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Fibrates: The Key to Unlocking Greater Cardiovascular Risk Reduction in Patients with Type 2 Diabetes

At a symposium held in conjunction with the American Association of Clinical Endocrinologists’ Annual Meeting in Chicago, Illinois, three leading specialists discussed the important role fibrates can have in safely and effectively controlling cardiovascular risk in patients with diabetes.

According to the Center for Disease Control (CDC), 20.8 million Americans have type 2 diabetes. Surprisingly, most of these patients will not die from diabetes. They will die from heart disease (Figure 1). Therefore, any treatment regimen for patients with type 2 diabetes must include a means to reduce their risk for cardiovascular events. This risk reduction was the focus of a recent symposium chaired by David G. Robertson, MD, Adjunct Clinical Professor at Emory University, Attending Physician at the Atlanta Diabetes Associates and Principal Diabetes Investigator at the Fuqua Heart Center at Piedmont Hospital in Atlanta, GA.

One reason patients with diabetes are at such high risk for cardiovascular events is that their LDL levels are relatively normal and the patients are believed to be ‘risk free’. Dr. Robertson said, “LDL cholesterol itself is not the driving abnormality that stands out compared to people without diabetes and people without metabolic syndrome,” adding that what is more significant in these patients is their high levels of small dense LDL particles and triglycerides and their low levels of HDL cholesterol. This atherogenic lipoprotein profile has a 2- to 4-fold excess risk of cardiovascular disease in patients with type 2 diabetes (Diabetes Care 2003;26 (suppl 1):S83-S86, Diabetes. 2002;52:453-462).

Since dyslipidemia in patients with diabetes often show low levels of HDL, one viable option for these patients are medications that increase HDL levels. Dr. Robertson used the remainder of his presentation to review some recent trials with fibrates that show their effect on reducing cardiovascular risk in patients with diabetes and dyslipidemia.

Clinical trials

Figure 1. Natural History of Type 2 Diabetes Survival

Heart diseases were involved in the majority of deaths (69.5%) of people with diabetes. Diabetes was listed as cause of death infrequently: 7.7% of males, 13.4% of females.

shown in Table 1, the reductions in relative risk for cardiovascular events seen in the fibrate trials were similar in range to those observed in statin trials (i.e., 10-30% risk reduction). A closer examination of the data, however, leads to some interesting observations. When only patients with diabetes were included in the analysis, the increase in risk reduction was significant (Table 2). Dr. Robertson said, “So it appears that the optimal situation for fibric acid therapy might be those patients with diabetes and those with metabolic syndrome.” To better address this issue, the FIELD study was developed that specifically examined the use of fibrate therapy (fenofibrate) in patients with type 2 diabetes. In this 5-year study involving 9795 patients with diabetes given either fenofibrate (200 mg/d, n=4895) or placebo (n=4900) (Lancet. 2005:366;1849-1861), patients were included in the trial if they had diabetes and a lipoprotein profile that was fairly normal (total cholesterol: 115-250 mg/dL; total cholesterol to HDL ratio of > 4 or triglyceride level > 89 mg/dL). Patients were excluded if they were on a concurrent lipid lowering therapy or had triglycerides > 443 mg/dL. In other words, Dr. Robertson noted that these patients showed no clear indication that they needed to be on lipid lowering therapy. In fact, only 38% of the study population met the specified definition of dyslipidemia (TG > 150 mg/dL and HDL-C < 40 mg/dL in men or < 50 mg/dL in women).

At the end of 5 years, investigators observed that the group given fenofibrate showed a non-significant 11% reduction (placebo – 5.9% event rate; fenofibrate – 5.2% event rate; P=0.16) in coronary heart disease (CHD) events (nonfatal myocardial infarction or CHD death). With regard to the secondary endpoint that measured all cardiovascular disease (CVD) events (composite of CHD events plus total stroke, CVD death, coronary and carotid revascularizations) it was observed that fenofibrate treatment led to a significant 11% reduction in outcomes (placebo – 13.9%; fenofibrate – 12.5%; P=0.035).

Dr. Robertson noted that the results from the FIELD study were confounded by the high percentage of patients who took other lipid lowering agents (predominantly statins) during the course of the study. In the placebo group, 36% of the patients ended up taking a statin to lower lipids compared to 19% in the fenofibrate treated group. Using a Cox regression analysis, the FIELD investigators reevaluated the data with the use of statins as a time-dependent covariate and observed that fenofibrate treatment led to a significant 19% risk reduction in CHD events and a significant 15% risk reduction in CVD events compared to placebo. Dr. Robertson added that fenofibrate-treated patients experienced other benefits as well. For example, there was a 30% reduction in the frequency of laser therapy for retinopathy in the fenofibrate group (placebo – 5.2%; fenofibrate – 3.6%), a 14% reduction in albuminuria (placebo – 11%; fenofibrate – 10%), a 15% increase in regression of albuminuria (placebo – 8%; fenofibrate – 9%), an 18% reduction in hospitalization for angina pectoris (placebo – 5.1%; fenofibrate – 4.3%), and a 31% reduction in vascular or neurologic amputations (placebo – 1.5%; fenofibrate – 1.0%). [All statistically significant findings].

**So it appears that the optimal situation for fibric acid therapy might be those patients with diabetes and metabolic syndrome.”**

**Table 1. Outcomes in Fibrate Trials: Overall Study Populations**

<table>
<thead>
<tr>
<th>Trial</th>
<th>N</th>
<th>Control</th>
<th>Drug</th>
<th>Rel. RR</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Prevention</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HHS</td>
<td>4081</td>
<td>41.4%</td>
<td>27.3%</td>
<td>34%</td>
<td>&lt;.02</td>
</tr>
<tr>
<td>Secondary Prevention</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BIP</td>
<td>3090</td>
<td>15.0%</td>
<td>13.6%</td>
<td>9.4%</td>
<td>.26</td>
</tr>
<tr>
<td>VA-HIT</td>
<td>2531</td>
<td>21.7%</td>
<td>17.3%</td>
<td>22%</td>
<td>.006</td>
</tr>
</tbody>
</table>

Rel. RR indicates relative risk reduction


**Table 2. Outcomes in Fibrate Trials: Diabetic or Metabolic Syndrome Subanalyses**

<table>
<thead>
<tr>
<th>Trial</th>
<th>N</th>
<th>Control</th>
<th>Drug</th>
<th>Rel. RR</th>
<th>P</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Prevention</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HHS*</td>
<td>292</td>
<td>13.0%</td>
<td>3.9%</td>
<td>71%</td>
<td>&lt;.005</td>
<td>11</td>
</tr>
<tr>
<td>Secondary Prevention</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BIP†</td>
<td>1470</td>
<td>18.4%</td>
<td>14.1%</td>
<td>25%</td>
<td>.03</td>
<td>23</td>
</tr>
<tr>
<td>VA-HIT†</td>
<td>769</td>
<td>29.4%</td>
<td>21.2%</td>
<td>32%</td>
<td>.004</td>
<td>12</td>
</tr>
</tbody>
</table>

Rel. RR indicates relative risk reduction

*Patients with TG >204 mg/dL and an LDL/HDL >5 (may or may not have had DM or the MS)
†Patients with the metabolic syndrome
‡Patients with diabetes


**Concluding remarks**

Dr. Robertson ended his presentation by stating “the fibric acid trials, including FIELD, have revealed that fibric acids do have an impact on cardiovascular events and do have an opportunity, even when used in conjunction with statins, to provide evidence of benefit.”
Role of Fibrates in the Reduction of Cardiovascular Risk in Patients With Low HDL-Cholesterol

George Steiner, MD, Professor of Medicine and Physiology at the University of Toronto and Director of the Lipid Research Clinic at the Toronto General Hospital in Toronto, Ontario, Canada continued the symposium with a discussion of the role HDL has in cardiovascular risk.

Dr. Steiner said that studies such as the Quebec Cardiovascular Study (Atherosclerosis. 2000;153:263-272) have shown the inverse relationship between the level of triglyceride and the level of HDL in patients at risk for cardiovascular events. As to which is a better marker for cardiovascular risk, Dr. Steiner argued that the two are too closely connected and said, “I regard the two, from a risk stratification, as being part of a package and very often when you correct the one you correct the other.”

Why is HDL good?
HDLs have many functions in the body. Dr. Steiner noted that they inhibit the oxidation of LDL and the production of atherogenic LDL particles. They also have anti-inflammatory properties and have been shown to decrease endothelial injury. Although these functions are important, Dr. Steiner said that HDL is best known for its removal of cholesterol from the body (reverse cholesterol transport).

How can low HDL levels be increased?
Weight reduction, increased physical activity, smoking cessation, and so forth can all increase HDL levels. Alcohol consumption may also increase HDL levels but Dr. Steiner warned, “I don’t personally advocate alcohol because, although it may in small amounts raise HDL, its detrimental effects can be greater than its beneficial effects.” In regard to pharmacologic therapy, niacin and fibrates are the most effective agents at increasing HDL levels.

Niacin
Niacin increases HDL levels by two possible mechanisms of action: 1) it decreases VLDL production by inhibiting the mobilization of fatty acid from the periphery or directly in the liver. This results in less VLDL triglyceride to exchange with cholesterol ester in the HDL particle and therefore the HDL particle keeps its cholesterol content up; 2) it may directly decrease the removal of HDL from the circulation. Unfortunately, niacin’s efficacy is associated with side effects that may be unsuitable for patients with diabetes. Dr. Steiner said that in addition to its common side effects (flushing, gastric irritation, hyperuricemia, liver problems), niacin treatment can also increase insulin resistance.

Fibrates
Fibrates and PPAR-α agonists can increase HDL levels via 5 ways. They can:
• Increase the activity of the Apo A-1 gene and hence the production of HDL
• Increase the activity in the Apo A-2 gene and hence the production of HDL
• Increase the activity of lipoprotein lipase (increases free Apo A-1)
• Increase the activity and expression of ABC A-1, to increase cholesterol efflux
• Increase the production of SRB-1, the scavenger receptor

The side effects associated with fibrates are very minor, and Dr. Steiner noted that any concern about the occurrence of rhabdomyolysis developing only happens with the older fibrate, gemfibrozil (with a statin) and not with the newer fibrate, fenofibrate (with a statin). Dr. Steiner further noted that if combination fibrate and statin are required then only fenofibrate should be used.

Dr. Steiner also pointed out that fibrates’ unique mechanism of action can lead to improvements in the microvasculature. Dr. Steiner stated that anatomical evidence showing the benefit of fibrate treatment was shown in the Diabetes Atherosclerosis Intervention Study (DAIS) (Lancet. 2001;357:905-910) in which patients given fenofibrate had decreased minimum lumen diameter progression, decreased percent stenosis progression, and a tendency, not significant, in decreased mean sigmoid diameter progression.

Concluding remarks
Numerous benefits exist when HDL levels are increased and both non-pharmacologic and pharmacologic interventions should be explained to patients with low HDL levels.

Assessing the Efficacy and Safety of Fibrate/Statin Combination Therapies in the Management of High Risk Mixed Dyslipidemic Patients

Dyslipidemia treatment often involves the use of statins. “Of course that means that LDL cholesterol is both the focus and the target of your treatment, but that approach unfortunately doesn’t affect other lipoproteins as much as we would like,” began Peter H. Jones, MD, Associate Professor of Medicine in the Section of Atherosclerosis and Lipid Research at Baylor College of Medicine in Houston, TX. In some patients, additional therapy is needed to reduce triglycerides and increase HDL, as addressed in the NCEP ATP III Guidelines which state, “For those high risk patients who have elevated triglycerides and low HDL-C levels, addition of a fibrate or nicotinic acid to LDL lowering ther-
apy can be considered.’ (Circulation. 2004;110:227-239). Dr. Jones noted that the American Diabetes Association (ADA) expanded on this to state that while LDL cholesterol lowering is the first priority and that statins are the preferred treatment, they also state that other agents can be used to lower LDL cholesterol, such as bile acid resins, cholesterol absorption inhibitors, fenofibrate or niacin. The ADA notes that the second priority for dyslipidemia treatment is to raise HDL levels (with niacin or fibrates) and the third priority is to lower triglycerides (with fibrates, niacin, or high dose statin) (Diabetes Care. 2004;27 (suppl 1):S68-S71). Dr. Jones also noted that the ADA guidelines recognize that many patients with diabetes have mixed dyslipidemia or combined hyperlipidemia and Dr. Jones said, “frequently what you’ll see in patients with diabetes and the metabolic syndrome is the atherogenic dyslipidemia with high triglycerides and low HDL.” The ADA recommends that first treatment choice for these patients is high dose statins, while second and third choices are a statin plus a fibrate or a statin plus niacin. Dr. Jones noted that while the rationale for favoring monotherapy with a statin is understandable, the statins’ ability to increase HDL and lower triglycerides is limited. “I tend to focus, in patients with combined hyperlipidemia/mixed dyslipidemia, particularly if they have low HDL, on fibrates or niacin alone with a statin in combination, and I tend to preferentially use fibrates because niacin may have some problems with worsening insulin resistance,” said Dr. Jones. To illustrate the logic behind the use of fibrates and statins together as a preferred treatment option, Dr. Jones discussed the mechanism of actions of the two drugs and concluded the combination of the two can safely offer a greater risk reduction compared to monotherapy (Table 3).

**Combination statin/fibrate therapy**

To test this hypothesis, Athyros et al. (Diabetes Care. 2002;25:1198-1202) compared the combination of a statin (atorvastatin) and a fibrate (fenofibrate) with monotherapy of each of the two medications in 120 patients with diabetes with combined hyperlipidemia. As shown in Figure 2, combination therapy led to almost all patients achieving their ADA targets for LDL and triglyceride levels and the combination had a significantly better impact on raising HDL levels in most patients. Similar improvements have also been seen with the combination of rosuvastatin with fenofibrate (Res Clin Pract. 2004;64:137-151) and in simvastatin with fenofibrate (Am J Cardiol. 2005;15:95:462-468). In that latter study, patients with combined hyperlipidemia were given simvastatin (20 mg/d) alone (n=207) or simvastatin (20 mg/d) and fenofibrate (160 mg/d) (n=411). After 12 weeks of treatment (and 6 weeks of diet therapy) the combination therapy group had more significant improvements in reducing triglycerides and LDL levels and increasing HDL levels.

**Concluding remarks**

Dr. Jones concluded the symposium by stating that the safety and efficacy of combination therapy with statins and fibrates will be best addressed when the ongoing ‘ACCORD Trial’ is complete in which simvastatin is compared to simvastatin plus fenofibrate involving over 5000 patients with diabetes. Dr. Jones is optimistic that the results will show the combination to be safe and effective and may also show the combination to decrease cardiovascular risk.

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**Table 3. Rationale for Fibrate/Statin Combination Treatment**

- Statins reduce the number of atherogenic (apo B-containing) lipoprotein particles through hepatic LDL-receptor–mediated process
- Fibrates reduce TG and postprandial lipemia by PPARα-mediated enhanced clearance (increased LPL activity, decreased apo CIII), and they increase LDL particle size
- Both statins and fibrates can reduce hepatic VLDL production and increase apo A1 production
- This observation raises the possibility that combined drug therapy with fibrates and statins will offer a greater risk reduction than can be achieved with LDL lowering alone

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**Figure 2. More Patients Achieve ADA Goals With Combined Drug Therapy**

![Graph showing ADA goals achievement with combined drug therapy](image)

All values are *P*<0.001 versus baseline
1*P*<0.05 versus fenofibrate
1*P*<0.05 versus both monotherapies
1*P*<0.05 versus atorvastatin


---

**Statins**

> Statins reduce the number of atherogenic (apo B-containing) lipoprotein particles through hepatic LDL-receptor–mediated process

**Fibrates**

> Fibrates reduce TG and postprandial lipemia by PPARα-mediated enhanced clearance (increased LPL activity, decreased apo CIII), and they increase LDL particle size

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Maximizing Therapeutic Response: A Multifaceted Approach to Osteoporosis Management

At a symposium held in conjunction with the American Association of Clinical Endocrinologists’ Annual Meeting in Chicago, Illinois, Michael Kleerekoper, MD, FACP, MACE of Saint Joseph Mercy Hospital in Ann Arbor, MI and Professor of Medicine in the Department of Internal Medicine and Obstetrics & Gynecology, and Pathology at Wayne State University School of Medicine in Detroit, MI, chaired a meeting with three leading experts on the management of osteoporosis to discuss ways to improve both treatment outcome and ways to monitor treatment outcome.

A multitude of structural changes occur within bones as we age and with those changes come increased risk of developing osteoporosis. While most research in osteoporosis has focused on trabecular bones, it is becoming clear that cortical bones are equally important and was the subject of the talk by M. Susan Burke, MD, FACP, Clinical Assistant Professor of Medicine, Thomas Jefferson University in Philadelphia, PA and Director of Internal Medicine Clinical Care Center at Lankenau Hospital in Wynnewood, PA.

There are several structural properties of cortical bone that are associated with fracture (Table 1). Two properties of cortical bone that can be modified are porosity and thickness.

Cortical porosity
Cortical porosity has been shown to increase significantly with increasing age and to be associated with femoral neck fracture (Radiology. 2000;217:179–187).

Non-modifiable
- Hip axis length
- Femoral neck angle
- Femoral neck length

Potentially modifiable
- Bone diameter
- Cross-sectional area

Modifiable
- Cortical porosity
- Cortical thickness

<table>
<thead>
<tr>
<th>Table 1. Structural Properties of the Hip Associated With Fracture</th>
</tr>
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<tbody>
<tr>
<td><strong>Non-modifiable</strong></td>
</tr>
<tr>
<td>• Hip axis length</td>
</tr>
<tr>
<td>• Femoral neck angle</td>
</tr>
<tr>
<td>• Femoral neck length</td>
</tr>
<tr>
<td><strong>Potentially modifiable</strong></td>
</tr>
<tr>
<td>• Bone diameter</td>
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<tr>
<td>• Cross-sectional area</td>
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<tr>
<td><strong>Modifiable</strong></td>
</tr>
<tr>
<td>• Cortical porosity</td>
</tr>
<tr>
<td>• Cortical thickness</td>
</tr>
</tbody>
</table>


Increased cortical porosity associated with femoral neck fracture

- Increased proportion of giant canals (composite osteons)
  - May result from merging of ≥2 simple osteons during bone resorption
  - Larger diameter but thinner walls than simple osteon
- Hip fractures correlate with number and width of composite canals


Figure 1. Increased Cortical Porosity

Osteoporosis Outcomes with Bisphosphonates: Cortical vs. Trabecular Bone

M. Susan Burke, MD, FACP

This symposium was made possible through an educational grant provided by Merck & Co., Inc.
increased risk for femoral neck fracture” (Figure 1).

Preliminary data suggest that cortical porosity may be reduced with bisphosphonate treatment. Dr. Burke noted a study by Roschger et al. (Bone. 2001;29:185-191) in which transiliac biopsies were performed on 24 patients who had taken either alendronate 10 mg daily or placebo for 2 or 3 years. Two-dimensional morphometry demonstrated a 46% reduction in cortical porosity with alendronate treatment (Figure 2). Although a different study with risendronate (5 mg taken daily for five years) (Calcif Tissue Int. 2004;75:469-476) did not show a change in cortical porosity, it is important to note that these two studies were designed differently and cannot be compared. Additional studies of all bisphosphonates are needed to further evaluate their impact on this property.

Cortical thickness

Decreased cortical thickness has also been associated with hip fracture (Osteoporosis Int. 2006;17:231-236). In a placebo-controlled study by Greenspan et al., hip structure analysis from DXA scans performed on women who received alendronate, estrogen, or both showed that alendronate increases cortical thickness in the femoral neck, intertrochanteric region and femoral shaft (J Bone Miner Res. 2005;20:1525-1532). Another study (Bare S, et al. Abstract SA414. 27th Annual Meeting of the American Society for Bone and Mineral Research; Nashville, Tennessee) showed that alendronate treatment reduced the remodeling rate of the endocortical area but did not have an impact on periosteal surface of cortical bone. Dr. Burke pointed out that this is a desirable effect for a therapeutic agent. Periosteal apposition (expansion of the diameter of long bones) occurs with age as an adaptation to bone loss; the resultant increased diameter of bone helps to maintain bone strength. “You wouldn’t want your agent to impact the periosteal area, you would want your agent just to reduce the endocortical resorption that occurs with aging.”

Concluding remarks

Dr. Burke ended her presentation by stating, “reduction of fractures in cortical rich areas with therapeutic agents requires substantial effects on both bone turnover and bone mineral density. Certain modifiable structural properties of the hip, such as cortical porosity and cortical thickness, are associated with fracture. How treatment impacts these properties is certainly going to be the subject of further investigation.”

Interpretation of Treatment Response Rates and Secondary Causes of Osteoporosis

Marjorie M. Luckey, MD, FACE, Associate Professor, Department of Obstetrics, Gynecology and Reproductive Science, Mount Sinai School of Medicine, New York and Director of Osteoporosis and Metabolic Bone Disease Center, Saint Barnabas Ambulatory Care Center in Livingston, NJ continued the symposium with a discussion of monitoring treatment outcomes in patients with osteoporosis. Dr. Luckey began, “the goal of therapy and, therefore, the gold standard of measuring therapeutic efficacy, is fracture prevention: since fracture risk reduction cannot be directly measured in individual patients, surrogate markers must be used instead.”

At first glance, bone mineral density and bone turnover markers appear to be ideal surrogates of therapeutic efficacy. In untreated patients, both of these parameters are predictive of fracture risk and both respond favorably to therapeutic intervention, as shown in Figure 3. A closer look, however, reveals that neither of these surrogates is ideal. Dr. Luckey stated, “there is significant controversy about how much these changes contribute to therapeutic efficacy and how they should be interpreted in individual patients,” adding, “when using these surrogates in clinical practice, it is critical to understand what the changes are and are not telling us about our patients.”

Looking more closely at bone mineral density data, Dr. Luckey noted that several meta-analyses (such as Wasnick and Miller, J Clin Endocrinol Metab. 2000;85:231-236) suggest a positive relationship between gains in bone mineral density and reduction of fractures. As such, cautioned Dr. Luckey, increases in bone density on therapy do not appear to be necessary for fracture prevention in individual patients. To illustrate, Dr. Luckey referred to a study by Watts et al. (J Clin Densitom. 2004;7: 255-261) which reexamined the three pivotal alendronate trials, and found that patients who lost bone mineral density were at highest risk of fracture while those who either maintained BMD or who gained BMD were at similarly lower risk. Similar results were seen in the FIT trial in which alendronate reduced fractures regardless of the changes in BMD, but those patients who continued to lose BMD remained at increased risk for fractures (Figure 4) (Osteoporosis Int. 2005;16:842-848). Dr. Luckey added,
“These findings suggest other unmeasured bone properties must account for the balance of the improvement in bone strength with therapy.” The clearest message from the BMD data is that “the primary goal of monitoring BMD is to assure prevention of bone loss and identification of those who continue to lose rather than requiring gains in bone density to declare therapeutic success.”

In clinical trials, bone turnover markers appear to be somewhat stronger predictors of efficacy for antiresorptive therapies. For example, using data from the risedronate trials, Eastell et al. (J Bone Miner Res. 2000;15:594), showed a strong relationship between the decline in turn-over markers and decreased fractures. Although this analysis suggests a plateau in the relationship between turnover markers and fracture risk, Dr. Luckey noted that no plateau was observed in a similar analysis of data from the alendronate trials (J Bone Miner Res. 2004;19:1250–1258). Unfortunately, cautioned Dr. Luckey, these markers are subject to a high degree of biological and assay variability which makes it difficult to reliably predict the rate of bone loss or to be certain of the response to therapy in individual patients. With that being said, serial markers may be of value in evaluating patients on therapy if they are collected under strictly standardized conditions. Decreases of ≥50% in urinary markers of bone resorption after 3 months or a ≥30% decrease in serum markers of bone formation after 6 months of antiresorptive therapy generally indicate successful therapy while a suboptimal response should stimulate further investigation and discussion to identify the cause.

Why does treatment fail

1. Measurement Error

Dr. Luckey noted that technical errors in bone density measurements and over interpretation of serial results seem to be the most common causes of apparent treatment failure. Serial bone density measurements can be affected by changes in machine, patient positioning, and scan analyses, as well as by new artifacts. For this reason, clinicians must carefully review scans to assure comparability prior to interpretation. In addition, knowledge of the least significant change (LSC) of the measurements specific to the bone density laboratory is required to be confident that the change noted is a biological change in the patient rather than one simply due to technical variability.

2. Poor persistence and/or improper dosing

Dr. Luckey noted that persistence with most medical therapies is quite poor and cited a study by Cramer et al. who followed patients taking a bisphosphonate and found that over half of the patients had stopped taking the medication by one year (most stopped taking the medication after their first prescription is filled) (J Bone Miner Res. 2004;19:suppl S448). Treatment failure can also occur if patients take their medication incorrectly. To illustrate, Dr. Luckey discussed a phone survey which found that a quarter of patients taking bisphosphonates took their medication with a calcium supplement or with food/drink, all of which block bisphosphonate absorption (Figure 5).

3. Inadequate intakes of calcium and vitamin D

Dr. Luckey also presented the results of a survey of household purchase records in which 73% of the households of patients on bisphosphonates did not purchase enough calcium to take even one tablet a day and 40% of them purchased...
Maximizing Therapeutic Response: A Multifaceted Approach to Osteoporosis Management

**Figure 5. Patient Compliance with Proper Dosing: 2005 Consumer Survey by Harris Polling**

**Calcium Supplement with Actonel/Fosamax**

- Take at Same Time or Within 30 Minutes (n = 372)
  - Yes: 74%
  - No: 26%

**Food or Beverage with Actonel/Fosamax**

- Take at Same Time or Within 30 Minutes (n = 372)
  - Yes: 77%
  - No: 23%

Data available from P&G Pharmaceuticals

Michael F. Holick, PhD, MD, Professor of Medicine, Physiology and Biophysics in the Section of Endocrinology, Diabetes and Nutrition at Boston University School of Medicine in Boston, MA concluded the symposium with a discussion on the importance of vitamin D and its role in maintaining bone health and in treating osteoporosis.

The major function of vitamin D is to provide adequate calcium and phosphorus to the body in order to maintain optimal metabolic functions. Vitamin D is also necessary for mineralization and maintenance of the skeleton. Dr. Holick said, “subclinical vitamin D deficiency will precipitate and exacerbate osteoporosis because it causes secondary hyperparathyroidism and increases osteoclastic activity,” adding, “more importantly, it also causes mineralization defect.”

To illustrate the importance of vitamin D in bone health, Dr. Holick cited a study he was involved with showing that tanners who had robust healthy levels of 25(OH)-vitamin D (~45 ng/mL) also had higher bone density while non-tanners had 25(OH)-vitamin D deficiency (~18 ng/mL) and lower bone densities (*Am J Clin Nutr.* 2004;80:1645-1649). These results are comparable to data from the NHANES database showing patients with higher 25(OH)-vitamin D levels had higher bone densities (*Am J Med.* 2004;116:634-639).

Since many persons with osteoporosis are vitamin D deficient, alendronate (Fosamax) now comes with vitamin D. Dr. Holick said, “if you put them on Fosamax plus D, they have higher 25(OH)-vitamin D levels then those on Fosamax.” Dr. Holick pointed out that in addition to helping bone density, the addition of vitamin D can help muscle tone which in turn can also reduce risk of falling. Dr. Holick stated that studies with ambulatory elderly women taking vitamin D found the women to have decreased risk of falling and decreased sway. “These trials have been very convincing, overall, to suggest if you’re on at least 800 units of vitamin D a day, it will decrease risk of falling by 22% and presumably decrease risk of fracture,” said Dr. Holick.

**Concluding remarks**

Generally, antiresorptive therapies are highly effective in preventing bone loss and reducing the risk of fractures. A statistically significant decrease in bone mineral density following treatment may indicate poor adherence to therapy, improper dosing or an underlying abnormality. Because bone loss is associated with a higher risk of fractures, it should prompt further evaluation and intervention if a cause is identified.

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**Vitamin D for Bone Health, Neuromuscular Health and the Prevention of Chronic Diseases**

Michael F. Holick, PhD, MD

Dr. Luckey also reviewed data from 173 otherwise healthy postmenopausal women with osteoporosis which demonstrated that 44% of these women had an occult underlying disease process that could influence their response to therapy. “The most common disorders were vitamin D deficiency, hypercalciuria and malabsorption,” said Dr. Luckey, adding that similar results were found when other investigators evaluated patients who were losing bone mass despite taking a bisphosphonate: “50% were found to have a previously unsuspected disorder by laboratory testing” (Lewiecki EM, et al. *J Bone Miner Res.* 17(suppl) S367).

**Concluding remarks**

Generally, antiresorptive therapies are highly effective in preventing bone loss and reducing the risk of fractures. A statistically significant decrease in bone mineral density following treatment may indicate poor adherence to therapy, improper dosing or an underlying abnormality. Because bone loss is associated with a higher risk of fractures, it should prompt further evaluation and intervention if a cause is identified.
Examining the Future of Incretin Therapy: A Retrospective and Interpretive Analysis

At a symposium held in conjunction with the American Association of Clinical Endocrinologists’ Annual Meeting in Chicago, Illinois, leading endocrinologists discussed the way incretin mimetics can help change the way we treat diabetic patients. The symposium was moderated by George Grunberger, MD, FACP, FACE, Chairman of the Grunberger Diabetes Institute and Clinical Professor in the Department of Internal Medicine and Genetics, Wayne State University School of Medicine, Detroit MI.

The Physiology of the GLP-1 System and Approaches to Drug Development

The ‘incretin effect’ refers to the difference in insulin response when a person is given oral glucose compared to intravenous glucose and the ‘incretins’ refer to the gut peptides that stimulate glucose-dependent insulin release. One of the main ‘incretins’ that affects glucose levels is glucagon-like peptide 1 (GLP-1) and its role in controlling glucose levels was discussed by Patrick J. Boyle, MD, Professor of Medicine in the Department of Medicine at the University of New Mexico School of Medicine in Albuquerque, NM. Dr. Boyle began by saying that studies in the 1980s determined that most of the ‘incretin effect’ was due to GLP-1 secreted from L-cells in the intestine. While GLP-1 receptors are present throughout the body, it is believed that receptors on the pancreatic islet cells that regulate insulin (increase secretion) and glucagon (decrease secretion) are responsible for GLP-1’s actions on controlling postprandial glucose levels. This hypothesis is supported by numerous human and animal studies showing that GLP-1 improves the health and function of pancreatic islet cells. For example, 6 weeks of GLP-1 infusion in humans led to a gradual improvement in insulin release (i.e., β-cell function). In addition, GLP-1 infusion in an animal model of diabetes (Zucker fatty rats) has been shown to affect β-cells (increases β-cell mass, enhances β-cell proliferation and decreases β-cell apoptosis) (Endocrinol. 2002;143:4397-4408). Dr Boyle noted that these studies are supported by in vitro studies showing that GLP-1 helps differentiate stem cells into β- and α-cell precursors (Diabetes. 2004;53:2143-2152).

Exenatide

Since GLP-1 is quickly degraded in the circulation (by the enzyme DPP-4), medications that are GLP-1 agonists or DPP-4 inhibitors have been investigated. To date, only one medication has been approved by the FDA and that is the GLP-1 agonist, exenatide. Dr. Boyle said, “exenatide binds to the GLP-1 receptor quite nicely, has high affinity and, after an injection of 50 nanomole there is little or no degradation in the following six hours. From a therapeutic standpoint, again, this ends up being a nice target peptide because it’s in the circulation at a high concentration for an established period of time.” Initial studies in humans established that exenatide could enhance first and second phase insulin secretion in diabetics (Figure 1) (Diabetes. 2004;suppl 2): A82). Surprisingly, while much of the in vitro and animal studies have shown GLP-1 to slowly improve the health of pancreatic islet cells, exenatide can still have a significant acute effect. As explained by Dr. Boyle, infusion of exenatide for only 3 hours can result in an increasing insulin release that is glucose dependent (Diabetes. 2004;53:2397-2403). In an elegant study by Degn and colleagues, slowly decreasing glucose levels in normal individuals leads to increasing levels of glucagon that can be attenuated by an exenatide infusion (Diabetes. 2004;53:2397-2403). Dr. Boyle believes that much of the effects of exenatide on managing postprandial glucose are due to its ability to inhibit glucagon release in type 2 diabetics but noted that more studies are needed to confirm this.

Other GLP-1 effects

In addition to the above mentioned actions by GLP-1, Dr. Boyle also said that GLP-1 can lower glucose levels by two other mechanisms: by reducing gastric emptying and by stimulating satiety centers in the brain. Dr. Boyle said, “normal individuals have a slower rate of gastric emptying than people with type 2 diabetes in the early phases of the disease,” adding, “that studies have shown that 6-week infusion GLP can lead to slower gastric emptying in diabetic patients” (Diabetologia. 1996;39:1546-1553). In addition, GLP-1 is an appetite suppressor. In a study by Zander et al., a 6-week infusion of GLP-1 led to a significant decrease in body weight (Lancet. 2002;359:824-830) that was believed to be due to the activation of GLP-1 receptors in the central nervous system that...
William T. Cefalu, MD, Douglas L. Manship, Sr., Professor of Diabetes and Chief of the Division of Nutrition and Chronic Diseases at the Pennington Biomedical Research Center at Louisiana State University System in Baton Rouge, LA continued the symposium with an overview of the clinical trials published with the incretin mimetics. At present, only exenatide has been FDA approved and was the focus of his presentation. Dr. Cefalu summarized the three large clinical trials with exenatide showing it reduced A1C, reduced postprandial glucose levels, and reduced body weight over a 30-week period (Diabetes Care. 2004;27:2628-2635. Diabetes Care. 2005;28:1083-1091. Diabetes Care. 2005;28:1092-1100). Dr. Cefalu said, “this is what separates the GLP-1 agonist from the other therapies we use. It’s the only class that really lowers glucose, and at the same time lowers the weight.” Concerning exenatide’s adverse event profile, Dr. Cefalu noted that in the clinical trials in which exenatide is given with a sulfonylurea, hypoglycemia may occur in some of the patients and it is recommended that the sulfonylurea dose be reduced. In addition, some patients may report mild to moderate nausea and the nausea improves over time. Dr. Cefalu said, “The patient needs to be educated on what to expect as far as gastrointestinal concerns. Most patients can tolerate the nausea knowing it will get better over time and knowing they’re going to get the benefit of glucose control and the weight loss.”
What are the long-term benefits of incretin therapy?

A one year open label extension of the 30-week trials was presented by Blonde and colleagues at last year’s American Diabetes Association Annual Meeting (Poster 447-P). As shown in Figure 2, A1C levels were maintained over the course of the 82-week study and in the patients who began with placebo then given exenatide at week 31, showed a dramatic reduction in A1C. Surprisingly even as A1C levels stabilized in these patients, they continued to lose weight (Figure 3). Since GLP-1 acts differently in the periphery (glucose control) than in the central nervous system (satiety), there is no correlation between the amount of weight loss and the drop in A1C but Dr. Cefalu did note that generally, more weight loss occurred in patients with greater BMI. Dr. Cefalu said, “the greater the weight loss appears to be in those individuals who probably need the most weight loss.” The improvements in glucose levels and the improvements in body weight may be responsible for the additional observation that these patients had improvements in blood pressure and lipid levels.

**Can incretins control both basal and postprandial glucose?**

One of the advantages that exenatide may have over many other diabetic therapies is its ability to reduce both fasting and postprandial glucose levels. For example, Dr. Cefalu discussed a study by Heine and colleagues comparing exenatide with insulin-glargine and showed both treatments to have similar blood glucose profiles prior to treatment (Ann Intern Med. 2005;143:559-569). Dr. Cefalu said, “In this particular study, once again, the exenatide-treated patients had a reduction of about 5.1 pounds as opposed to an increase in four pounds for the insulin treated group — a difference between the two groups of about nine pounds.”

**Other incretin based therapies**

In addition to exenatide, Dr. Cefalu noted that other incretin-based therapies are in development, including a GLP-1 agonist (liraglutide) undergoing phase 2 studies and three DPP-4 inhibitors undergoing phase 3 (vildagliptin, sitagliptin) or phase 2 studies (saxagliptin). All of these have been shown to reduce A1C levels in studies. The main difference between the GLP-1 agonist exenatide and the DPP-4 inhibitors appears to be weight loss. Patients taking a DPP-4 inhibitor neither gain nor lose weight whereas patients taking a GLP-1 agonist generally lose weight.
Analysis of the Initial Outcomes of Incorporating the Use of Exenatide One Year Later

Carol Hatch Wysham, MD, FACE
Clinical Assistant Professor of Medicine at the University of Washington, College of Medicine, Seattle and Clinical Assistant Professor of Pharmacotherapy at Washington State University in Spokane, WA concluded the symposium. Dr. Wysham was a principal investigator in one of the clinical trials with exenatide and provided the audience with an example of one of the patients that was enrolled in the clinical trial to illustrate the safety and efficacy profile of exenatide.

This patient had been on placebo for the first 12 weeks of the study then switched to exenatide for 40 weeks during the open label extension. Dr. Wysham described the patient as a 62-year-old male, with a type 2 diabetes for seven years. He came into the study on metformin, 850 t.i.d, but had never had good glucose control. Initial A1C was 8.2 percent, his weight was 227 pounds, and mean fasting glucose was approximately 168.

Wysham described the patient as a 62-year-old male, with a type 2 diabetes for seven years. He came into the study on metformin, 850 t.i.d, but had never had good glucose control. Initial A1C was 8.2 percent, his weight was 227 pounds, and mean fasting glucose was approximately 168. At the end of 12 weeks of metformin and placebo, his profile had not changed but following the open label extension plus continued use for 3 years following the switch, the patient’s medical profile is vastly improved (Table 1).

Dr. Wysham noted that in clinical trials, approximately 25% of the patients did not lose any weight and also said that in her practice, about 15% of her patients do not lose weight. In regard to nausea, Dr. Wysham stated that it occurs in at least half if not more of her patients taking exenatide and said that approximately 10% of her patients cannot tolerate the medication. Dr. Wysham said, “most patients in my practice report improvement within about three to seven days after beginning therapy. I’ve had people who have had pretty significant nausea, last as long as three weeks,” adding, “I encourage patients to eat low fat and to eat slowly when they’re first getting on the medication and have used low dose meclozine in patients who were willing to continue to work through the medication side effects.” Dr. Wysham reiterated what Dr. Cefalu said that if the patient knows nausea may develop they are often willing to tolerate it temporarily.

“I encourage patients to eat low fat and to eat slowly when they’re first getting on the medication and have used low dose meclozine in patients who were willing to continue to work through the medication side effects.”

Concluding remarks
Dr. Wysham ended the symposium by reminding the audience that antihyperglycemic therapy that is only directed at correcting the imbalance of insulin action and secretion have limited value due their many shortcomings (i.e., weight gain, hypoglycemia, poor postprandial control, progressive beta cell function loss). In contrast, therapy with exenatide is associated with improved glycemic control, modest weight loss, and low incidence of hypoglycemia.

Carol Hatch Wysham, MD, FACE

Table 1. Case Study: Ongoing Use

<table>
<thead>
<tr>
<th>Clinical observations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight dropped steadily until month 12 into LTE, then leveled off until trip to Argentina</td>
</tr>
<tr>
<td>After enforcing lifestyle change, weight and A1c dropped further</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patient observations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continues to feel well. Plans to continue exenatide after study ends</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>A1c (%)</th>
<th>Weight (lbs)</th>
<th>BMI</th>
<th>Mean FBG (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>8.2</td>
<td>227</td>
<td>30.8</td>
</tr>
<tr>
<td>Week 30</td>
<td>8.2</td>
<td>227</td>
<td>30.8</td>
</tr>
<tr>
<td>Week 42</td>
<td>6.9</td>
<td>223</td>
<td>30.3</td>
</tr>
<tr>
<td>Week 82</td>
<td>5.3</td>
<td>211</td>
<td>28.6</td>
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<tr>
<td>Year 2</td>
<td>5.3</td>
<td>217</td>
<td>29.4</td>
</tr>
<tr>
<td>Year 2.5</td>
<td>5.3</td>
<td>217</td>
<td>29.4</td>
</tr>
<tr>
<td>Year 3</td>
<td>5.0</td>
<td>205</td>
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</tr>
</tbody>
</table>

Actual case study.
Through the Looking Glass: Current and Future Perspectives on the Role of Hormonal Interplay in Glucose Homeostasis

At a symposium held in conjunction with the American Association of Clinical Endocrinologists’ Annual Meeting in Chicago, Illinois, three leading specialists discussed how amylin can control postprandial glucose levels in patients with diabetes.

Introduction

A symposium moderated by Paul Jellinger, MD, MACE, past president of AACE and the American College of Endocrinology (ACE) and Professor of Medicine on the voluntary faculty at the University of Miami in Miami, FL began with an overview of important aspects of glycemic control in diabetic patients followed by the observation that even when fasting blood sugar is normalized, postprandial hyperglycemia remains problematic and is often overlooked. Dr. Jellinger said, “Without looking for postprandial hyperglycemia, you would never know that a good part of a patient’s day may be spent in the hyperglycemic state.”

One option to control postprandial hyperglycemia is the peptide amylin and Dr. Jellinger introduced the three speakers who provided an overview of amylin’s role in reducing postprandial glucose levels in diabetic patients.

Pathophysiology and Pharmacokinetics as Well as Current Clinical Trial Data

Stephen L. Aronoff, MD, FACE, Clinical Associate Professor of Medicine at the University of Texas Southwestern Medical School, Clinical Endocrinologist, Endocrine Associates of Dallas and Director of the Research Institute of Dallas in Dallas, TX began his presentation by noting that most patients on insulin continue to have postprandial glucose levels that rise more than 100 mg/dL above the preprandial level. Dr. Aronoff said, “In trying to obtain near-normal control, we do a very poor job of controlling the postprandial glucose and we put our patients at increased risk of hypoglycemia.”

Numerous factors are responsible for diabetics having exaggerated postprandial glucose, including their paradoxically elevated glucagon levels, which increase hepatic glucose output. Furthermore, they have accelerated gastric emptying rates. One natural peptide that can control both of these contributors to postprandial hyperglycemia is the peptide amylin.

Amylin

Pancreatic β-cells secrete both insulin and amylin. Dr. Aronoff said, “Type 1 diabetics are almost totally deficient in amylin just as they are in insulin,” adding, “Type 2 diabetics tend to have basal amylin levels that appear to be near normal but in response to a meal, just like insulin, they fail to secrete more.” Under normal conditions, amylin suppresses glucagon (thus decreasing hepatic output), regulates gastric emptying, and promotes satiety. All of these actions are impaired in diabetic patients following a meal.

Pramlintide

Pramlintide is a synthetic analog of amylin and studies have shown pramlintide can mimic three important actions of amylin. It reduces inappropriately high postprandial glucagon secretion, slows gastric emptying and reduces caloric intake (Metabolism. 2002;51:636-641. Horm Metab Res. 2002;34;504-508. Diabetologia. 1998; 41:577-583. Diabetologia. 2005; 48: 838-848). Dr. Aronoff noted that pramlintide is indicated to be given at mealtime as adjunct therapy for both type 1 and type 2 diabetics who are currently taking insulin but unable to reach their treatment goal.

This symposium was supported by an unrestricted educational grant from Amylin Pharmaceuticals.
Pramlintide and clinical trials

Dr. Aronoff summarized the major clinical trials involving adjunct pramlintide therapy in patients with type 2 diabetes. As shown in Figure 1, taking pramlintide at mealtime significantly lowered postprandial glucose excursions in type 2 diabetics also taking insulin. In addition to lowering postprandial glucose levels, patients taking pramlintide had significantly lower A1C, required significantly less insulin, and had significant weight loss (Figure 2). Similar results were observed in patients with type 1 diabetes. Dr. Aronoff said, “in the type 1 diabetics, glycohemoglobin fell significantly within four weeks and was maintained significantly lower up through 26 weeks of the trial. The patients who were on pramlintide tended to have little change in insulin requirements, but those on placebo had a significant increase in insulin requirements. Further, the patients on placebo tended to gain weight while the patients on pramlintide lost weight.”

Dr. Aronoff stated that the adverse events reported with pramlintide are generally gastrointestinal (i.e., nausea) and more common in type 1 diabetics than in type 2 diabetics. “In all the clinical trials with pramlintide, less than 5% of patients dropped out of the studies because of persistent or severe nausea,” stated Dr. Aronoff. In the original trials, hypoglycemia did occur in some type 1 diabetic patients taking pramlintide but Dr. Aronoff noted that this was likely due to the original trial design which used fixed insulin dosing. In trials in which the dosing was titrated, no increased risk of hypoglycemia occurred.

Concluding remarks

Dr. Aronoff ended his presentation by saying, “pramlintide is a synthetic analog of human amylin which is a naturally occurring neuroendocrine hormone synthesized by the pancreas and co-secreted with insulin. It regulates the rate of glucose appearance in the circulation. It reduces postprandial hyperglycemia and glucose fluctuations and it improves glycemic control with mean reduction of weight.”
Case Studies in the Current Treatment of Patients With Type 1 and Type 2 Diabetes – Where We Are Now

David Kruger, MSN, APRN-BC, BC-ADM, nurse practitioner in diabetes at the Henry Ford Health System in Detroit, MI was heavily involved with the clinical trials discussed by Dr. Aronoff and shared some of her insights on how to treat patients with pramlintide more safely and effectively.

**Patient choice**
Ms. Kruger said, “pramlintide should be considered only in patients with insulin-using type 1 or type 2 diabetes who have failed to achieve treatment goals.” Ms. Kruger added that the list of patients that should not receive pramlintide may shorten as we learn more about pramlintide but at present, she said the medication should not be used for patients with the following criteria:

- Poor compliance with current insulin
- Poor compliance with self-monitoring
- A1C > 9%
- Recurrent severe hypoglycemia
- Hypoglycemia unawareness
- Confirmed gastroparesis
- Use of medications that stimulate gut motility
- Children

**Dosing (for type 2 diabetes)**
Ms. Kruger said that patients with type 2 diabetes should start a pramlintide dose of 60 mcg (10 units) at mealtime while reducing mealtime insulin by 50%. When no significant nausea occurs for 3-7 days, the pramlintide can be increased to 120 mcg (20 units). Concerning nausea, Ms. Kruger said, “if a patient is having nausea, wait until the nausea passes before you increase the dose. If you increase the dose and the patient gets nausea, go back to the last dose and wait a little bit longer. And in some instances you might find that the patient gets nausea at breakfast but not at lunch and dinner so I have some patients who take a smaller dose at breakfast and they take a larger dose at lunch and dinner. So that has to be very individualized.” Ms. Kruger also noted that when you start pramlintide, “you do want to follow the schedule of decreasing the insulin dosing. It’s really important. Are there patients that don’t need a decrease in their insulin dosing? Absolutely. But you’re not going to know right off the bat who those patients are.”

**Other factors**
Since one of pramlintide’s mechanisms of action is to activate central satiety centers, Ms. Kruger said that patients taking pramlintide need to recognize those signals of being full. Ms. Kruger said, “I tell patients to take less food than you think you’re going to need, chew slow and pay attention to the sense of fullness. Stop eating when you are full.” Symlin does not need to be adjusted for physical activity. If a patient is experiencing hypoglycemia it’s the insulin that causes the hypoglycemia, not the pramlintide and if the patient is having hypoglycemia, then you need to adjust insulin.

Ms. Kruger said, “pramlintide should be considered only in patients with insulin-using type 1 or type 2 diabetes who have failed to achieve treatment goals.”

Ms. Kruger also stated that pramlintide should be given subcutaneously in the abdomen or thigh and stressed that it should be injected at least 2 inches away from the insulin site to avoid mixing (and the two drugs should never be mixed). Ms. Kruger noted that it should be administered just prior to each meal and if a snack is greater than 250 calories or greater than 30 grams of carbs, they can take a fourth injection.

**Case study**
Ms. Kruger ended her presentation with a case study showing the benefits of adding pramlintide to a treatment regimen. Ms. Kruger said, “Sheri is 57 years old with a nine-year history of diabetes, struggled with her treatments, very similar to what we all see in practice. A1C is elevated. Treatment has progressed over the years. She started with metformin. She couldn’t tolerate the metformin, was discontinued for GI symptoms. TZD was added. She gained 20 pounds, refused to take it. We started her on insulin. Despite the insulin regimen, A1C was 10.3. She weighed 258 pounds. Switched her to NovoLog mix 70/30 twice a day and her A1C came down to 9.1 but she gained 10 pounds.” At this point, pramlintide was added (10 units/60 mcg, tid) and the insulin dose was cut in half. She quickly returned to her normal insulin dosing and since she had no nausea for 7 days, we again temporarily reduced her insulin dose by 50% while increasing her pramlintide dose to 20 units/120mcg. The patient was seen at 2 weeks, 6 weeks, and three months to ‘tweak’ the insulin dose and Ms. Kruger said that at the end of 3 months, her A1C dropped to 7.1%, her weight went down 19 pounds, and both her fasting and postprandial glucose levels were reduced. Her total insulin dose was about 70% of her original dosing. Ms. Kruger added, “she was reluctant to take the three injections when she began but she loved the improved control and for the first time she felt like she was in control.”

Ms. Kruger presented two other case studies then concluded her presentation with a reminder that patients who take insulin are well aware how their body responds to insulin and when pramlintide is added, they must rethink that and work closely with a provider. Ms. Kruger said, “we recommend that patients starting on Symlin to work with a diabetes educator. The time commitment to starting Symlin can be thought of as that needed to start an insulin pump,” adding that the improved quality of life these patients feel is worth the effort and extra injections. That is why patients should be monitored closely in the beginning. Ms. Kruger said, “I tell the patients — give us about six months and for most patients the outcome is well worth the effort.”

David Kruger, MSN, APRN-BC, BC-ADM
Future Therapeutic Applications: Where We are Going

Steven Edelman, MD, Professor of Medicine in the Division of Endocrinology, Diabetes, and Metabolism at the University of California, San Diego in San Diego, CA concluded the symposium with an overview of some recent studies involving pramlintide and obesity. Prior to that, however, he shared a letter from one of his patients to illustrate how this drug can improve patients’ quality of life. Dr. Edelman read “I have had diabetes for 20 years. I am now 34 years old. I’ve had excellent control for the past ten years, enjoyed the benefits of an uneventful pregnancy and healthy child. Exercise regularly and eat well. I didn’t think my control could get much better on pramlintide. My A1C is always within a range I am comfortable with. However, pramlintide has really changed, has been truly amazing and literally life-changing for me. I’ve always had a sense of being hungry constantly. This I believe was due to taking insulin and being diabetic. Since starting pramlintide, I am full after eating three square meals a day and I have no desire to constantly snack. My postprandial readings are much better even after pizza and the occasional margarita. I have lost 15 pounds. I am an avid exerciser but now I have even more energy than I’ve ever had before. I feel better and have noticeble mood swings due to the changes in blood sugars. The nausea was short-lived for me. It took me about a week to figure out my new basal and bolus rates. Now almost three months later pramlintide has become part of my routine. I have accepted the injections into my routine again though I can’t for the life of me figure out why they don’t have a pramlintide pen.”

After reading this letter, Dr. Edelman reminded the audience that simply using insulin to control sugar levels only addresses half of the problem (glucose disappearance) and clinicians need to remember that amylin can help to decrease glucose appearance (via reduced hepatic glucose production and reduced gastric emptying). Pramlintide can also reduce glucose appearance in a simpler manner, by reducing the amount of food the person wants to eat and that was the subject of the final portion of Dr. Edelman’s presentation.

Pramlintide for obesity program
Dr. Edelman concluded his presentation with a discussion of a study he is involved with that utilizes the satiety qualities of pramlintide. In a randomized, double-blind, placebo-controlled multicenter study in obese subjects (160 non-diabetics, 44 diabetics), patients were started with 60 mcg pramlintide/meal (3 times per day) and titrated up to 240 mcg/meal. No other intervention was used. Preliminary data from the trial was presented at this year’s Endocrinology Society Meeting (Abstract P1-701) and as shown in Figure 3, both diabetics and non-diabetics had significant weight loss with most adverse events being mild and transient. Overall, the mean decrease in weight was two pounds per week and Dr. Edelman stated that because the drug works centrally, the patients ate less (20-25% less) simply because they were satisfied and not due to gastrointestinal side effects.

Concluding remarks
Dr. Edelman ended his presentation by reminding the audience that when you have patients with an A1C of 7% and you want to get them down to 6 or 6.5, “it generally means you have to reduce postprandial blood sugar because you’re already getting your fasting down to near normal,” said Dr. Edelman. Pramlintide can lower postprandial glucose and lower A1C but Dr. Edelman noted that the biggest benefits of pramlintide are getting patients off the glycemic ‘roller coaster’, getting them to feel full after a meal, and getting them feeling like they are back in control.
Introduction

In the 1970s and early 1980s, large external insulin pumps (AutoSyringe™) and glucose meters began to enter the market to help persons with diabetes but most medical experts felt that home glucose monitoring was not feasible. It was simply too complicated. That all changed in 1983 when the Minimed 502 was introduced at the American Diabetes Association convention (note: the first pump commercially used was the Minimed 504 in 1985) and followed by the publication of the DCCT Research Group study (Diabetes Care 1985;18: 361-376) in which 42% of the individuals in the study used pumps during the final year of the study and had a 0.2%-0.4% decrease in A1C values.

With each passing year, the number of patients using insulin pumps and glucose monitors increases as improvements in their safety, efficacy, ease of use, and awareness continued. These improvements were the subject of a symposium chaired by Cleresa Levetan, MD, FACE, Clinical Professor at the Lankenau Institute for Medical Research, Jefferson Health System in Wynnewood, PA.

The popularity of the pump is due to many reasons, including:

- Freer lifestyle
- Improved blood sugars
- Ability to exercise without losing control
- Peace of mind
- Improved outcomes, less nocturnal hypoglycemia
- Improved quality of life

One drawback to the original pumps was that they did not completely control the extreme fluctuation of blood glucose levels than can arise. Dr. Levetan quoted a report by Dr. Cox who wrote ‘Good HbA1c does not necessarily mean ‘good’ blood sugars. Patients report feeling discouraged and confused when congratulated for a good HbA1c, while they feel bad because of wildly fluctuating blood glucose levels” (Int J Clin Pract. 2002 (suppl 129):20-29). This was well illustrated in a study by Bob Rizza (New Engl J Med. 1980;131:1313-1318) in which type 1 diabetes patients were able to get a mean glucose of 100 over the 24-hour period, but diabetic patients continued to have twice the glycemic excursions compared to non-diabetics. Dr. Levetan noted that these excursions can have a significant impact on the microvascular system and clinicians need to better control them.

Fortunately, recent improvements in both our understanding of glycemic control and in pump/monitoring technology make it possible for patients to wear insulin pumps and glucose monitors to better manage and control glucose levels. Dr. Levetan ended her introduction by stating that the changes in the use of insulin pumps and glucose monitors means endocrinologists must reexamine how they manage their patients and how they manage their office. Both of these subjects were addressed in the speakers following Dr. Levetan.

How Insulin Pumps and Glucose-Sensing Technology Can Benefit Your Practice

As new technologies and new educational programs become available, trying to determine the best way to bill for patients can be problematic. Fortunately, Scott W. Lee, MD, Associate Professor of Medicine at the Loma Linda University Medical Center in Loma Linda, CA provided an informative overview of how his department set up their billing system.

To illustrate how he bills patients, Dr. Lee used an example of a typical dia-
abetic patient who will receive a pump. During the first visit, a history, an exam, and a medical decision will generally fall under a range of codes (i.e., 99212-99215) (Table 1). Following the initial visit, the next set of visits in which the pump/sensor training and placement occur, will involve codes 95250-95251. Once the pump is working properly, further evaluations can be coded with 99212-99215.

Many physicians and centers have been successful in negotiating with nongovernmental payors for global rates for insulin pump initiation and training.

### Table 1. CGM Coding & Billing

<table>
<thead>
<tr>
<th>Clinical Protocol Is Practice Specific</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visit 1: Pre-CGM evaluation (99212 - 99215)</td>
</tr>
<tr>
<td>E/M codes 99211 - 99215</td>
</tr>
<tr>
<td>G-codes</td>
</tr>
<tr>
<td>Visit 2 &amp; 3: CGM technical component (95250)</td>
</tr>
<tr>
<td>95250 is billed when sensor is removed</td>
</tr>
<tr>
<td>Billable by nurse, CDE, or other healthcare professional</td>
</tr>
<tr>
<td>No visit needed CGM interpretation code (95251)</td>
</tr>
<tr>
<td>Physician non-face-to-face</td>
</tr>
<tr>
<td>Visit 4: Post-CGM evaluation (99212 - 99215)</td>
</tr>
<tr>
<td>E/M codes</td>
</tr>
<tr>
<td>99212 - 99215</td>
</tr>
</tbody>
</table>

### Table 2. CSII Therapy Coding & Billing

<table>
<thead>
<tr>
<th>Billing for insulin pump initiation and training</th>
</tr>
</thead>
<tbody>
<tr>
<td>99211: E/M code performed by RN, LVN, NA or CDE</td>
</tr>
<tr>
<td>G0108 &amp; G0109: Diabetes education</td>
</tr>
<tr>
<td>New education codes effective January 2006</td>
</tr>
<tr>
<td>99860: Education and training for patient self-management by a qualified, non-physician healthcare professional using a standardized curriculum, face-to-face with the patient (can include caregiver or family), 30 minutes for each patient</td>
</tr>
<tr>
<td>99861: 2 - 4 patients</td>
</tr>
<tr>
<td>99862: 5 - 8 patients</td>
</tr>
<tr>
<td>These codes are not paid separately by Medicare</td>
</tr>
<tr>
<td>Coverage for private payors varies by plan</td>
</tr>
</tbody>
</table>

Insulin pumps and coding

Dr. Lee told the audience that many physicians and centers have been successful in negotiating with nongovernmental payors for global rates for insulin pump initiation and training. Dr. Lee cautioned that when deciding which insulin pump to use, the long-term benefits of increasing office efficiency (i.e., minimize phone time and non-billable time) should be part of the decision-making process.

Dr. Lee also noted that while the long-term strategy is to have a new CPT code for intensive insulin management of pump training, until those codes are established, the E&M codes can be used.

Education

Medicare and some payors require ADA recognition to use G codes to bill for diabetes education. G codes may also be used to instruct patients for insulin pump training. Dr. Lee noted that billing for insulin pump training varies and new codes are available for education (Table 2).

Counseling

Much of the time spent with a diabetic patient involves counseling. Dr. Lee said that over half of any session usually involves simply talking to the patients about results, risk factor reduction, importance of compliance, etc. “When greater than 50 percent is spent in counseling, time becomes the key controlling factor to determining your level of E&M service. In fact, the CMS guidelines say that you do not need to document history, exam, or medical decision making. You simply need to document the total time spent and that you spend greater than 50% of that time in counseling and then you review the items that you in fact counsel the patient on,” stated Dr. Lee, adding, “so my nurse practitioner as an extension of myself and my practice, often will bill by counseling as I do a lot of counseling within my own practice. I actually have an E&M tool.” In addition, Dr. Lee said, “for those practices that actually do have a mid-level provider such as a nurse practitioner or a PA, I always recommend that you do an incident-to billing because with an incident-to billing you can bill at 100% of what the normal E&M code is so they’re billing at the same level as a physician but there are certain criteria that must be met for the incident-to criteria versus a non-incident-to criteria. You need to do a reduced fee of about 85%.”

When greater than 50 percent is spent in counseling, time becomes the key controlling factor to determining your level of E&M service.”

Concluding remarks

Dr. Lee ended his presentation by reminding the audience that continuous insulin pumps and glucose monitors are the best way to control glucose levels and it is important that clinicians be familiar with the coding system to more efficiently manage both their patient and their office.
Where Does Insulin Pump Therapy Fit into the Continuum of Diabetes Management? And Where Is It Heading?

Bruce W. Bode, MD, FACE, Medical Director of the Diabetes Center of Atlanta in Atlanta, GA concluded the symposium with a discussion of recent advances in pump technology. Reiterating what was said by Drs. Levetan and Lee, Dr. Bode noted that the benefits of pump therapy are numerous, including improved glycemic control, improved pharmacokinetic delivery of insulin, (i.e., less hypoglycemic episodes than NPH-based therapy and less insulin required), and improved quality of life.

How effective are insulin pumps?
Insulin pump efficacy is dependent on how well you monitor glucose. Dr. Bode said, “we’ve done a lot of work showing that when you monitor upwards of four times a day, you get A1Cs at 7 or less and you even approach 6.5 as you get into the six or more times a day range,” adding, “insurance companies mandate that you have to monitor your glucose at least three or four times a day in order to be considered for an insulin pump” (Figure 1). Another important aspect of how effective the pump will be is the patient’s ability to count carbohydrates. Dr. Bode noted, “carb counting is extremely important but it’s probably the most difficult things patients have to do is to figure out really what are the carbs in the food and how to adjust it.” Dr. Bode cautioned that many patients find it difficult to count carbs and often use the WAG (wild ass guess) approach to counting. While this is extremely inaccurate, Dr. Bode said it is a reality and improvements in diabetes education and smart pumps have allowed us to help patients who have difficulty counting carbs.

Smart pumps
‘Smart pump therapy’ takes place when the glucose monitors and insulin pumps interact to improve the accuracy of the bolus dosages. The insulin pumps can be customized for different glucose targets, correction factors, and carb ratios for different times a day. Dr. Bode noted that many patients find it difficult to calculate their insulin dose for a meal based on the current blood glucose and the amount of carbohydrate to be eaten, as well as taking into account any active insulin remaining from their last bolus. The ‘smart pump’ removes that guesswork and does this calculation for the patient. For example, a doctor can use a program called the ‘bolus wizard’ to set the carb to insulin ratio at each meal, the insulin sensitivity factor (correction factor) and the glycemic target at different times of day. Dr. Bode cautioned that some practitioners may set glycemic targets too high (i.e., 150 mg/dL) and he suggested that with the smart pumps, a normal target would be 100 or even 90 and for pregnant diabetics, it would be 80 mg/dL. “You should never set a target above 110 mg/dL with smart pump technology,” stated Dr. Bode.

As far as guessing what the carbohydrate to insulin ratios, correction factors, and basal rates should be, Dr. Bode said, “you don’t need to guess; we’ve done a lot of work using mathematical formulas to determine what the appropriate initial settings should be. Since you now have these smart pumps, we just apply math to it.” Dr. Bode provided an example (Table 3) and said “we initially ask how much total insulin they’re on and we’ll reduce that by 25% and we’ll take half as total bolus and half as total basal.” As for other correction factors, Dr. Bode said it varies with each patient
but generally, carbohydrate to insulin ratio on average is six times body weight in kilograms divided by total daily dose and the correction factor on average is 1,700 divided by total daily insulin dose. As for the basal insulin, Dr. Bode said it is almost always less than 50% of the total daily dose but will rise up to 60% if the patient is using an incretin or pramlintide. With these starting points established, the pump can be programmed accordingly. Dr. Bode further noted that both basal and bolus infusions can be adjusted. “Most adults have a dawn rise. It’s not dramatic. It’s not double the original basal, but they have a dawn rise often starting at 4:00 in the morning,” said Dr. Bode, adding, the basal infusion can be adjusted to compensate for that. In children, that early dawn phenomenon often occurs two hours after going to sleep and lasts until about midnight to 1:00 in the morning. And some children need less insulin from 4:00 to 8:00 in the morning (Figure 2). Dr. Bode used this example to illustrate that the advantage of the continuous glucose sensing with insulin pump therapy is that fine adjustment in the pump can be achieved to avoid unnecessary hyper- and hypoglycemic excursions.

Dr. Bode said that the new pump and monitoring technologies require some programming and education with the patient but most problems can often be fixed via fax or e-mail. Dr. Bode said “and then for the office visits, we typically try to have somebody see them within the first week or two of starting a pump but if we’re worried about them, we’ll see them in the next couple of days. If we aren’t worried, we’ll see them one to two weeks later and tell them to communicate with us by fax or e-mail,” adding, “then once stable, they see us quarterly.” Dr. Bode also said that nomograms for programming smart pumps can be found on his website at www.adaendo.com.

**Concluding remarks**

Dr. Bode is hopeful that current trials with the new sensor-augmented pump (Figure 3) will continue to improve efficacy and safety of pumps for any diabetic patients who cannot reach target. “I think continuous sensing not only will revolutionize our diabetes care, it’s going to actually promote continuous insulin delivery also,” concluded Dr. Bode.
Osteoporosis: Challenges of the Everyday Practice: Insights from Gender Differences and Rare Bone Disease

At a symposium held in conjunction with the American Association of Clinical Endocrinologists’ Annual Meeting in Chicago, Illinois, Donald Bergman, MD, FACE, past president of AACE and Clinical Professor at Mount Sinai School of Medicine in New York, NY chaired a symposium on osteoporosis in which three leading endocrinologists discussed recent advances in our understanding bone turnover markers for osteoporosis in men and women and how those markers may be used in the standard endocrinologist’s office.

Jonathan Reeve, DM, DMc, FRCP, FMedSci, Director of Research in the Bone Division, University Department of Medicine at Addenbrooke’s Hospital in Cambridge, United Kingdom began the symposium with a brief review of the relationship between osteoporosis and age: “hip fractures for example rise dramatically in women during their postmenopausal years and gradually increase in men as well.” One way to better understand the changes in aging bone is to examine the changes in chemical and mechanical influences that affect bone strength. For example, one disease that may prove to be of great importance to our understanding of aging bone and/or osteoporosis is sclerosteosis. This condition is caused by a genetic defect in which sclerostin is not expressed. Although the function of sclerostin is still unclear, it is believed to switch off bone formation and the net result is “the bones get wider and wider, the skull gets thicker and thicker, the cranial nerves get compressed,” said Dr. Reeve.

Dr. Reeve also discussed several diseases that lead to a disproportionate amount of mineralization or bone tissue (osteomalacia, osteopetrosis, osteogenesis imperfecta, and Paget’s disease) and showed that bone strength is weakened whether the bone has too much or too little mineralization (Figure 1).

Small changes in the chemistry can have a significant impact on the geometry, mineral density, and/or quality of bone. Furthermore, as people age the changes in hormone levels and a life-long repetition of mechanical loading can also alter bone strength. To illustrate, Dr. Reeve mentioned the Melbourne Femur Collection showing how posterior and superior regions of the femur neck get thinner with age, while the inferior regions get thicker (Figure 2). He also pointed out that bending resistance does not decline with aging and that the sharp rise in fractures in the elderly may be due to cortical thinning, which allows for a compression failure at the weak point in the bone.

Concluding remarks
Dr. Reeve concluded that poor bone health can result from abnormal adaptation mechanisms, an unsuitable loading experience, resetting of homeostatic regulators, failure of mineral supply, acquired failures in cell survival and/or genetic disorders. All of these can play a part in bone health, fracture risk, and how the body responds to therapy.

“There are multiple ways a bone can break. When we’re thinking about treating patients in the future, it’s very helpful to know how the bone is at risk of breaking. One of the ways we can do this better is with new technologies that enable us to look at the structure of bone so we can model its strength and study cortical and trabecular bone separately.”

Bone Quality: Lessons from Disease State Models

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Figure 1. Relationship Between Bone Turnover and Bone Strength

Male Osteoporosis: Comparing the Similarities and Differences to Osteoporosis in Women

John Bilezikian, MD, MACE, Professor of Medicine and Pharmacology at the College of Physicians and Surgeons as well as Director of the Metabolic Bone Program and the Chief of the Division of Endocrinology at Columbia University in New York, NY continued the symposium with a discussion of male osteoporosis. “Our current knowledge of male osteoporosis is limited,” noted Dr. Bilezikian, adding, “about one quarter of osteoporotic individuals and osteopenic individuals in the United States are men. Despite this fact, the number of papers devoted to the subject of male osteoporosis is woefully small.” (Figure 3).

There are several reasons why men are less likely than women to develop osteoporosis. An important factor is the absence of a male equivalent to menopause in which male sex hormones are abruptly reduced. Other factors are also important. For example, men have greater peak bone mass, greater cross-sectional area, and maintain their bone integrity for a longer period of time than women. Dr. Bilezikian noted that since fractures occur about 10 years later in men than in women, their shorter life span might be another reason why fragility fractures are not seen as much.

Dr. Bilezikian also commented on an important protective factor in men. Acquisition of peak bone mass is greater in men than in women; a point commonly attributed to the presence of androgens. But he noted that recent studies have identified estrogens in men are important as well. “Clearly, estrogens in the male are critically important for the achievement of optimal peak bone mass. They are also important for linear bone growth, the pubertal growth spurt and for epiphyseal maturation. In addition, there is growing recognition that
estrogens in the male are important for the maintenance of bone mass." Dr. Bilezikian further noted other protective factors, not well explained, namely the point that men generally fall less often than women and therefore have fewer fractures.

**Male risk factors**

The risk factors for osteoporosis in men are fairly well established (Table 1). The three most common are hypogonadism, glucocorticoid use, and alcohol abuse, which account for about half of the etiologies of osteoporosis in men.

Dr. Bilezikian noted there is debate about the T-score cutpoint to use in men to diagnose osteoporosis in men. The T-score of -2.5 could reference the female or the male database. Some endocrinologists assert that absolute risk of fracture is a function of the actual bone density in g/cm² (superior 2). This reasoning leads to the suggestion that the female referent database should be used in men to diagnose osteoporosis. Other endocrinologists argue that we should use gender-specific norms since men have greater bone density and they fracture at higher bone density levels. This position that holds that relative risk as a function of bone density is important leads to the suggestion that the male referent database be used. The International Society of Clinical Density, of which Dr. Bilezikian is a past president, recommends that the male database be used at this time.

**Treatment for male osteoporosis**

Generally, treatment for osteoporosis follows the same principles for men as for women. If the etiology is known and can be treated, it is. Calcium, vitamin D and weight-bearing exercise are cornerstones of management programs. If pharmacological intervention is indicated, bisphosphonates or teriparatide is effective. A randomized, placebo-controlled clinical trial by Orwoll and colleagues showed that daily alendronate (10 mg/day) in men for two years increased bone mineral density. There was a significant reduction in vertebral fractures when captured as adverse events. (New Engl J Med. 2000;343:604-610). Risedronate has also been investigated in men. In an open label study by Ringe et al. (Rheumatology Int. 2006;26:427-431), men with primary or secondary osteoporosis were treated for 1 year with risedronate (5 mg/day), calcium (1,000 mg/day) and vitamin D (800 IU/day). The control group was given alfacalcidol 1 µg/day plus calcium 500 mg/day or vitamin D 1,000 IU/day plus calcium 800 mg/day. After one year, there was a 58% decrease in vertebral fractures in the risedronate group (Figure 4). Dr. Bilezikian also noted that the use of the anabolic skeletal agent, teriparatide, has been shown to increase bone density in men with osteoporosis (J Bone Min Res. 2003;18:9-17).

**Concluding remarks**

Dr. Bilezikian concluded that both sexes are susceptible to osteoporosis and while some differences do exist, there are many similarities (Table 2). “This is a disease that does not respect gender. It occurs in men and it occurs in women. Our job is to learn as much as we can about the similarities and differences of this disease between men and women so we can come up with the most rational approaches to therapy.”

---

**Table 1. Risk Factors, Besides Bone Density, Generally Well Established in Men**

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Medical Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>COPD</td>
</tr>
<tr>
<td>Family history</td>
<td>Neurological disorders</td>
</tr>
<tr>
<td>Falls, fractures</td>
<td>Hyperthyroidism</td>
</tr>
<tr>
<td>Low weight or weight loss</td>
<td>Post-gastrectomy</td>
</tr>
<tr>
<td>Smoking</td>
<td>Medications</td>
</tr>
<tr>
<td>Excess alcohol</td>
<td>Steroids</td>
</tr>
<tr>
<td></td>
<td>Anticonvulsants</td>
</tr>
</tbody>
</table>

Orwoll, 2002.
Fink et al. 2004.

**Table 2. Osteoporosis: Differences Among the Genders**

<table>
<thead>
<tr>
<th>Similarities</th>
<th>Differences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Occurs</td>
<td>Awareness</td>
</tr>
<tr>
<td>Volumetric density</td>
<td>Peak Bone Mass</td>
</tr>
<tr>
<td>Bone loss with aging</td>
<td>Areal density</td>
</tr>
<tr>
<td>Importance of Sex Steroids</td>
<td>Anabolic effects of androgens</td>
</tr>
<tr>
<td>Effects of bisphosphonates and teriparatide</td>
<td>No male menopause</td>
</tr>
<tr>
<td></td>
<td>Fewer falls</td>
</tr>
<tr>
<td></td>
<td>Many fewer clinical trials of therapy</td>
</tr>
</tbody>
</table>

**Figure 4. Vertebral Fracture Efficacy of Risedronate 5 mg at 1 Year in Men**

Patient Management in Osteoporosis: How Do You Measure Success?

Robert Lindsay, MD, PhD, FRCP, FACE, Past President of the National Osteoporosis Foundation, and Chief of Internal Medicine at the Helen Hayes Hospital in West Haverstraw, NY and Professor of Clinical Medicine at Columbia University in New York, NY concluded the symposium with a discussion on how to best monitor treatment outcomes in patients with or at risk of osteoporosis.

Monitoring treatment effectiveness in patients with osteoporosis is problematic since the best method would be to watch the patient NOT break a bone. A more practical method is to measure markers of bone strength (i.e., bone mineral density and/or bone turnover) although both of these methods have their limitations too. Low bone mineral density is a good predictor of fracture risk but it is not a very good predictor of treatment response. “Our patients like to see bone density increase in response to treatment; it really makes them feel good as they watch the numbers improve. It’s difficult often to explain that the treatment may be working when bone density remains unchanged or even declines. I think there’s a role for bone density as a monitoring tool since many times it does improve and even if not outside the error of the test such small improvements are encouraging,” noted Dr. Lindsay. As for bone turnover markers, Dr. Lindsay said they may be a more reliable indicator of the reduced fracture risk associated with treatment and the changes in turnover can be seen in months (instead of years). Using serial markers during treatment may also promote compliance and/or patient participation. In one study discussed by Dr. Lindsay, patients who were told their biochemical markers indicated the treatment was working continued to take their medications. In contrast, patients who were told their markers were unchanged or showed no direct evidence of efficacy had a greater tendency to stop taking their medicine. “These data suggest that giving feedback works, in terms of insuring persistence.”

**Which marker is best?**

Dr. Lindsay prefers to measure both bone density and bone turnover, if possible. Although it is more expensive and assay variability can be high, the combination does provide some insight into treatment efficacy while also promoting patient compliance. “For antiresorptives, my preference is to use serum CTX (Crosslapses) based on a fasting blood sample, and to do spine bone density because that’s where you’ll see the maximum change. For bone forming agents, the largest dynamic response seems to occur with the amino terminus peptide of type 1 collagen (P1NP) and against spine bone density. I do measurements at baseline and three months for biochemical markers and baseline and 12 months for bone density. Thereafter, there’s no real need to follow anything except to insure that fractures are not occurring.”

**Table 3. Intervention: Effect on Fractures**

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Vertebral Fractures</th>
<th>Relative Risk†</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Treatment</td>
<td>548 (9%)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Early-Treatment*</td>
<td>41 (4%)</td>
<td>0.49</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Late-Treatment*</td>
<td>38 (11%)</td>
<td>0.99</td>
<td>0.96</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Non-Vertebral Fractures</th>
<th>Relative Risk†</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Treatment</td>
<td>561 (10%)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Early-Treatment*</td>
<td>49 (5%)</td>
<td>0.56</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Late-Treatment*</td>
<td>46 (13%)</td>
<td>1.18</td>
<td>0.31</td>
</tr>
</tbody>
</table>

*Compared to No Treatment group

**Early treatment was important to reduce the risk of both vertebral and non-vertebral fractures.**

**Treat early**

One of the best ways to insure treatment efficacy is to identify and treat the patients who fracture immediately after the fracture occurs. Dr. Lindsay discussed a longitudinal study he presented at last year’s American Society for Bone and Mineral Research (ASBMR) Annual Meeting in which over 7000 patients were identified and followed after an acute vertebral fracture. Eighty percent received no treatment and 15% were treated within 3 months of the incident. Early treatment (3-4 weeks after fracture) was associated with a 51% reduction in subsequent vertebral fractures, comparable with the clinical trial data.” Similar results were observed with non-vertebral fractures (Table 3).

**What if a fracture occurs on treatment?**

In general, biphosphonates are very effective if taken early, taken regularly, and taken properly. The key factor to treatment effectiveness is often keeping the patient on the medication. Dr. Lindsay acknowledged, “in the real world setting, as we know, adherence and compliance are not that good.” If a fracture does occur, the physician should make sure that the prescription was refilled, the medication was taken and taken properly. If the medication was taken properly, then switching medications is advised.
Insulin Considerations of Today Affect Outcomes of Tomorrow

At a symposium held in conjunction with the American Association of Clinical Endocrinologists’ Annual Meeting in Chicago, Illinois, three leading endocrinologists discussed recent advances in our understanding insulin as both a standard treatment for patients with diabetes but also as a cardioprotective agent for patients with myocardial infarction or coronary artery bypass grafting.

Paresh Dandona, MD, FACE Distinguished Professor of Medicine and Pharmacology and Head of the Division of Endocrinology, School of Medicine and Biomedical Sciences at State University of New York in Buffalo and Kaleida Health began the symposium with a discussion on the roles that insulin and glucose have in inflammatory processes. Dr. Dandona began by saying that we need to change our perception of insulin as an atherogenic agent. “We have now shown in our laboratory that insulin has a profound anti-inflammatory effect,” said Dr. Dandona, adding, “chronic inflammation of the vessel wall is the essence behind atherogenesis. So we clearly need to have a sort of paradigm shift there.”

One method to test the inflammatory action of insulin is to use glucose-insulin-potassium (GIK) infusion to measure changes in inflammatory mediators. As such, Dr. Dandona showed the audience that obesity is a pro-inflammatory state and obese people have high levels of many inflammatory mediators. When obese, nondiabetic patients are given a GIK infusion (a small dose of insulin plus small amounts of glucose to prevent hypoglycemia), the inflammatory mediators are reduced (i.e., reduced superoxide generation, P47 levels, NF-κB binding) (J Clin Endocrinol Metab. 2001;86:3257-3265). Dr. Dandona also noted that plasma markers indicate that insulin may also have anti-thrombotic and pro-fibrinolytic properties.

Is insulin a cardioprotective agent? The idea that insulin has a powerful anti-inflammatory effect can be used to help patients with acute myocardial infarction. Dr. Dandona and others (Circulation. 2004;109:849-854) demonstrated that by using the GIK clamp in patients with ST elevation myocardial infarcts (who were also given standard therapy), they were able to show that the infusion of insulin had a profound effect on many parameters (e.g., Figures 1-3). For example, CRP concentration was reduced 40% within 24 hours of insulin infusion. Dr. Dandona also stated that the GIK infusion led to markedly diminished rise

Hyperglycemia, Insulin Signaling and Cardiovascular Disease

Figure 1. GIK- MI- Insulin

Figure 2. GIK- MI- Plasma CRP

Figure 3. GIK- MI- Inferior Wall CK
in protein kinase (CK) and CK-MB levels as well as reduced serum amyloid A levels. In addition, PAI-1 were also suppressed, suggesting that insulin is profibrinolytic in acute myocardial infarction. Furthermore, Dr. Dandona stated that a marker for oxidative stress, P47, was also significantly suppressed in the patients given insulin. The reduction in CKMB concentrations suggests a cardioprotective effect of insulin.

Completing the above study, Visser et al. found that the rise in CRP levels following coronary artery bypass grafting (CABG) (Br J Anaesth. 2006;95: 448-457) could be dramatically reduced with the GIK infusion.

Dr. Dandona cautioned that an important caveat to the GIK infusion method is that the amount of glucose infused should be small. To illustrate, Dr. Dandona mentioned the CREATE-ECLA study, in which 10,000 MI patients received GIK infusions and a higher mortality rate was observed in these patients. Dr. Dandona said that the amount of glucose infused in these patients was 25-30 g/hr and much higher than the 5 g/hr used in the studies discussed above. Dr. Dandona added, “the tendency to insulin resistance and hyperglycemia is so great, that in the first few hours, you need not infuse any glucose at all. Because the amount of insulin that you give will probably just be just enough to bring the blood glucose levels down to normal. So as a result then, these guys saw a null result from their experiment.”

In summary, Dr. Dandona said the CREATE-ECLA study “is the best evidence of the toxic effect of glucose,” adding that glucose levels at admissions to a hospital is a strong predictor of mortality. “So we need to do studies to obliterate this blemish on insulin therapy in the acute myocardial infarction and we are starting a large multi-center study to confirm the anti-inflammatory and cardioprotective effect of insulin in myocardial infarction,” said Dr. Dandona.

**Concluding remarks**

Dr. Dandona concluded his presentation by stating that insulin is anti-inflammatory, profibrinolytic, antithrombotic, antiplatelet, vasodilatory, anti-apoptotic, and cardioprotective. “And glucose is just the opposite and therefore, glucose leads to damage during acute myocardial infarction, stroke and other inflammatory conditions in the hospital,” stated Dr. Dandona, adding, “that when we use insulin, we cannot be trigger happy in terms of the amount of glucose we infuse because if we induce hyperglycemia, we will undo the entire effect of insulin.”

### Current Options for Insulin Therapy

George E. Dailey, III, MD, FACE, Clinical Professor of Medicine and the head of Diabetes Research at Scripps Clinic in La Jolla, CA, continued the symposium with a presentation on the insulin treatment options currently available for patients with diabetes. Dr. Dailey began by noting that a key factor in clinical outcome is not only what medication the patient takes but also when. Dr. Dailey said, “it is important that we get more insulin use early in the course of treatment for diabetes and I think you would all agree with this.” In this regard, the United States appears to be lagging behind since only 25%-27% of patients with type 2 diabetes are taking insulin (compared to 60% in the U.K. based on the UKPDS five-year follow-up study). “We need to at least double the number of patients who are currently insulin treated. And I think one of our responsibilities as specialists is to try to empower and facilitate earlier insulin use in primary care,” stated Dr. Dailey. In order to do that, clinicians must also be aware of the insulin options available to them and Dr. Dailey used the remainder of his presentation to review the newer long-acting insulin analogs and the rapid-acting insulin analogs available.

### Long-acting insulin analogs

There are two long-acting insulin analogs available, insulin detemir and insulin glargine. Dr. Dailey discussed a study presented at the 41st Annual Meeting of the EASD (European Association for the Study of Diabetes) in Athens, Greece that compared the two long-acting insulins in patients with type 1 diabetes (Pieber et al., 2005 EASD, Abstract 242). In this study, patients were given insulin detemir twice a day or insulin glargine once a day (6-week titration period plus 20-week maintenance period) and at the end of the study, the two medications showed

### Table 1A. Results

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Detemir</th>
<th>Glargine</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Final A1C</td>
<td>8.2%</td>
<td>8.2%</td>
<td>NS</td>
</tr>
<tr>
<td>FBS</td>
<td>139 mg/dL</td>
<td>126 mg/dL</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>9-Point Profile*</td>
<td>“Similar”</td>
<td>“Similar”</td>
<td>NS</td>
</tr>
<tr>
<td>Weight Gain</td>
<td>+ 0.5 kg</td>
<td>+ 1 kg</td>
<td>NS</td>
</tr>
<tr>
<td>Pre-meal</td>
<td>B 43.9 mg/dL</td>
<td>B 40.3 mg/dL</td>
<td>NS</td>
</tr>
<tr>
<td>Variability</td>
<td>L 43.4 mg/dL</td>
<td>L 45.4 mg/dL</td>
<td>NS</td>
</tr>
<tr>
<td>(SD BG)*</td>
<td>D 47 mg/dL</td>
<td>D 52 mg/dL</td>
<td>&lt; 0.05</td>
</tr>
</tbody>
</table>

*Self-measured glucose values

very similar favorable results although the incidence of hypoglycemia (major and nocturnal), was higher in patients taking insulin glargine (Table 1a and 1b). Dr. Dailey added that one possible problem with interpreting the data is that insulin detemir has a duration of action up to 18-20 hours but most studied administer it twice daily. In another study involving patients with type 1 diabetes (Diabetes. 2004;53:1614-1620) the efficacy of action was compared between insulin detemir, insulin glargine, and NPH insulin over a 4-day period and it was observed that insulin detemir had the lowest variability of action.

To date, a head-to-head comparison in type 2 diabetes has not been published.

**Rapid-acting insulin analogs**

Of great concern to many endocrinologists is the dramatic effect brief periods of postprandial hypoglycemia can have on the vasculature and Dr. Dailey said we need to be more aggressive in trying to attenuate postprandial glucose levels. Fortunately, there are several rapid-acting insulin analogs available to accomplish this (insulin-lispro, insulin-aspro, insulin glulisine) (Figure 4) and of the three available, insulin glulisine appears to have the fastest onset of action and resorption rate (Exp Clin Endocrinol Diabetes. 2005;113:435-443). Clinically, these three insulins appear to work extremely well at controlling postprandial glucose levels but Dr. Dailey acknowledged that meta-analyses comparing the three rapid-acting insulins have concluded that there is only a minimal A1C advantage with rapid-acting insulin analogs. Dr. Dailey argued, “I think that is because the proper studies really haven’t been done on a large scale.” To illustrate his point, Dr. Dailey showed the audience a well-designed study by Lalli et al. (Diabetes Care. 1999;22:468-477) that compared regular insulin with insulin lispro but in this study, the clinicians stabilized basal insulin (ie, NPH administered up to 4 times daily in the lispro group) while adding meal-time insulin (a common mistake in other studies). Dr. Dailey said that after a year of this regimen, the patients were able to stabilize their glucose levels. “So if very careful adjustment is made at the background insulin, you clearly have an A1C advantage that is lost in many of the multi-center trials that have been done up to now.” Dr. Dailey added, “when we are trying to convince a Pharmacy Director or a P & T Committee for instance to pay for an insulin analogue, they cite these meta-analyses and so I think there is really a need to understand this better and to get better data. And hopefully we will.”

### Table 1B. Results: Adverse Effects

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Detemir</th>
<th>Glargine</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Hypoglycemia*</td>
<td>33.2</td>
<td>33.1</td>
<td>NS</td>
</tr>
<tr>
<td>Major Hypoglycemia*</td>
<td>0.1</td>
<td>0.3</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Nocturnal Hypoglycemia*</td>
<td>4.3</td>
<td>6.6</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

*Episodes per patient-year

### Figure 4. Rapid-acting Glulisine: Substitutions on Insulin B Chain

![Glulisine: Replacement of asparagine B3 with lysine and lysine B29 with glutamic acid](image)

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**Setting a Course for the Future**

The symposium concluded with a presentation by Vivian Fonseca, MD, FACE, Professor of Medicine and Pharmacology and Chief, Section of Endocrinology and Metabolism at Tulane University Health Sciences Center in New Orleans, LA on future treatment options available to control diabetes. Dr. Fonseca noted that future treatment options need to address 5 barriers:

- Reduce cardiovascular risk
- Minimize weight gain
- Minimize hypoglycemia
- Reduce variability in glucose levels
- Improve delivery methods.

The reduction in cardiovascular risks associated with proper treatment of diabetes was well documented in the DCCT-EDIC (Diabetes Control and Complications Trial/ Epidemiology of Diabetes Interventions and Complications) studies which showed that intensive therapy in patients with type 1 diabetes can greatly reduce the risk of microvascular and macrovascular complications (New Engl J Med. 2000;342:381-389. New Engl J Med. 2003;348:2349-2352. New Engl J Med. 2005;353:2643-2653). Unfortunately, intensive therapy can also cause hypoglycemic episodes and weight gain that in turn feed back to cause cardiovascular problems. In regard to weight gain, Dr. Fonseca said the addition of metformin to insulin therapy minimizes the weight gain that you get with insulin therapy and that newer
agents such as GLP-1 analogs may also be useful in reducing weight gain (see below).

**Novel methods of insulin delivery**

Dr. Fonseca stated that several delivery options are possible (i.e., dermal insulin, intranasal insulin, oral insulin, spray, inhaled insulin) but only inhaled insulin is currently showing any promise. Dr. Fonseca acknowledged that while oral insulin is an attractive concept, its absorption is highly variable and said, “we still don’t have the right formulation for clinical practice.”

With regard to inhaled insulin systems, several are in development (Figure 5) with the Exubera preparation being the most studied and shown to be both fast acting and as effective as conventional insulin therapy in controlling AIC levels (Diabetes Care. 2005;28:1077-1082. Diabetes Care. 2004;27:2622-2627). Dr. Fonseca noted that one important advantage of using an inhaled insulin preparation is that patients will likely be more willing to use it multiple times a day (as compared to injected insulin). As for safety concerns, studies have shown inhaled insulin to have no effect on pulmonary function tests following 24 weeks of treatment (Diabetes Care. 2004;27:2356-2362) but Dr. Fonseca cautioned that a recent 2-year follow-up study has shown both treatment groups (inhaled versus conventional) to have a slight decline in pulmonary function. Dr. Fonseca warned, “whether this is a function of the diabetes state or the patients getting older, we do not know but we need to be cognizant of it.” One interesting finding in these studies has been that some patients (type 1) treated with inhaled insulin developed increased serum insulin antibodies (29% versus 3% in control group). Dr. Fonseca noted that this autoimmune phenomenon does not appear to occur in patients with type 2 diabetes and their presence in type 1 patients has not impacted their treatment.

**Reversing the decline in β-cell function — can it be done?**

“I want to now turn to the problem that we all face in clinical practice which is progressive β-cell failure in type 2 diabetes,” stated Dr. Fonseca. This was first highlighted in the UKPDS study (Diabetes. 1995;44:1249-1258) but Dr. Fonseca further stated that there is hope.

“We now know that replication of β-cells continues right through the natural history of the disease, particularly lean individuals at a higher rate than in non-diabetics.” Therefore efforts to develop a drug that not only improves glycemic control but also increases β-cell function and/or mass and decreases body weight is a desired long-term treatment option.

This ideal treatment may exist in the form of an incretin peptide. Numerous studies have shown the incretin, GLP-1 to have a profound effect on controlling glucose, insulin and glucagon levels (Diabetologia. 1993;36:741-744) as well as reducing AIC levels and body weight (Lancet. 2002;359(9309):824-830). Furthermore, GLP-1 appears to trigger satiety in patients and may even prevent beta-cell death (Endocrinology. 2003;144:5149-5158). These and other observations have led to a plethora of experiments to find an incretin-like compound that can reverse the steady decline seen in type 2 diabetic patients. Of the compounds studied, only the GLP-1 agonist, exenatide, has been FDA approved but other GLP agonists (direct and indirect) are in development. Dr. Fonseca stated that studies have shown exenatide to reduce AIC by about one percent. In a comparison of exenatide with insulin glargine, Heine et al. (Am Intern Med. 2005;143:559-569) showed that both treatments had similar AIC reductions but the main difference in the two groups was that while the patients taking insulin gained weight, the ones taking exenatide lost weight. Although most exenatide studies have focused on its use as monotherapy, Dr. Fonseca said that the cardioprotective properties of insulin should not be ignored and hopes that future studies showing the combination of insulin with an incretin will be performed.

**Concluding remarks**

“Diabetes is a complex disorder with multiple hormones. While insulin is very important, we also need to consider several other things that go along with insulin, not only insulin delivery, but things that we haven’t talked about like insulin action in the periphery and liver where insulin sensitizers may be needed,” concluded Dr. Fonseca, adding that other factors such as the incretins, amylin, and glucagon also need be examined in more detail to better develop a treatment option that is safe and effective in the long term.
American Thyroid Association Guidelines

In February 2006, the American Thyroid Association (ATA) Guidelines Task Force published their comprehensive, evidence-based guidelines for the management of differentiated thyroid cancer (Thyroid. 2006;16:109-142). A review of these guidelines was presented by the president of the ATA, Ernest M. Mazzaferri, MD, MACP, Professor of Medicine at the University of Florida Gainesville and Emeritus Professor of Internal Medicine and Physiology at Ohio State University in Columbus, OH. The guidelines used literature from 1995 to 2004 and the recommendations were based on the U. S. Public Health Service's rating system (Table 1).

The comprehensive nature of both thyroid cancer and the guidelines made it impossible for Dr. Mazzaferri to discuss the guidelines in detail but he did provide the audience with a few highlights as listed below.

**Diagnosis**
The guidelines state that thyroid sonography should be performed in all patients with one or more suspected thyroid nodules (B recommendation) whereas routine measurement of serum thyroglobulin during the initial evaluation is not recommended (F recommendation). The guidelines also gave a rating of 'I' for routine measurement of serum calcitonin (i.e., neither for nor against).

The guidelines also recognized that non-diagnostic fine needle aspirations (FNAs) are problematic and gave an 'A' recommendation that nodules that are repeatedly non-diagnostic require close observation or should be surgically excised. Dr. Mazzaferri added, “this is one of the most common reasons for delayed diagnosis of thyroid cancer and this is a very important recommendation.”

If the cytology is indeterminant or suspicious for neoplasm, Dr. Mazzaferri said a radioiodine thyroid scan should be considered. If a hyperfunctional nodule is not observed then the patient should undergo a lobectomy or total thyroidectomy (C recommendation).

In pregnant women, a sonogram is recommended to monitor a nodule with malignant cytology in the early stages of pregnancy but if the nodule grows substantially by week 24, then surgery should be considered. However, if the nodule is stable by mid-gestation, then surgery may be delayed until after delivery (or if diagnosed in the second half of the pregnancy) (C recommendation).

**Initial management**
Dr. Mazzaferri began his discussion of the initial management of thyroid cancer by describing ATA's definition of an ‘absence of tumor’. Dr. Mazzaferri said, “after total or near total thyroidectomy and thyroid remnant ablation, disease-free status comprises all of the following: no clinical evidence of disease, no imaging evidence of tumor (by that we mean ultrasound evidence of tumor, undetectable Tg levels during TSH suppression and stimulation and in the absence of interfering antibodies),” adding, “this is something you ought to draw a red circle around. This is the current, around the world, definition of being free of disease.”

Having said that, Dr. Mazzaferri began his discussion of preoperative management and noted that preoperative neck ultrasonography of the contralateral lobe and cervical (central and bilateral) lymph nodes is recommended for all patients undergoing thyroidec-
tomy for malignant cytologic findings. Dr. Mazzaferri said “there is good evidence this changes the direction of surgery in a substantial number of patients and this is a B recommendation.”

Concerning surgery for nondiagnostic FNA, Dr. Mazzaferri said the guidelines state that for patients with isolated indeterminate solitary nodule who prefer more limited surgical procedure, thyroid lobectomy is recommended. Dr. Mazzaferri said, “this is what should be done in the majority of patients, unless there are some other issues and it is a C recommendation.” In contrast, a total thyroidectomy was given an A recommendation for patients with:
- Large tumors (> 4 cm) when marked atypia is seen on biopsy
- When the biopsy reading is ‘suspicious for papillary cancer’
- Family history of thyroid cancer
- History of radiation exposure

For patients with malignancy on FNA, the initial surgical procedure should be a near total or total thyroidectomy in most patients (A recommendation). Dr. Mazzaferri added, “there are some places when lobectomy alone might be sufficient — if it’s a very small nodule (< 1 cm), low risk, isolated, intrathyroidal papillary carcinomas, in the absence of lymph node metastases.”

A central neck dissection should be considered for patients with papillary thyroid carcinoma and suspected Hurthle carcinoma (B recommendation) while a near total or total thyroidectomy without central node dissection may be appropriate for follicular cancer and when follow-up by 131I therapy is used.

For lateral neck compartmental lymph node dissection, Dr. Mazzaferri said it should only be performed in biopsy proven metastatic cervical lymph nodes. “This is especially important when the nodes are enlarged and likely to fail 131I treatment, based on lymph node size, number and other factors, such as aggressive histology,” said Dr. Mazzaferri, adding, “in other words, if you do ultra-stenography ahead of time and you find malignant lateral neck nodes, we recommend this surgery, unless there is some mitigating circumstance that makes you want to do something else” (B recommendation).

Dr. Mazzaferri said a completion thyroidectomy should be performed (or offered) for patients in whom near total or total thyroidectomy would have been recommended had the diagnosis been initially available (B recommendation).

For postoperative remnant ablation, Dr. Mazzaferri said the guidelines recommend 131I remnant ablation for patients with stage 3 and 4 disease. Most stage 2 patients may qualify but the procedure should only be used in selected patients with stage 1 disease (i.e., those with multifocal tumor, nodal metastases, extrathyroidal or vascular invasion and aggressive histologies) (B recommendation).

Dr. Mazzaferri noted that the use of recombinant human TSH for remnant ablation is approved in Europe, but not in the United States. Dr. Mazzaferri said, “remnant ablation can be performed following thyroxine withdrawal or with recombinant human TSH. You can use it as an off label, as long as the patient understands what you’re doing and you have some reason to do it. This is a B recommendation.”

“Much has changed in follow-up in the last five years,” said Dr. Mazzaferri, adding, “and these guidelines reflect that.”

Follow-up
“Much has changed in follow-up in the last five years,” said Dr. Mazzaferri, adding, “and these guidelines reflect that.” An A recommendation is given for measuring thyroglobulin every 6-12 months and Dr. Mazzaferri stressed that measurements should be taken from the same assay in the same laboratory and should be performed in patients who have undergone a total or near total thyroidectomy and thyroid remnant ablation. In addition, an A recommendation is given for measuring thyroglobulin antibodies.

As for the role of thyroglobulin during follow-up, Dr. Mazzaferri said “low-risk patients who have had remnant ablation, negative neck ultrasound sonography, and their TSH suppressed thyroglobulin is undetectable at six months after initial treatment, should then have Tg measured 12 months later, after either withdrawal or recombinant human TSH stimulation to verify the absence of tumor. This is an A recommendation.”

Dr. Mazzaferri also noted that one of the biggest changes in the new guidelines is that whole body radioactive iodine scans are not routinely required in low-risk patients with negative TSH-stimulated thyroglobulin and cervical ultrasound. “That’s the vast majority of patients, that’s probably 85% of the patients we’re following and this is an A recommendation,” stated Dr. Mazzaferri. In contrast, neck ultrasonography should be performed 6 to 12 months after surgery and repeated annually for at least 3 to 5 years (B recommendation).

With regard to TSH during follow-up, the guidelines state that in patients with persistent or recurrent disease, the serum TSH should be maintained below 0.1mU/L (B recommendation). In patients who are clinically free of disease but who present with high-risk disease should have levels between 0.1 and 0.5 for at least 5 to 10 years (C recommendation). Finally, in patients free of disease (i.e. most patients), the TSH should be kept within a low/normal range (0.3 and 2 mU/L).

Metastatic disease
In patients with persistent/recurrent disease confined to the neck, the guidelines recommend (B) a complete ipsilateral or central compartmental dissection of the involved compartments while sparing vital structures. In contrast, currently there is insufficient evidence to support the use of one method of 131I administration over another nor for the use of recombinant human TSH mediated therapy for patients with metastatic disease being treated with 131I (I recommendation). However, recombinant human TSH mediated therapy may be used in patients with underlying comorbidities that make iatrogenic hypothyroidism risky, in patients with pituitary disease interfering with the rise in TSH, and in patients where the therapy delay is thought to be harmful (C recommendation).

Concluding remarks
Dr. Mazzaferri ended his presentation by reminding the audience to read and use the guidelines (a free pdf available at (www.thyroid.org) and to remember that the guidelines will change as more evidence becomes available.
Impact of Hypothyroidism

Paul Ladenson, MD, Director of the Division of Endocrinology and Metabolism, and the John Eager Howard Professor of Endocrinology continued the symposium with a discussion on short-term hypothyroidism. Dr. Ladenson stated that for the past 50 years, one of the most unpleasant responsibilities of endocrinologists and nuclear medicine physicians has been to discontinue (or not begin) thyroxine therapy in their patients with previously treated thyroid carcinoma. While it is a very effective method for generating an endogenous TSH response for thyroglobulin monitoring and radiiodine scanning patients, Dr. Ladenson said this approach has well known limitations. In addition to the limited efficacy in some patients, almost all patients report adverse events during induced hypothyroidism. Dr. Ladenson discussed how short-course hypothyroidism affects the central nervous system (CNS), the cardiovascular system, and other systems in the body.

As expected, hypothyroidism was found to disrupt their quality-of-life scores across many areas (i.e., physical functioning, role physical, role emotional, mental health & vitality).

CNS effects
The effects of hypothyroidism on the CNS was well documented in a study by Constant et al. (J Clin Endocrinol Metab. 2001;86:864-870), who followed 10 thyroid cancer patients who underwent thryroidectomy followed by thyroxine therapy (euthyroidism), then withdrawal (hypothyroidism). During the study, 18O-H2O and 18F-FDG PET scans were used to measure cerebral blood flow and glucose metabolism and it was observed that short-term hypothyroidism caused a 23% reduction in cerebral blood flow and a 12% reduction in central glucose metabolism.

Dr. Ladenson also discussed a recent study he was involved with (J Clin Endocrinol Metab. 2006;91:878-884) in which patients were given the SF36 quality-of-life questionnaire during three different episodes: 1) when they were on thyroxine therapy; 2) when they were given recombinant TSH for the first cycle of diagnostic testing, and 3) when they were withdrawn from thyroxine therapy for the second cycle of diagnostic testing. As expected, hypothyroidism was found to disrupt their quality-of-life scores across many areas (i.e., physical functioning, role physical, role emotional, mental health & vitality) but the scores were significantly improved when the patients took T4 or recombinant TSH. Dr. Ladenson stated, “about three quarters of the patients were limited in climbing stairs when withdrawn from thyroid hormone versus only 40 percent after recombinant TSH,” adding, “also, three quarters of (hypothyroid) patients actually missed work because of physical health decreases whereas one out of five patients missed work when tested with recombinant TSH. Similar results were seen in response to a variety of specific questions related to mental health and vitality.” The database for this study can be seen at cjcem.endojournals.org.

Cardiovascular effects
Hypothyroidism also causes increased levels of noradrenaline, adrenaline, aldosterone, and cortisol (Endocr Relat Cancer 2004;11:345-356), which could be contributors to the hypertension observed with hypothyroidism. In addition, cardiac output, systolic blood flow and heart rate decrease during hypothyroidism. Dr. Ladenson stated, “it’s well known that a number of atherogenic markers, particularly total and LDL cholesterol, rise in chronic hypothyroidism,” adding, “this has also now been shown in a number of studies in short-term hypothyroidism.” Dr. Ladenson noted that all of these cardiovascula changes are mild, but endocrinologists should be aware of them in patients with underlying intrinsic cardiovascular disease that could be exacerbated.

Other consequences
Hypothyroidism has also been shown to affect other organ systems, where it leads to reduced gastric emptying (J Gastroenterol Hepatol. 2004;24:391-395), increased creatinine clearance (Am J Nephrol. 2004; 24:41-45) and decreased bone formation and resorption (Eur J Endocrinol. 1998;138:667-673). Dr. Ladenson stated that all of these changes are typically subclinical but endocrinologists need to be attentive of these effects in patients with gastric apoena, gastric reflux disease, renal problems, osteoporosis, etc.

Finally, Dr. Ladenson mentioned that hypothyroidism can be problematic in patients taking warfarin. “Thyroid hormone therapy alters the rate of metabolism of vitamin K dependent clotting factors. With a slowing of their clearance, there may be a need for an increase in anticoagulant therapy during short-term hypothyroidism,” stated Dr. Ladenson, adding, “Similarly, it’s well known that the metabolism of both digoxin and phenobarbital is altered during chronic hypothyroidism and it may occur with short-term hypothyroidism.”

Concluding remarks
There is strong evidence that short-term hypothyroidism causes many of the things that chronic hypothyroidism does, particularly in the central nervous system at the biochemical, clinical and health and quality-of-life levels. “All of these consequences can, of course, be avoided with recombinant thyrotropin in appropriate patients,” said Dr. Ladenson, adding, “one wonders if a decade from now we may be looking back at thyroid hormone withdrawal much like we look back at the pneumoencephalogram...”
Novel Therapies for Advanced or Metastatic Thyroid Carcinoma

Steven I. Sherman, MD, FACE, Professor and Chair of the Department of Endocrine Neoplasia and Hormonal Disorders at the University of Texas, MD Anderson Cancer Center in Houston, TX concluded the symposium with a summary of clinical trials underway to help patients with advanced thyroid carcinoma. Dr. Sherman began, “the mortality due to thyroid cancer has been the third fastest growing of all forms of cancer over a 10-year period of time.” This sobering statistic illustrates the need to improve treatment options for these patients and Dr. Sherman referred to the new guidelines, which state that unresponsive patients should be asked to participate in a clinical trial. Dr. Sherman said there are three broad approaches to attacking advanced cancer in current studies and they are abnormal signaling, epigenetic modifications, and cell cycle approaches to therapy.

The mortality due to thyroid cancer has been the third fastest growing of all forms of cancer over a 10-year period of time.”

Abnormal signaling
In regard to abnormal signaling, Dr. Sherman stated that the multitargeted receptor tyrosine kinase inhibitor AMG706 has begun phase II clinical trials. In addition, another multiplex tyrosine kinase inhibitor, zactima may prove to be effective in treating thyroid cancer. Dr. Sherman said that Sam Wells’ group at Duke University is leading a multicenter study of zactima in hereditary medullary carcinomas. Another drug, sorafanib (Nexavar) has also begun trials.

Dr. Sherman said that some anecdotal reports from these trials have been promising. “Patients with medullary carcinoma with profound diarrhea, resistant to multiple therapies, see their diarrhea resolve without the need of any narcotic or other antidiarrheal medications when being treated with zactema.

It’s just an incredible clinical change,” stated Dr. Sherman, adding, “we’ll be looking forward to the formal analysis of these studies as they complete.”

Epigenetic modifications
In epigenetic modifications, the two most significant modifications involving cancer cells are DNA hypermethylation and histone deacetylation. “Both of these have the capacity, when applied to the right gene, to silence the expression of the gene,” said Dr. Sherman, adding, “it turns out, in differentiated thyroid cancer a wide number of genes are silenced as a result of epigenetic modifications.”

In one Phase II study underway, a DNA methylation inhibitor called decitabine is being studied to see if radioiodine uptake can be restored by reversing or preventing the epigenetic modifications in patients with advanced disease. The design of the trial is shown in Figure 1 in which Dr. Sherman’s group at MD Anderson is leading the several centers involved in the trial.

Cell cycle control
Dr. Sherman briefly discussed an ongoing multicenter Phase II study examining the efficacy of a proteosome inhibitor, bortezomib (Velcade), in patients with metastatic disease. It has been hypothesized that a proteosome inhibitor will permit higher levels of p27 which acts as a tumor suppressor.

Concluding remarks
Dr. Sherman ended his presentation by acknowledging that more work needs to be done in this field. However, he is optimistic that improvements in the development of thyroid cancer cell lines as well as improvements in developing specific therapies that target patient specific abnormalities and/or the use of combination therapies will greatly improve our understanding and management of thyroid cancer.

Dr. Sherman encouraged the clinicians in the audience to look at various websites that provide details on the ongoing trials and their inclusion/exclusion criteria.

Two such websites are www.cancer.gov/clinical trials and www.thyroidtrials.org.

Figure 1. NTCTCSG 001: Phase II Trial of Decitabine to Restore RAI Uptake
Overcoming Insulin Resistance: A Practical Approach to Initiating Insulin Therapy

At a symposium held in conjunction with the American Association of Clinical Endocrinologists’ Annual Meeting in Chicago, Illinois, three leaders in clinical endocrinology presented recent data on the use of insulin therapy for three common types of type 2 diabetes: adult patients not responding to current oral hypoglycemic agents; adult patients not responding to current insulin therapy; and adolescent patients.

Alan J. Garber, MD, PhD, FACE, Professor of Medicine, Biochemistry & Molecular Biology and Cellular Biology in the Department of Medicine at Baylor College of Medicine in Houston, TX began the symposium with a description of a patient with diabetes whose profile is fairly common in his practice. Dr. Garber said, “This is BQ, a 54-year-old Latino. He has had type 2 diabetes for 11 years. His father and mother both had diabetes and died of cardiovascular complications. They were further complicated by a preceding amputation, in the father, and near blindness, in the mother. The patient, along with his spouse, presented for evaluation due to moderate to severe erectile dysfunction. The patient has a history of coexisting hypertension and dyslipidemia. Current medications include metformin, 1,000 mg bid, rosiglitazone, 4 mg once daily, glimepiride, 4 mg once daily, irbesartan, 300 mg once daily, amlodipine, 10 mg once daily and rosuvastatin, 10 mg once daily. When you examine the patient, the patient has decreased vibration and pinprick sensation below the knees, absent Achilles tendon reflexes. The peripheral pulses are, however, intact and the patient has evidence of background but non-proliferative retinopathy. Lab results show an A1C of 10.2%, a fasting glucose of 214 mg/dL, creatinine, 1.2 mg/dL, LDL cholesterol 97 mg/dL, HDL 41 mg/dL and there are 67 mg of albumin per gram creatinine in the urine. You counsel the patient that better diabetes control is a good idea to avoid his parents’ fate.”

The next question is how do you best treat this patient? Dr. Garber answered this by reviewing the guidelines for treating type 2 diabetes which state that A1C should be below 7% according to ADA targets, or below or equal to 6.5% according to IDF and AACE targets. While Dr. Garber agreed with this statement, he also stated that he prefers to examine preprandial and postprandial glucose levels more closely.

Dr. Garber said, “simply normalizing fasting glucose levels and improving glucose toxicity may do much for preprandial blood sugar control but does relatively less for the prandial excursions you see with a weakened and enfeebled pancreas that characterizes the earlier stages of type 2 diabetes.”

As for treatment, there are numerous insulin regimens available, including:
1. rapid-acting insulin analog before each meal
2. short-acting human insulin before each meal
3. NPH
4. Basal insulin analog
5. Premixed human insulin
6. Premixed analog insulin
7. Basal-bolus insulin therapy

When choosing a regimen, it is necessary to tailor an insulin program to the patient’s lifestyle (both eating and exercise patterns). Dr. Garber said, “there is no reason to have the patient revamp his or her lifestyle to suit the pharmacodynamics of an insulin program. That’s not likely to be successful.” Dr. Garber continued his presentation by reviewing some of the data supporting the various insulin regimens available.

When choosing a regimen, it is necessary to tailor an insulin program to the patient’s lifestyle (both eating and exercise patterns).

Basal insulin therapy
The first insulin trial discussed by Dr. Garber was the Treat-to-Target study by Riddle et al. (Diabetes Care. 2003;26: 3080-3086). This study involved 756 people with type 2 diabetes, who were inadequately controlled (A1C >7.5%) on one or two oral agents. Treatment in
this study consisted of continuing their medication, while also receiving once-daily insulin glargine or NPH at bedtime. Dr. Garber said, “they were able to show that both insulins got fasting glucose down from about 200 to about 120 mg/dL.” In this case, the difference between the two agents was the number of nocturnal hypoglycemic episodes and in this study, glargine showed fewer episodes than NPH. He continued by presenting the results from a study by Hermansen et al. (Diabetes Care. 2006; 29:1269-1274). In this study, 475 individuals with type 2 diabetes and on oral agents but with an A1C between 7.5-10%, were given insulin detemir or NPH insulin for 24 weeks and had mean decreases in A1C of 1.8% and 1.9% respectively, while continuing their oral agents. However, the risk of overall hypoglycemia was reduced by 47% in the insulin detemir group compared to the group receiving NPH. In addition, mean weight gain was significantly lower in the detemir group (1.2 kg) as compared to the NPH group (2.8 kg).

Premixed insulin analog therapy
Another option to start this patient on insulin would be to use premixed insulin analogs. Dr. Garber noted that these premixes tend to have a reduced risk of hypoglycemia, flexible injection timing, and reduced postprandial glucose. The three most common premixed insulin analogs are: biphasic insulin aspart 70/30 (“BIAsp 30”), premixed insulin lispro 75/25 and premixed insulin lispro 50/50 (“Mix 25” and “Mix 50”), which have the percentage of rapid-acting insulin analogs set at 30%, 25%, and 50% respectively. Dr. Garber noted that premixed insulin analogs tend to have fewer hypoglycemic episodes and tend to better mimic the rapid mealtime response (Figure 1). Although these premixes can effectively lower A1C to target levels with one dose, multiple doses (2 or 3) may be required to adequately control meal excursions and/or reach target.

Biphasic insulin aspart 70/30 was tested by Raskin and colleagues in the INTIATE Trial (Diabetes Care. 2005;28:250-265). In this study, biphasic insulin aspart 70/30 was given twice daily (pre-breakfast and pre-dinner) and compared with once-daily insulin glargine in patients with type 2 diabetes that were inadequately controlled on oral antidiabetic drugs. After 28 weeks of treatment, the biphasic insulin aspart 70/30 treated group had a lower mean A1C (6.9%) compared to the glargine-treated group (7.4%). However, the biphasic insulin aspart 70/30 group did tend to gain more weight and have more hypoglycemic episodes.

Dr. Garber noted that improvements in glycemic control and reaching target have also been shown with the other premixes. In a crossover study by Malone and colleagues (Clin Ther. 2004;26:2034-2044) Mix 25 and glargine were compared and it was observed that 42% of the Mix 25-treated group reached a treatment goal of A1C<7% compared to only 18% in the glargine group.

Finally, Dr. Garber discussed the 1-2-3 Study he was involved with to address the safety and efficacy of various dosing strategies (Diabetes Obes Metab. 2006;8:58-66). Dr. Garber said, “we took 100 patients with type 2 diabetes, failing oral agents and decided to start them all on one injection of premixed analog, in this case biphasic insulin aspart 70/30, before the evening meal, based upon the hypothesis that at least the majority of calories ingested in the United States occur between the time of the onset of the evening meal and when these patients go to sleep that night,” adding, “if after 15 weeks, the A1Cs got to 6.5%, we declared victory and that was the end of the study for that cohort of patients. If, on the other hand, they did not get to 6.5%, they went on to a second injection of biphasic insulin aspart 70/30 before breakfast.” If an A1C of 6.5% was achieved, the treatment was considered a success but if not achieved, a third injection before lunch was added. Dr. Garber presented the results showing that approximately one-third of the patients taking once daily biphasic insulin aspart 70/30 achieved a target of A1C<6.5% and 46% achieved A1C<7%. Of the 100 patients enrolled in the study, 74 completed the trial and no patients discontinued treatment due to hypoglycemia or weight gain.

It is unfortunate that in this country insulin is often initiated too late to avert the complications of diabetes.

Concluding remarks
Dr. Garber ended the program by stating that in patients with type 2 diabetes such as BQ, insulin is effective. He concluded that there are a number of ways you can prescribe insulin to get patients that are poorly controlled under control and “it’s up to you to choose a program that will be successful in your patients, bearing in mind their lifestyle.” Dr. Garber added that it is unfortunate that in this country insulin is often initiated too late to avert the complications of diabetes.
Case 2: A Patient with Long-Standing Type 2 Diabetes Treated with Basal Insulin Requiring Better Control

Philip Levy, MD, FACE, Clinical Professor of Medicine at the University of Arizona College of Medicine in Phoenix, AZ continued the symposium with a discussion of insulin use in patients who are failing current basal insulin therapy. Dr. Levy described a patient (“KW”), a 64-year-old woman who had diabetes for 10 years and continued to have problems managing her glucose. When first diagnosed with diabetes, she was given metformin. Three years later her A1C started to rise and glimepiride was added. Following that, insulin glargine was added and her dose was increased to 44 units/day based on her fasting glucose and the Treat-to-Target algorithm. She was also given lisinopril to “protect her kidneys” and atorvastatin to control her cholesterol. Unfortunately, her A1C continued to be high (9%) and she admitted that even though she had been compliant with her medication, she had not been very compliant with her diet or exercise programs and continued to smoke cigarettes (5 per day). She also had arthritis and found it difficult to give herself the insulin injections.

Based on the above data, Dr. Levy asked the audience if the patient was a candidate for adding a thiazolidinedione (TZD). The audience was split on what to do and Dr. Levy said that it was probably not a good idea to add a TZD since it would only bring down her A1C about 1-1.5%, even under ideal conditions. As for how to treat this patient, Dr. Levy said, “in a patient like this, where she is dependent on her family, we want to keep her number of injections down to the minimum and have mealtime dosing convenience. We have a choice of either basal/bolus insulin, as you saw before, free mixing twice daily, a premixed insulin twice daily, or basal only,” reminding the audience that “she is already on basal only and she’s not doing well.” Dr. Levy noted that of the insulin analogs available, the premixed formulations would be the best choice for this patient since they only have to be taken once or twice a day and they can control both fasting and postprandial glucose. Dr. Levy noted this patient is similar to the patients used in the study by Malone et al. (Diabetes Medicine. 2005;22:374-381) in which patients with diabetes who had failed to control their blood glucose with insulin alone or with oral agents were given premixed insulin lispro 75/25 twice daily. These patients were found to improve their A1C by 1% as compared to 0.42% among patients taking glargine and the percentage of patients achieving an A1C <7% was 30%, as compared to 12% of patients taking glargine. Raskin et al. observed similar results with biphasic insulin aspart 70/30 (Diabetes Care. 2005;28:260-265) (Figure 2). In patients who have difficulty achieving a treatment goal with once or twice daily

Figure 2. INITIATE: 8-Pt BG Profiles – Baseline and Wk 28

Blood Glucose (mg/dL)

Baseline

Week 28

BIAsp 30 Glargine

*BIAsp 70/30 lower BG vs glargine P <.05; †Glargine lower BG vs BIAsp 70/30, P <.05


Figure 3. The 1–2–3 Study: Achievement of A1C Targets

A1C ≤ 6.5%

A1C < 7.0%

Overcoming Insulin Resistance: A Practical Approach to Initiating Insulin Therapy

Concluding remarks
Dr. Levy concluded his presentation by reminding the audience that transitioning to a new regimen is fairly straightforward. In patients going from once-daily long-acting insulin to a twice-daily premixed insulin, he recommended that the daily dose be divided (half before breakfast, and half before supper) and this new regimen should be started 18-24 hours after the last basal dose was given.

Case 3: An Adolescent Patient with Newly Diagnosed Type 2 Diabetes

The symposium concluded with a discussion about adolescents with type 2 diabetes by Naomi Neufeld, MD, FACE, Clinical Professor of Pediatrics at the UCLA School of Medicine in the Department of Pediatrics at Cedars-Sinai Medical Center in Los Angeles, CA.

Childhood obesity and diabetes
Numerous factors contribute to the increase in type 2 diabetes in adolescents. While many will agree that genetics is one factor, obesity plays an important role even in teenagers. Unfortunately, in our society that encourages the use of soft drinks in schools, fast food suppers, and excessive TV, it is quite easy for children to become obese. In a study by the California Center for Public Health Advocacy, 28% of children (in grades 5, 7, and 9) are overweight. Dr. Neufeld also referred to an editorial by Dr. Rocchini (New Engl J Med. 2002;346:954-955) who wrote, ‘the obvious way to prevent an epidemic of obesity-related diabetes would be to emphasize primary and secondary prevention of obesity.’ Dr. Neufeld also noted that puberty itself is a risk factor for insulin resistance and in obese adolescents; we need to monitor them more closely for signs of insulin resistance and/or diabetes.

Acanthosis nigricans
Another sign to look for in teenage patients with diabetes is acanthosis nigricans which is a dark velvety pigmentation of the skin in the flexural areas of the neck, groin, axillae, and knuckles. Dr. Neufeld pointed out that in Texas, a house bill was passed calling for schools to screen for acanthosis nigricans in 9 border counties. These screenings are performed in grades 1, 3, and 5. Dr. Neufeld acknowledged that there are many pros and cons to screening for acanthosis nigricans and the debate on performing these tests continues elsewhere in the United States.

The adolescent patient
To illustrate some of the characteristics of type 2 diabetes in adolescents, Dr. Neufeld described a patient of hers. ‘He is a 15-year-old African-American boy with a recent history of polyuria and polydipsia, who was admitted to our pediatric ward from the emergency department with a blood glucose of 650 mg/dL. Prior to admission, he stated he had drunk one gallon of fruit punch, one gallon of Sunny Delight and two gallons of water. He was noted to have ketosis on admission but not ketoadiposis,” said, Dr. Neufeld, adding, “for the past several years, the mother noted this grainy, dark skin around his neck. He had been evaluated by the pediatrician for diabetes. At that time, his workup was negative, his fasting blood glucose was normal, his hemoglobin A1C was normal. At that time, he weighed 210 pounds. During the year prior to his coming to the emergency room, he had gained 50 pounds. He did very little physical activity, which is not unusual, and watched up to five hours of TV per day, also not unusual. In addition, he had a family history of type 2 diabetes in multiple relatives. During the physical exam he had a BMI of 36, elevated blood pressure, normal turgor, moist mucous membranes, no ketosis on his breath, acanthosis nigricans in his neck and in the axilla, and no thyromegaly. He was in puberty, and his upper arm circumference was 39 centimeters. Lab results showed his blood glucose was markedly elevated, sodium was in the low/normal range, anion gap was normal, A1C was 9.1%, triglycerides were markedly elevated, HDL was low.” While in the hospital, he was started on a 2,000 calorie ADA diet and on biphasic insulin aspart 70/30, 20 units in the morning, 10 in the evening.

Concluding remarks
Dr. Neufeld ended the presentation with the outcome of her 15-year-old patient, and said that he was seen in the office 1 week after discharge. His blood glucose values remained elevated so his insulin dose was increased to 25 units of biphasic insulin aspart 70/30 in the morning and 15 units in the evening. He was also started on metformin, 1,000 mg daily, taught carbohydrate counting, and encouraged to exercise 45 minutes a day. At a 3-month follow-up he had an A1C of 6.0% , while he was still obese, and dyslipidemic, Dr. Neufeld said his glucose levels are becoming controllable, and concluded, “this gives us some hope that we can reverse this disease as he loses weight and presumably delay its further presentation until he gets much older.”
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