemia are associated with fetal risk. In a "State of the Art" symposium, the design, implementation, subject characteristics, and results of the seven-year, multi-national, observational study known as HAPO—the Hyperglycemia and Adverse Pregnancy Outcomes—were presented. HAPO was an attempt to decipher the precise threshold for fetal complications from maternal hyperglycemia not yet in the range where GDM could be diagnosed.

Dr. Lowe from Chicago, IL introduced the study design of HAPO and characteristics of enrolled subjects. Pregnant females were recruited through 31 weeks of gestation and underwent a 75-g oral glucose tolerance test (OGTT) on the ~28th week of gestation. Those younger than 18 years and women who were uncertain about their last menstrual period, had multiple pregnancies, or had a prior history of gestational or Type 2 diabetes were excluded. OGTT results were revealed to the subject and their physician if fasting plasma glucose (FPG) exceeded 105 mg/dl or the 2-hour OGTT plasma glucose exceeded 200 mg/dl, or if any value fell below 45 mg/dl. Other subjects and their physicians were blinded to the results. Routine prenatal care was provided to all the participants. A random plasma glucose was drawn at 34-37 weeks; subjects with values >160 or <45 mg/dl were removed from the study. After delivery, cord blood was measured for glucose and C-peptide levels, and a neonatal blood sample taken one to two hours after delivery. Neonatal anthropometric measurements were made within 72 hours of delivery.

Out of the eligible 25,505 subjects who had an OGTT, 746 (2.9%) were eventually unblinded and 1,434 (5.6%) dropped out; 23,325 deliveries were available for analysis. Study subject characteristics included mean age 29.2 ± 5.8 years, BMI 27.7 ± 5.1 kg/m², FPG 80.9 ± 6.9 mg/dl, 1-hour and

2-hour OGTT plasma glucose values of 134 ± 30.9 mg/dl and 111 ± 23.5 mg/dl, respectively. 48.3% were white, 11.6% black, 8.5% Hispanic, and 29% Asian; 22.6% had a family history of diabetes.

Dr. Oats from Australia next reviewed the maternal outcomes in relation to the gestational blood glucose values. 13.2% developed hypertension, and 23.7% required a C-section. Two women died (one due to pulmonary embolus and one due to pneumonia/respiratory failure), nine women had eclampsia, 187 (0.8%) experienced a major obstetrical hemorrhage, 26 (0.1%) required an ICU transfer, and 172 (0.74%) needed readmission to the hospital. Subjects were divided into seven groups based on glucose increments of FPG and 1- and 2-hour post-load glucose. Prevalence of neonatal birth weight >90 th percentile was 5.4% in the lowest maternal glucose septile, compared to 27% in the highest, with a linear relationship of neonatal birth weight to increasing maternal FPG from <75 mg/dl to >100 mg/dl. There was a similar linear increase in the risk of C-section across all maternal glucose values.

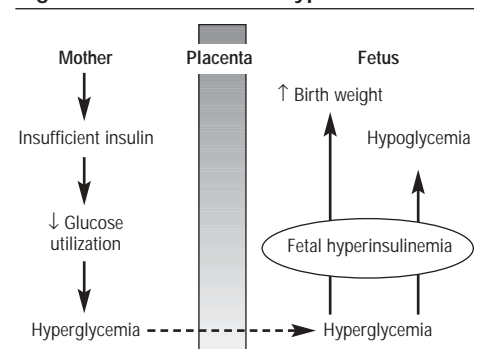
Dr. Persson from Karolinska Institute examined the neonatal outcomes. There were 130 perinatal deaths (5.6/1000 deliveries)—89 intrauterine and 41 neonatal/infant. Neonatal characteristics of the entire cohort included gestational age 39.4 ± 1.7 weeks, birth weight 3292 ± 52.9 g, length 49.7 ± 2.4 cm, and head circumference 34.3 ± 1.4 cm. Neonatal complications included 321 (1.3%) with major malformations, 312 (1.3%) with shoulder dystocia/birth injury, 97 (0.4%) with respiratory distress syndrome, 1,947 (8.4%) with hyperbilirubinemia, 667 (2.9%) requiring hospital readmission, and 1,857 (8%) requiring neonatal ICU admission. There was an increased risk of neonatal hypoglycemia in the highest maternal plasma glucose group (OR 2.7) as compared to the lowest group. After correcting for other confounders, the risk of neonatal hypoglycemia was evident only

in the maternal group with FPG >100 mg/dl. Neonatal hyperinsulinemia (C-peptide >90 th percentile) was seen in 1,670 babies (8.4%). There again was a linear increase in C-peptide levels across all groups as maternal glycaemic measures increased.

Dr. Hod from Israel examined the effects of fetal hyperinsulinemia on birth weight and hypoglycemia. There was a linear increase in birth weight >90 th percentile and risk of neonatal hypoglycemia with increasing fetal C-peptide levels. Based on these data, Dr. Hod presented an adaptation of the Pedersen hypothesis, underscoring the important role of fetal hyperinsulinemia in determining birth weight and neonatal hypoglycemia (Figure 4).

The study's chairperson, Dr. Metzger reminded the audience that the association between maternal hyperglycemia and adverse fetal outcomes appears to be continuous and linear. It is difficult, however, based on these findings to suggest specific changes in the current diagnostic criteria for gestational diabetes at this time. That is, there is no threshold value above which a sudden increase in complications are observed. He stressed the importance of having a consensus forum for further input from key organizations with interest and expertise in maternal-fetal medicine. Such a conference is planned for May 2008 at which point the HAPO data will be translated into clinical recommendations.

Figure 4. The Pedersen Hypothesis



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