

Diabetes 2005

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Not Your Traditional Risk Factors



Important data on diabetes presented at the 65th Annual Scientific Sessions of the American Diabetes Association come to you in **Diabetes 2005**, a newsletter CME program that is being offered to you by Yale University School of Medicine with the support of Takeda Pharmaceuticals America, Inc. and Eli Lilly and Company. Fax or e-mail delivery to your office of **Diabetes 2005** will be followed by a **Diabetes 2005** booklet (ACC and ADA newsletters) in the mail. After successfully completing the quiz and evaluation therein contained and remitting a \$10 certificate fee to the Yale Office of Continuing Education, 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 2005 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.

Yale University School of Medicine is accredited by the Accreditation Council for Continuing Medical Education to sponsor continuing medical education to physicians. Yale University School of Medicine designates this continuing medical education activity for a maximum of 5.5 Category 1 credits towards the AMA Physician's Recognition Award. Each physician should claim only those hours of credit that he/she actually spent in the educational activity.

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Inflammation is thought to play a central role in insulin resistance and atherosclerosis. With recent emphasis on inflammatory markers and their potential role in mediating atherosclerosis, a symposium was held entitled, "Non-Traditional Cardiovascular Risk Factors." Speakers highlighted the importance of assessing novel risk factors in global risk stratification of selected patients at risk of cardiovascular disease (CVD).

C-reactive protein (CRP) has been found in numerous studies to be predictive of cardiovascular events in patients with and without CVD. However, its exact role has not been fully elucidated, with many awaiting the results of the JUPITER trial. (JUPITER randomized 15,000 patients with CRP > 2 mg/l [considered average] and LDL-cholesterol [LDL-C] < 130 mg/dl to rosuvastatin 20 mg daily for 3-4 years with major CV event as the primary outcome.) With this as a background, Dr. C. Ballantyne from Houston discussed the diagnostic role of CRP. He cited the results of the Framingham offspring study in which a progressive increase in CRP levels with increasing number of metabolic syndrome components was identified. This observation was more pronounced in women than in men. According to Dr. Ballantyne, CRP should not be checked in all individuals, but rather in patients at intermediate risk (i.e., 10-20% over 10 years) as a part of global risk assessment. In those warranting CRP assessment, two measurements separated by two weeks should be performed. In persons with levels ≥ 10 mg/l (low < 1, average 1-3, high > 3 mg/l) acute illness (such as viral or bacterial infection) should be ruled out. Among those with high levels, as Dr. Ballantyne pointed out, there is no available therapy to reduce CRP alone without reducing other CVD risk factors such as LDL-C (i.e., statins) or glucose/insulin resistance (i.e., thiazolidinediones).

Dr. Ronald Krauss of Berkeley highlighted the importance of LDL-C particle size in determining CVD risk. Small, dense LDL-C particles have less affinity for receptor binding, with greater potential

for endothelial transport, proteoglycan binding, and oxidation. As a result they are more atherogenic than larger, more buoyant LDL-C particles. Insulin resistance, apo-B, and total cholesterol/HDL-cholesterol ratio have been associated with the small, dense LDL-C pattern "type B." Small LDL-C particle size has been shown to be predictive of coronary artery disease and correlates with carotid intimal media thickness (IMT), a surrogate marker of atherosclerosis. In the angiographic study, SCRIP, the progression of atherosclerosis was restricted to patients with pattern B rather than those patients with the more favorable LDL-C pattern A. Due to the lack of a specific drug that improves particle size alone, the therapeutic impact of modulating LDL-C particle size remains debatable.

Lastly, Dr. Kuller from Pittsburgh defined the role of electron beam computed tomography (EBCT) in determining the coronary artery calcification (CAC) scores and the burden of atherosclerosis. Ideally the CAC score, measured in Agatston units, should be zero. CAC levels between 0-100 are indeterminate, and levels > 100 should be further evaluated (definitive high-risk scores are in the > 400 range). CAC scores tend to be much higher in males as compared to females. Despite initial criticism, they have been shown to be highly reproducible and good predictors of cardiovascular mortality in diabetic and non-diabetic patients. Calcium scores, essentially a marker of subclinical coronary atherosclerosis, are also strongly correlated with other surrogates of vascular disease, such as carotid IMT, aortic compliance, and ankle-brachial index (ABI). Progression of CAC scores can be measured; however, it is not clear if aggressive treatment reduces CAC or slows its progression. EBCT may be used in selected groups of individuals with intermediate risk of CVD, where risk stratification is needed. In older individuals (> 65 years), there is a high prevalence of atherosclerosis and EBCT does not serve as an adequate discriminating factor. At this point, EBCT is an evolving technology, that merits further investigation.

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Not Your Traditional Risk Factors

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CVD and Diabetes

Many abstracts this week addressed CVD in diabetic patients. The use of insulin sensitizing medications, metformin (MET), and thiazolidinediones (TZD) may have beneficial effects on atherosclerosis, but there are yet no outcome data in patients following acute myocardial infarction (AMI). Investigators from Yale and the University of Colorado (256-OR) evaluated the one-year outcome among 8,872 antihyperglycemic-treated diabetic patients following discharge for AMI, including 6,641 on neither sensitizer (sulfonylurea, 3,515; insulin, 3,509), 1,273 on MET, 819 on a TZD, and 139 on both MET and TZD. After multivariable adjustments including more than 70 patient, physician, and hospital covariates, compared with patients discharged on neither sensitizer, mortality rates at one year were not significantly different in those prescribed either MET or a TZD, but were significantly lower in those prescribed both drugs (HR 0.52, $p=0.004$). TZD therapy was associated with a borderline higher risk of all-cause readmission predominantly due to a higher risk of heart failure readmission. The authors

concluded that monotherapy with an insulin sensitizer is not associated with a significantly lower risk of death. Yet when two sensitizers are combined, they may provide synergistic benefit. While provocative, we would emphasize caution in interpreting these retrospective data, with mortality and readmissions ultimately assessed in relatively few "exposed" patients.

Hyperglycemia: A CVD Risk Factor

There are numerous studies showing an association between postprandial hyperglycemia and cardiovascular events. Hosoi and colleagues from Japan (714-P) measured carotid IMT, plaque score, and daily profile of blood glucose levels on second and third hospital days in known Type 2 diabetes patients ($n=274$, age 62.8 years, HbA1c 9.4%, BMI 24.4 kg/m²). The maximum plasma glucose was 280 mg/dl and excursion was 145 mg/dl. With multivariate regression analysis the mean IMT was significantly associated with total-cholesterol/HDL-cholesterol, peak plasma glucose levels, and systolic blood pressure. HbA1c and fasting plasma glucose levels were not associated with carotid IMT. Plaque score was associated with age, total cholesterol/HDL-cholesterol, and peak plasma glucose levels.

These data suggest that postprandial hyperglycemia is a more powerful predictor than HbA1c of carotid IMT in diabetic subjects. In related studies using animal models (761-P), investigators from Japan have demonstrated that acute rises in blood glucose accelerate monocyte adhesion to endothelial cells from rat thoracic arteries, the initial step in atheroma development. Moreover, the effect is greater than that induced by persistent hyperglycemia (768-P). These data are consistent with epidemiological evidence that postprandial glucose spikes are more closely aligned with cardiovascular risk than fasting glucose.

Those findings did not dissuade Schaan *et al.* from Brazil (724-P) in evaluating the relationship between progressively higher levels of fasting plasma glucose (FPG) and insulin resistance with angiographic detected CAD (using Humphries and Califf scores for CAD extension and severity). The patients were classified as normal (FPG < 88 mg/dl), high-normal (FPG=89-99 mg/dl), abnormal (FPG=100-125 mg/dl), and diabetic (FPG ≥ 126 mg/dl or a previously established diagnosis). Progressive scores of angiographically detected CAD were associated with increasingly higher levels of glucose and HOMA-IR, an index of insulin resistance. Interestingly, a significant risk of CAD was observed even at normal glucose levels, as shown (Table 1).

The well recognized two- to four-fold increased risk of cardiovascular disease in diabetes compels the scientific community to continue to elucidate the mechanisms that link these two conditions. Our enhanced understanding of the pathophysiologic mechanisms involved will be followed by more successful preventive strategies.

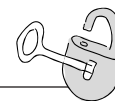
Table 1. Severity of Hyperglycemia, Insulin Resistance, and CAD

	Normal FPG (n=36)	High-normal FPG (n=34)	Abnormal FPG (n=28)	Diabetes (n=47)	p-value
HbA1c (%)	5.65 ± 0.05	5.6 ± 0.04	5.97 ± 0.09	6.89 ± 0.23	< 0.001
HOMA-IR	1.78 ± 0.2	3.13 ± 0.4	4.64 ± 0.6	7.89 ± 1.8	0.001
% CAD (Humphries)	27	30	36	50	0.03
% CAD (Califf)	39	50	60	70	0.006

FPG=fasting plasma glucose



Activating PPARs – TZDs & Beyond



The results of numerous thiazolidinedione (TZD) studies were presented this week, several improving our understanding of their broad-spectrum of activity. These insulin sensitizing drugs exert their metabolic (and vascular) effects by activating the nuclear transcription factor, peroxisome proliferator-activated receptor (PPAR)- γ . Data on so-called dual (PPAR- α/γ) agonists (e.g., muraglitazar, tesaglitazar) and a non-TZD, PPAR- γ agonist/antagonist (e.g., metaglidasen) were also presented.

Lipid Effects

Differential effects between pioglitazone and rosiglitazone are becoming more apparent

as the results of comparative trials are presented. Tan *et al.* conducted a multicenter, double-blind study in which 802 Type 2 diabetes patients previously treated with diet alone (25%) or one oral anti-hyperglycemic agent were randomized to four weeks of placebo followed by either pioglitazone (30 mg daily for 12 weeks then 45 mg daily for an additional 12 weeks) or rosiglitazone (4 mg daily for 12 weeks then 4 mg twice daily for 12 weeks) (1-OR). The use of lipid-lowering agents was prohibited prior to and during the study. Pioglitazone decreased atherogenic index of plasma (AIP), a marker related to cardiovascular risk, and triglycerides and increased HDL-cholesterol, significantly more so than rosiglitazone (Figure 1), with similar effects on HbA1c (-0.7%

and -0.6%, respectively) and markers of insulin resistance. The long-term impact of these differences in lipid effects remains unclear.

β -cell Effects

Type 2 diabetes is a chronic disease characterized by a progressive decline in β -cell function. A population-based model of Type 2 diabetes has been developed based on an analysis of glucose-insulin homeostasis to assess the effects of therapeutic agents on disease progression. Using this model, Post *et al.* from the Netherlands and the United Kingdom utilized data from 1,269 patients enrolled in two studies, each of two years duration, to compare the effects

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Activating PPARs...

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of metformin, sulfonylurea, and TZDs (15-OR). A significant improvement in β -cell function was observed throughout the two-year period in all groups that received pioglitazone ($p < 0.001$). These results suggest that TZDs promote " β -cell rest," as has been suggested by several investigators. If this effect exists, its impact on the eventual need to add other agents, particularly insulin, remains unknown.

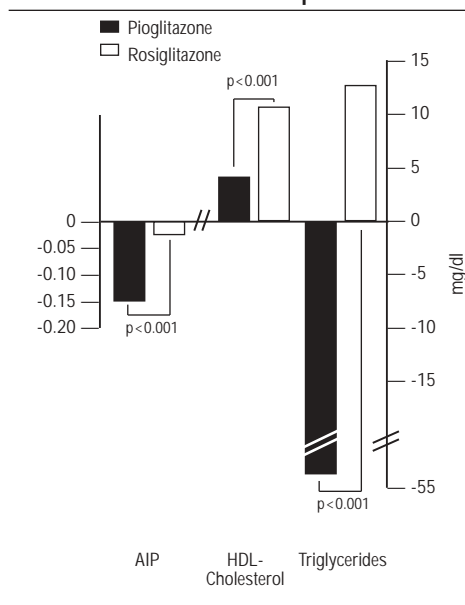
NASH

Increased fat deposition in the liver, associated with insulin resistance, contributes to the pathophysiology of diabetes, and when severe, may also result in cirrhosis. Patients with non-alcoholic steatohepatitis (NASH) are insulin resistant and frequently have impaired glucose tolerance (IGT) or Type 2 diabetes. Belfort *et al.* from San Antonio presented results from the first double-blind study in which 46 patients with biopsy-proven NASH and IGT/diabetes were randomized to pioglitazone 45 mg/day or placebo for six months (79-OR). Among the first 32 completers, elevated transaminase values decreased in all patients who received the TZD ($p < 0.01$ vs. placebo). Furthermore, pioglitazone decreased hepatic fat by 50% as measured by magnetic resonance spectroscopy ($p < 0.05$), as well as histological evidence of inflammation/necrosis, steatosis ($p < 0.01$), possibly fibrosis, and combined pathological score ($p < 0.03$), as compared to placebo.

Safety Issues

Many clinicians using TZDs are concerned about warnings in patients with heart failure as well as edema and weight gain. Wilding *et al.* studied echocardiographic structure and function in 224 Type 2 diabetes patients with class I/II heart failure who were randomized to receive rosiglitazone 4-8 mg/day or placebo in addition to background anti-hyperglycemic agents for 52 weeks (80-OR). Ejection fraction was similar between groups at baseline and at 52 weeks (37.8% and 36.8% for TZD and placebo, respectively). Over the treatment period, there were few exacerbations of heart failure (6% vs. 4% for TZD and placebo, respectively), although more episodes of worsening edema (26% vs. 9%) and dyspnea (26% vs. 17%) occurred in the TZD group. These episodes generally did not lead to hospitalization or premature discontinuation of the TZD and could be managed with a diuretic.

Figure 1. Least Square Mean Change From Baseline Lipid Levels



Karalliedde *et al.* evaluated different approaches to the management of TZD-related fluid retention (81-OR). They studied 381 diabetes patients who were receiving a sulfonylurea alone (25%) or with metformin, to which rosiglitazone 4 mg twice daily was added for 12 weeks. Those who experienced volume expansion ($n = 260$), defined by a reduction in hematocrit of $> 0.5\%$, were randomized to seven days of continued rosiglitazone with no diuretic (control), furosemide 40 mg/day, hydrochlorothiazide 25 mg/day, or spironolactone 50 mg/day or to discontinuation of rosiglitazone. After 12 weeks, mean hematocrit fell by 2.9% and mean weight increased by 1.8 kg. After randomization, the adjusted treatment difference (vs. control) in hematocrit reduction was significant for spironolactone (1.13%, $p = 0.004$) and hydrochlorothiazide (0.87%, $p = 0.039$). Body weight decreased by 1.2 kg and 1.0 kg, respectively. That spironolactone was the most effective diuretic for TZD-associated fluid retention is consistent with PPAR- γ agonist activation of the aldosterone-sensitive sodium transport channel in distal nephrons.

In a five-year study of diabetes patients being treated with pioglitazone and no other TZD, maximal mean weight gain ($\sim +6$ kg) occurred at 30 to 36 months, with stabilization thereafter (468-P). The investigators previously identified predictors of weight gain with TZDs, including increased weight prior to initiation of therapy, female gender, and recent onset of diabetes. Of

note, weight gain during TZD therapy does not appear to affect the beneficial treatment effects on glycemia or dyslipidemia. Calorie restriction and a reduction in TZD dose can ameliorate weight gain.

The safety of TZD administration in patients following solid organ transplantation was addressed by Asnani and Louisiana colleagues (2027-P). Eight patients with diabetes (seven developed post-transplant and one with a pre-transplant diagnosis) received either pioglitazone ($n = 5$) or rosiglitazone ($n = 3$) for an average of 5.5 months. There was a significant improvement in HbA1c from 9.9% to 6.8% ($p = 0.017$). Neither drug caused alterations in dosing or serum levels of concomitant immunosuppressants (mycophenolate, tacrolimus). The investigators suggested that TZDs appear to be a safe and effective alternative for management of diabetes in patients following solid organ transplantation.

Emerging Agents

Several compounds that activate PPAR receptors are in development. Defronzo *et al.* presented results of a double-blind, randomized study of 1,159 Type 2 diabetes patients inadequately controlled on metformin who were randomized to 24 weeks of pioglitazone or muraglitazar, a dual (α, γ) PPAR agonist (14-OR). Kendall *et al.* shared comparative trial data demonstrating positive results with muraglitazar (refer to "Late-Breaking Clinical Trials," Issue 4). Goldstein *et al.* studied the effects of tesaglitazar, another dual agonist, on glucose and lipid levels in a randomized, double-blind, placebo-controlled, dose-ranging study (83-OR). Generally these agents appear to be equally effective on glucose as the current TZDs, with better lipid effects, but possibly increased risk of weight gain and edema. Rosenstock *et al.*, however, conducted a three-month multicenter, double-blind, randomized, placebo-controlled study of metaglidasen, a non-TZD PPAR- γ agonist/antagonist, in combination with insulin (44-OR), suggesting no induction of weight gain at all. At this time, muraglitazar has been submitted to the FDA for approval. The other drugs remain in development.

It is quite likely that within one to two years, the landscape of PPAR-based therapies for Type 2 diabetes will expand significantly. We anxiously await the cardiovascular outcomes studies with these agents, the first of which will be announced in September at the annual congress of the European Association for the Study of Diabetes in Athens, Greece, where *Diabetes 2005* will be in attendance.



Diabetic Nephropathy



Up to 40% of all diabetic patients develop diabetic nephropathy, the most common cause of end-stage renal disease (ESRD), and over 50% of all patients on dialysis have diabetes. Data presented by Burrows *et al.* (821-P) at this week's meeting suggest that although there has been an explosion in the number of patients with diabetes, the age-adjusted incidence of ESRD due to diabetes has declined in younger populations (-23% in those < 45 years of age and -10% in those 45 and 64 years of age between 1996 to 2002; $p < 0.01$ for each comparison), remained stable among those 65 to 75 years, and increased only in those > 75 years (+22%, $p < 0.01$).

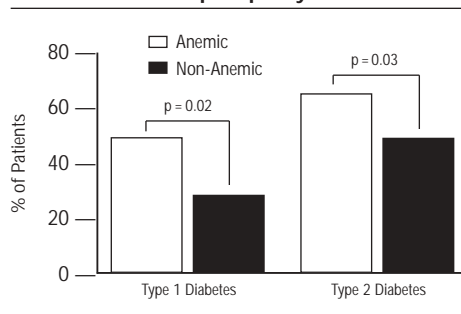
Pathology of Diabetic Nephropathy

During a symposium entitled "Nephrons, Diabetes, Nutrition, and the National Kidney Foundation Guidelines—Enhancing Care Coordination," Katherine Tuttle elaborated on the underlying pathophysiology of diabetic nephropathy. In those with diabetes, increased blood glucose levels result in hyperfiltration, leading to endothelial injury and glomerulosclerosis. Hypertension further augments the effects of hyperglycemia on the glomeruli.

Diet plays a significant role in the incidence of nephropathy, with the widely promulgated high-protein diets having deleterious effects similar to those of hyperglycemia. These effects are suggested in an NHANES study population, in which a three-fold higher risk of chronic kidney disease (CKD) was observed among those with 19% of calories from protein compared to those with < 12%. On the other hand, Dr. Tuttle reviewed the results of numerous studies showing a 50% reduction in the progression of diabetic nephropathy in those maintaining a low-protein diet.

Dr. Mark Molitch from Chicago reported that 25% of persons with CKD also suffer from anemia. These findings were supported by the findings of Fischer *et al.* (832-P) who documented anemia in between 22% (Type 2) and 26% (Type 1) of patients with diabetes. Anemic patients with diabetes were significantly more likely to have nephropathy (Figure 2). These findings, coupled with those of the RENAAL study that showed a two-fold higher risk of CKD progression in those with anemia, emphasize the importance of early identification and treatment.

Figure 2. Percentage of Patients with Nephropathy



Patient Management and Treatment Recommendations

In addition to incorporation of a low-protein diet, several other patient management recommendations were made by dietitians, Jane Greene and Patricia Weber (Table 2).

In patients with diabetic nephropathy and hypertension, the use of combination angiotensin-converting enzyme inhibitor (ACEI) and angiotensin receptor blocker (ARB) therapy appears particularly beneficial. Ljubic and associates from Croatia (813-P) treated 195 hypertensive patients with Type 2 diabetes with lisinopril ($n = 69$), losartan ($n = 48$), or the combination ($n = 36$). C-reactive protein (CRP) decreased significantly in those treated with lisinopril either alone ($p < 0.001$) or in combination with losartan ($p = 0.03$). Pulse pressure, systolic and diastolic blood pressures, and albumin excretion rates were significantly reduced in all treatment groups ($p \leq 0.05$), with the combination producing the most pronounced reductions. These findings suggest that combination ACEI/ARB therapy may potentially preserve renal function more than either drug alone while also reducing vascular risk.

During the symposium, Dr. Molitch reported that the identification and treatment of diabetics with anemia and secondary hyperparathyroidism, which leads to bone loss and a four-fold increased risk for hip fracture, is largely ignored by endocrinologists. Those with anemia warrant treatment with elemental iron (>200 mg/day), vitamin B12, and folate, with recombinant human erythropoietin used to maintain serum hemoglobin >12. Calcitriol, which decreases parathyroid hormone levels and improves bone density, may decrease mortality in those with CKD.

Table 2. Patient Management Recommendations

Hypertension/Lipid/Glucose Targets

- Blood pressure < 130/85 mm Hg or < 125/75 mm Hg if macroalbuminuria present
- LDL-cholesterol < 100 mg/dl in those with CKD stage 1 to 4*
- Glucose control: HbA1c < 7%

Lifestyle and Dietary Parameters

- Regular exercise, smoking cessation, moderation of alcohol intake
- Limit protein intake by CKD* stage: 0.8 mg/kg/day in CKD stage 1 or 2; 0.6 to 0.8 mg/kg/day in stage 3 or 4. Monitor nutrition closely in those with stage 5 to avoid risk of protein malnutrition
- Carbohydrates should comprise 50 to 60% of daily caloric intake
- Limit sodium intake to < 2 gm/day
- Limit potassium intake to 50-75 mEq/day (in most patients ACEI/ARB can be continued if potassium < 5.5 mEq/l)
- Ensure calcium intake of 2 gm/day (avoid vitamin D if high calcium:phosphate)

* CKD stages: glomerular filtration rate (GFR) in ml/min/m²: 1=>90; 2=60-89; 3=30-59; 4=15-29; 5=<15

Diabetics with difficult-to-manage nephropathy, anemia, or secondary hyperparathyroidism and those who develop risk factors (Table 3) should be referred to a nephrologist.

Table 3. Features Warranting Nephrology Referral

- Rapid decline in glomerular filtration rate (GFR)
- Sudden onset of nephrotic syndrome
- Refractory hypertension
- Active urinary sediment (hematuria)
- Signs and symptoms of systemic disease
- > 30% reduction in GFR after starting ACEI and/or ARB therapy



The Politics of Food



In a morning plenary session, Dr. Marion Nestle of New York University presented "The Politics of Obesity: Where is Diabetes?" Despite the raging debate and publicity regarding obesity, unfortunately the issue of diabetes is often lost. Dr. Nestle cited the recent JAMA paper from the Centers for Disease Control declaring that overweight individuals may actually have *improved* health outcomes. Regrettably, the statement "except for diabetes" was overshadowed in that article. She was less than favorable about the newly revised Food Pyramid released in April 2005 by the US Department of Agriculture, claiming its new focus on personal choices increases confusion and gives a much less clear message of optimal dietary intake.

A predominant theme in Dr. Nestle's presentation was the role of big business on the influence of food consumption. Within the US, the food industry spends \$36 billion annually for marketing alone. Strategies often focus on misleading statements and a large percentage of the marketing budget is directed at children. She shared countless examples of "it's now better for

you" in advertisements for popular foods, when in reality, the foods remain high in sugar content and calories. Children are targeted for three reasons: (1) brand loyalty (that will persist into adulthood); (2) the "pester factor" (influence on parent while in the grocery store); and (3) the recent notion that "kid cuisine" should be different from adults (exciting shapes, colors, etc.). Dr. Nestle also shared that a prominent player in the tobacco industry owns a large food corporation and uses similar marketing tactics as previously used to promote cigarettes. There is speculation that "fat is becoming the next tobacco" with respect to corporate deception to the public.

Several alarming statistics were provided. Most notable is the overabundance of the food supply in the US. Currently, there is enough food to provide 3900 kcal daily to each person in the US. This is twice what is needed and an increase in 600 kcal per day since 1980. Over \$1 trillion dollars are spent on food annually and Americans consume one-half of their food intake outside of the home. Because food is "big business," corporate

dollars are large and used to lobby governmental groups and influence decision-making. Deregulation of health claims on foods was given as an example.

Lastly, use of the health care provider groups to endorse food products is also deceiving, yet a powerful force influencing purchasing decisions. The American Heart Association may lend its seal of approval to a low/no-fat product, despite it having a considerable amount of sugar. Additionally, logos such as the American Diabetes Association (ADA) appear on several sugar-laden foods. When one reads the fine print, the manufacturer declares *sponsorship* of the ADA, not necessarily *endorsement* by—yet it is perceived to be one in the same. Like many organizations, the ADA accepts funding/donations from companies whose products may be considered to be in direct conflict (e.g., sponsorship is noted on sugary cereals by Post as well as Coca-Cola) with its mission.

In closing, Dr. Nestle urged critical awareness by all and the need for collaboration among health professionals, the food industry, the government, and an informed public.



So Many Posters, So Little Time...



White *et al.* presented results at year 10 from the follow-up Epidemiology of Diabetes Interventions and Complications (EDIC) study, in which patients with Type 1 diabetes previously treated with intensive therapy (IT) vs. conventional therapy (CT) were compared (919-P). Despite similar HbA1c levels over time, progression of retinopathy was significantly reduced in the former IT group in both adults (48.1% vs. 74.5%, $p < 0.001$) and adolescents (72.6% vs. 86.3%, $p = 0.036$). The difference between IT and CT was statistically significant among adults, but not adolescents, for reduction in severe non-proliferative and proliferative retinopathy, and in need for laser therapy. These observations support the initiation of IT as early as safely possible in both adults and adolescents with diabetes. This remarkable, long-lasting benefit has been termed "metabolic memory."

A side benefit of metformin therapy may be a reduced risk of cancer according to the findings of Donnelly and UK investigators (160-OR). Based on recent work suggesting that the upstream regulator of AMPK (the target enzyme

for metformin) is the protein kinase LKB1 (a known tumor-suppressor), the investigators performed a pilot case-control study. A population of 1,276 patients with Type 2 diabetes hospitalized with cancer in 1993-2001 and 2,452 diabetic controls without cancer were identified and matched for age, diabetes duration, and sex. The investigators found the risk of cancer was indirectly related to amount of metformin and duration of treatment.

Although metformin is contraindicated in patients with heart failure due to concerns of lactic acidosis, there is growing debate around this issue. Eurich *et al.* from Canada, using the Saskatchewan Health database, identified 1833 subjects with incident heart failure and Type 2 diabetes and grouped them by antidiabetic treatment (metformin monotherapy [$n=208$], sulfonylurea monotherapy [$n=773$], or combination therapy [$n=852$]) (457-P). Over an average follow-up period of 2.5 years, metformin alone (HR 0.7) or in combination (HR 0.61) was associated with a significantly lower all-cause mortality rate compared to the sulfonylurea group, with

no difference between groups in time to first hospitalization. While the results of this observational study suggest that metformin may be safe in heart failure patients, these findings need to be confirmed in a randomized, controlled clinical trial.

Peripheral neuropathy is the most common diabetic microvascular complication, with approximately 50% of patients having some form. There are various techniques for diagnosing diabetic polyneuropathy, however their utilization has been controversial. Jurado *et al.* from Spain (68-OR) evaluated four different ways of detecting peripheral neuropathy: vibration perception thresholds by neurothesiometer and quantitative tuning fork, and the Semmes Weinstein monofilament using two standard criteria, in a random sample of 305 Type 2 patients. The investigators compared the findings to that of a comprehensive neurological clinical evaluation. All four methods were shown to have high specificity (94-97%) but relatively low sensitivity (28-52%) for detecting the presence of neuropathy. Thus, these standard tools will miss many patients with early neuropathy.