In this issue:

- The Parathyroid Cell: Exploring Treatment Options for Common and Uncommon Parathyroid Disorders
- The Kidney is a Key Link between Diabetes and Cardiovascular Disease: Managing Risk
- Understanding Female Sexual Dysfunction and the Role of Testosterone
- The Beta Connection: Glycemic Control and Hypertension
- Hot Topics in Thyroid Disease
- Advancing Care and Compliance in Diabetes: New Evidence, Tools, and Techniques
- Vitamin D Today: Reducing the Risk of Falls and Fractures
- Individualized Treatment Options: Addressing Unmet Needs for Osteoporosis
- Insulin Sensitizers for the Treatment of Type 2 Diabetes: Implications for Cardiovascular Disease Risk Management
- Optimizing Thyroid Hormone Therapy of Hypothyroidism
- The Incretin Effect: How a New Class of Pharmacologic Agents May Enhance the Future of Diabetes Management

Washington, DC

Summary of industry-supported symposia conducted in conjunction with the 14th Annual Meeting of the American Association of Clinical Endocrinologists
# Table of Contents

The Parathyroid Cell: Exploring Treatment Options for Common and Uncommon Parathyroid Disorders ................................................... 1

The Kidney is a Key Link between Diabetes and Cardiovascular Disease: Managing Risk ................................................................. 5

Understanding Female Sexual Dysfunction and the Role of Testosterone ...................................................................................... 9

The Beta Connection: Glycemic Control and Hypertension .............................................................................................................. 13

Hot Topics in Thyroid Disease .......................................................................................................................................................... 17

Advancing Care and Compliance in Diabetes: New Evidence, Tools, and Techniques ........................................................................ 21

Vitamin D Today: Reducing the Risk of Falls and Fractures ........................................................................................................... 25

Individualized Treatment Options: Addressing Unmet Needs for Osteoporosis ........................................................................... 29

Insulin Sensitizers for the Treatment of Type 2 Diabetes: Implications for Cardiovascular Disease Risk Management ....................... 33

Optimizing Thyroid Hormone Therapy of Hypothyroidism .............................................................................................................. 37

The Incretin Effect: How a New Class of Pharmacologic Agents May Enhance the Future of Diabetes Management ......................... 41
The Parathyroid Cell: Exploring Treatment Options for Common and Uncommon Parathyroid Disorders

While surgery has been the most common treatment for patients with primary hyperparathyroidism (PHPT) and parathyroid carcinoma, there is still some controversy surrounding when surgery is necessary and how hypercalcemia should be managed. At a symposium held May 19, 2005, during the American Association of Clinical Endocrinologists’ Fourteenth Annual Meeting and Clinical Congress, a panel of experts discussed clinical strategies for managing PHPT and parathyroid carcinoma.

The Parathyroid Cell: A Look into the Calcium-Sensing Receptor

The concept of a calcium-sensing receptor developed in parallel in the clinic and the laboratory beginning in the 1970’s,” began Dolores Shoback, MD, Professor of Medicine, University of California, San Francisco. The groundwork for the syndrome of familial benign hypercalcemia began when a boy presented with headaches and hypercalcemia and 11 more families in a four-generation kindred were identified with the syndrome. They had normal parathyroid hormone levels, normal or low serum phosphorus levels, and remarkably low urinary calcium excretion.

About 50% of the family members were affected by hypercalcemia and a similar biochemical phenotype. The high degree of penetrance in the family indicated that this syndrome was autosomal dominant. The biochemical profile suggested that there was an abnormality in an extracellular calcium-sensing mechanism.

Thirty years after the initial description of this familial syndrome the calcium-sensing receptor was identified by molecular cloning from a parathyroid cell cDNA library. The receptor is a member of the large family of G-protein coupled receptors (Brown EM, et al. Nature. 1993;366:575-580) and belongs to a subfamily of “chemical-sensing” receptor molecules. The receptor is widely expressed and found in the parathyroid, kidney, C-cells, brain, stomach, intestine, bone, cartilage, and skin. Familial benign hypercalcemia is usually caused by heterozygous loss-of-function mutations in the calcium receptor gene. “Many different mutations have been described,” Dr. Shoback explained.

The calcium-sensing receptor is responsible for the very steep, inverse relationship between the ionized calcium concentration in the bloodstream and the level of parathyroid hormone secretion. Studies in normal subjects and in cultured parathyroid cells have allowed for the determination of a set-point for parathyroid hormone secretion, which is the calcium concentration required for half-maximal suppression of parathyroid hormone. “Any change, even slight, either down or up, in ionized calcium leads to marked changes in the level of parathyroid hormone secretion,” said Dr. Shoback. In pathologic parathyroid tumors, there is an error in this set-point. For example, in patients with parathyroid adenomas, which cause the majority of cases of PHPT, the set-point is shifted to the right (i.e., to a higher calcium concentration). The receptor also responds to a remarkably varied group of ligands including gadolinium, polyamines, basic polypeptides, amino acids, and amino glycoside antibiotics that are used to treat infections.

Calcimimetics, such as cinacalcet HCl, shift the set-point for parathyroid hormone secretion to the left, or to a lower calcium concentration. “In other words, the calcimimetics enhance the sensitivity of any given calcium concentration in its ability to suppress PTH secretion,” she explained. These agents work allosterically to activate calcium-sensing receptors, which in turn inhibit parathyroid hormone secretion. Suppression can be shifted with the calcimimetics because they also shift the signaling responses that the parathyroid cell produces when it is exposed to extracellular calcium. “Not only do calcium receptors play a key role in inhibiting parathyroid hormone secretion, they also

This program was supported by an unrestricted educational grant from Amgen.
are coupled to the inhibition of cell proliferation in the parathyroid glands,” Dr. Shoback stated. Because of this, calcimimetics theoretically treat both hyperproliferation and the hypersecretion seen in states of hyperparathyroidism.

Calcimimetics, such as cinacalcet HCl, shift the set-point for parathyroid hormone secretion to the left, or to a lower calcium concentration.

Calcilytics, another class of drugs that act on calcium-sensing receptors, act antagonistically by interfering with the ability of calcium to activate the receptor. In animals, the prototype calcilytic compound NPS2143 causes a dramatic and rapid rise in the parathyroid hormone level, which is sustained for a few hours. In ovariectomized rats, calcilytics actually increase the formation of osteoid and increase bone formation. “We may be able to stimulate a burst of parathyroid hormone, which may be able to bring about an anabolic action on bone,” explained Dr. Shoback, “much like the effects from intermittent pulsatile injection of parathyroid hormone fragments used for the treatment of osteoporosis.”

There are several parathyroid diseases. Familial benign hypercalcemia is associated with few clinical consequences. In contrast, neonatal severe hyperparathyroidism, which often occurs in these same families, is associated with significant complications. “These children have homozygous loss-of-function mutations in their calcium receptor genes; both calcium receptor alleles are mutated in these children,” she said. Survival is dependent upon parathyroidectomy in infancy or early childhood.

Autosomal dominant hypocalemia is due to heterozygous gain-of-function mutations, typically in the calcium receptor gene. These mutations alter the receptor so that it is constitutively active. The biochemical phenotype of this genetic disorder is low serum calcium, low serum parathyroid hormone, and high urinary calcium levels. Patients have minimal symptoms. Another parathyroid disease is a form of hypercalciuric hypercalcemia that is caused by autoantibodies that block or interfere with calcium receptor function. These antibodies not only immunoprecipitate the calcium receptor protein in the laboratory, they can actually interfere with the actions of calcium and end up stimulating PTH release. They interfere with the ability of parathyroid cells to signal the presence of high calcium levels. In addition, autoantibodies that activate calcium receptors have also been identified, and they cause the opposite phenotype-acquired hypoparathyroidism.

“The receptor is not a classical tumor suppressor in the parathyroid,” said Dr. Shoback. However, several studies indicated that there was a reduction in the calcium receptor number in tissues from patients with PHPT, although there was a great deal of variability. Furthermore, evidence suggested that calcium-sensing receptor messenger RNA and protein expression were reduced. “The lower the level of expression of the receptor in adenomas, the farther to the right was the set-point for secretion in the patient,” she added.

“I think some very powerful and interesting compounds that may be able to interrupt calcium receptor function at normal serum calcium concentrations will be developed. These compounds may be helpful in the treatment of disorders of bone loss like postmenopausal osteoporosis,” concluded Dr. Shoback.

**Advancements in Treatment Options for Parathyroid Carcinoma**

“The three main organs for calcium movement in the body are bone, kidney, and the gut,” said Munro Peacock, MD, Professor of Medicine, Indiana University, School of Medicine, Indianapolis. Calcium homeostasis is a complex mechanism that acts through a number of receptors, including the vitamin D receptor and the calcium receptor. “There are calcium receptors throughout the body, but those in the kidney and in the gut are particularly important because these are homeostatic organs,” he explained.

In the presence of parathyroid cancer, the parathyroid cells still secrete parathyroid hormone. In general, the tumor cells contain calcium receptors, although there may be some tumors in which the calcium receptor is either increased in number or absent. “The action of PTH is the same as in the normal situation; it acts on bone and kidney to increase serum calcium,” explained Dr. Peacock. Parathyroid cancer spreads locally and by metastasis, and the metastases continue to secrete parathyroid hormone. Severe hypercalcemia is usually a mark of parathyroid cancer, an uncommon disease that accounts for less than 1% of the cases of PHPT. Parathyroid cancer is treated surgically; however, in most cases the cancer has spread and metastasized.

“Unfortunately, it is very resistant to radiation and chemotherapy, so the major clinical problem is how to manage a patient with metastatic cancer who
is dying with severe hypercalcemia,” he said.

Dr. Peacock summarized a study he and his associates conducted of cinacalcet HCl in patients with parathyroid cancer in which surgery had failed and the cancer was spreading (J Bone Miner Res. 2002;17(Suppl 2):N87-92). Many of the patients had been treated with high dose bisphosphonates. During the 16-week dose titration phase, the daily dose was titrated up to 280 mg of cinacalcet HCl. With treatment, the mean serum calcium decreased, but not into the normal range (8.5 to 10.2 mg/dL). Overall, 15 of the 21 patients achieved a serum calcium reduction of 1 mg/dL, the others did not respond to treatment. However, there was very little change in the predose serum parathyroid hormone level. Dr. Peacock recommends using 30 mg of cinacalcet HCl, twice daily to start and then titrating up based on serum calcium levels, not parathyroid hormone levels. The most frequent adverse events were nausea and vomiting.

The disease course and diversity of response to cinacalcet HCl treatment was summarized for three of the study patients. The first patient had serum calcium in the 14.5 mg/dL range and initially responded well to parathyroidectomy and thyroidectomy. However, about two years later, nodules were spreading in her neck and the serum calcium and parathyroid hormone levels increased. At study baseline, she had severe hyperparathyroidism. Her disease responded rapidly to the cinacalcet HCl, and the serum calcium levels returned to the normal range. “There couldn’t be a better response in terms of getting serum calcium down,” explained Dr. Peacock. The serum parathyroid hormone level came down slightly; however, it remained at a high level. This patient also had a good response in terms of her quality of life.

The second patient had in situ thyroid carcinoma and was treated with radioactive iodine. Three years later, she developed high serum calcium and was diagnosed with parathyroid cancer. Despite an initial response to surgical intervention, the serum calcium and parathyroid hormone levels gradually increased. At study baseline, this patient had serum calcium in the 14 mg/dL range and high serum parathyroid hormone levels. After starting cinacalcet HCl, it was very difficult to achieve serum calcium levels that even approached the normal range. “The serum PTH level actually increased over time,” he said. She developed severe nausea, which affected the titration schedule and caused problems with compliance.

The third patient had serum calcium in the 21 mg/dL range, a very high bone turnover, and a large mass in the parathyroid. He was treated with parathyroidectomy and then went into severe hungry bone syndrome. He became hypocalcemic and was treated with calcitriol and calcium supplementation. At study baseline, serum calcium was 8.6 mg/dL, serum parathyroid hormone was high, and bone turnover was still high. He had severe hyperparathyroid bone disease in addition to parathyroid cancer. “He is normocalcemic, but still has hungry bones to a certain extent and he would not be a good candidate for cinacalcet HCl,” said Dr. Peacock.

“Although cinacalcet HCl can be very useful, we need to identify which patients will respond,” concluded Dr. Peacock.

Primary Hyperparathyroidism: Pathophysiology and Opportunities for New Therapies

John Bilezikian, MD, Professor of Medicine, Chief, Division of Endocrinology, and Director, Metabolic Bone Diseases Program, Columbia University, College of Physicians and Surgeons, New York, discussed the pharmacological alternatives to surgery for PHPT, since many patients do not meet current guidelines for surgery.

In symptomatic patients, there are clear-cut indications for surgery: marked hypercalcemia, kidney stones, fractures, overt classical neuromuscular disease, or parathyroid cancer. “In asymptomatic patients with hyperparathyroidism, treatment decisions are more complicated,” he said. In 2002, an NIH Workshop on the Management of Asymptomatic Primary Hyperparathyroidism revised guidelines for parathyroidectomy. According to these guidelines, surgery is indicated if serum calcium is 1 mg/dL above normal, urinary calcium is greater than 400 mg/24 hours, serum creatinine is abnormal, bone density T-score is less than -2.5 at any site (lumbar spine, femoral neck, or radius), and the patient is less than 50 years of age. Therefore, patients who do not meet this criteria, those who do meet the criteria but have extenuating medical conditions, and those who refuse surgery, are candidates for nonsurgical approaches.

Dr. Bilezikian reviewed three classes of pharmacological agents: selective estrogen receptor modulators (raloxifene), bisphosphonates, and calcimimetics. He did not discuss in any detail estrogens in view of the data from the Women’s Health Initiative that has led to marked restriction in its use. Nevertheless, there is evidence in the older literature that estrogens reduce the serum calcium concentration in PHPT. The adverse event profile of estrogen precludes its use in PHPT, and it is not an approved indication for this disorder. In fact, the three classes of drugs that Dr. Bilezikian reviewed are not specifically approved for PHPT. The calcimimetic cinacalcet HCl is approved for treatment of hypercalcemia in patients with parathyroid carcinoma and for the treatment of secondary hyperparathyroidism in patients with chronic kidney disease on dialysis.

There is limited experience with raloxifene. Dr. Bilezikian summarized the results of a placebo-controlled study
of 18 women with asymptomatic PHPT who were treated with 60 mg of raloxifene daily for 8 weeks (Rubin MR et al. Clin Endocrinol Metab. 2003;88:1174-1178). By week 8, there was a significant but modest reduction in serum calcium and bone turnover markers. There were no changes in parathyroid hormone, vitamin D, or urinary calcium measurements.

A placebo-controlled, one-year trial of cinacalcet HCl, by Peacock et al., found the treatment to be associated with prompt return of serum calcium to the normal range, which was maintained for the duration of the study.

Six studies have been published on the bisphosphonate alendronate in PHPT. One of these is a placebo-controlled, single-crossover study in which 44 subjects were treated with either placebo or 10 mg of alendronate daily for one year. In year 2, subjects on alendronate in year 1 continued with this therapy for another year. Subjects who received placebo in year 1 were crossed over to receive alendronate in year 2 (Khan AA, et al. J Clin Endocrinol Metab. 2004;89:3319-3325). There was a significant increase in bone density in those patients who received alendronate in year 1, and a maintenance of those gains in bone density in year 2. The placebo group had no change in bone density in those patients who received alendronate in year 1, but a significant increase in bone density after alendronate treatment in year 2. Alendronate treatment was also associated with reduced bone turnover markers, and stable serum calcium and parathyroid hormone levels.

Dr. Bilezikian next summarized three studies of cinacalcet HCl in PHPT. The first study, by Shoback et al., was a proof-of-concept study (J Clin Endocrinol Metab. 2003;88:5644-5649). Subjects received placebo or one of three doses of cinacalcet HCl (30, 40, and 50 mg) twice daily for 15 days. All doses were associated with a reduction in serum calcium levels, which returned to baseline levels after a seven-day washout period (Figure 1). Although the serum calcium was significantly reduced with the drug, there were no short-term reductions in the first hours after drug administration. In contrast, parathyroid hormones fell quickly (within hours) after drug administration. This pulsatile decline in parathyroid hormone levels tended to return toward baseline levels thereafter.

A placebo-controlled, one-year trial of cinacalcet HCl, by Peacock et al., found the treatment to be associated with prompt return of serum calcium to the normal range, which was maintained for the duration of the study (J Clin Endocrinol Metab. 2005;90:135-141). The placebo group showed no change in serum calcium levels. Again, serum parathyroid hormone levels were significantly, although modestly, decreased with cinacalcet HCl treatment.

Reporting on a third study, Dr. Bilezikian cited work again by Peacock et al. who reviewed five studies of cinacalcet HCl, dividing them into three groups: those who failed parathyroid surgery, those who met at least one NIH criteria for surgery but didn’t have parathyroid surgery, and those who had mild asymptomatic disease and did not meet any NIH criteria. “Cinacalcet HCl was well tolerated and effective in normalizing the serum calcium in all three groups for up to three years,” said Dr. Bilezikian.

In summary, cinacalcet HCl normalizes serum calcium and modestly reduces parathyroid hormone in PHPT. The normalization of serum calcium seems to be maintained for at least three years.

In summary, cinacalcet HCl has the potential to fill an unmet need as an effective alternative to surgery in some patients with PHPT,” concluded Dr. Bilezikian.
The Kidney is a Key Link between Diabetes and Cardiovascular Disease: Managing Risk

Anemia is a nontraditional risk factor for cardiovascular disease in patients with chronic kidney disease (CKD), and diabetic CKD patients are more likely to have anemia than those with normal renal function. At a symposium held May 18, 2005, during the American Association of Clinical Endocrinologists’ Fourteenth Annual Meeting and Clinical Congress, three experts discussed risk factors of cardiovascular disease and anemia in diabetic CKD patients and highlighted the benefits of early and aggressive intervention.

Diabetic Nephropathy: A Growing Concern

“Approximately 40% of patients with type 2 diabetes develop diabetic nephropathy,” began Hans-Henrik Parving, MD, Professor and Chief Physician, Steno Diabetes Center, Gentofte, Denmark. Some patients with chronic kidney disease (CKD) will develop end-stage renal disease (ESRD), but the major concern for these patients is cardiovascular disease.

“Microalbuminuria is a powerful indicator of risk for vascular manifestations, such as retinopathy, neuropathy, and foot ulcers,” said Dr. Parving. It also enhances cardiovascular morbidity, all-cause mortality (especially cardiovascular), and predicts development of diabetic nephropathy. About 24% of Americans have metabolic syndrome, a pre-diabetes condition. Among these patients, the prevalence of elevated albumin excretion is 14% and prevalence of CKD is 6%. The question of whether treatment of metabolic syndrome will prevent CKD is currently being investigated.

Just being obese appears to be an independent risk factor for ESRD, according to a study by Chi Yuan (J Am Soc Nephrol. 2004;15:43A). People who were morbidly obese had a five-fold increased risk for ESRD compared to normal-weight individuals. Each factor in the metabolic syndrome further increases risk for microalbuminuria, up to an 18% increased risk in people with all five metabolic risk factors. In addition, mortality from cardiovascular disease is increased 3.5% in people with metabolic syndrome compared to those without the syndrome (Läkka et al. JAMA. 2002;288:2709-2716).

Each factor in the metabolic syndrome further increases risk for microalbuminuria, up to an 18% increased risk in people with all five metabolic risk factors.

Dr. Parving described the DEMAND study (Developing Education on Microalbuminuria for Awareness of Renal and Cardiovascular Risk in Diabetes), which evaluated the global prevalence and determinants of micro- and macroalbuminuria in type 2 diabetes and looked at protective treatment for cardiovascular risk factors in these patients (J Am Soc Nephrol. 2004;15:565A-566A). The study included 30,000 type 2 diabetics without known proteinuria or kidney disease in 33 countries. Half (51%) had normal urinary excretion rate, 39% had microalbuminuria, and 10% had macroalbuminuria. People living in Asia had a higher risk of developing kidney disease than those living in Europe or North America.

The DEMAND study also found that an estimated glomerular filtration rate (eGFR) of less than 60 mL/min/1.73 m² indicates CKD. The investigators found that 17% of patients with normal albumin excretion rate had reduced kidney function, raising micro- and macroalbuminuria. “Reduced kidney function is a powerful independent predictor of cardiovascular disease,” said Dr. Parving.

“From this study, it’s clear that earlier detection and more aggressive multifactorial treatment aimed at renal and vascular protection are urgently needed,” said Dr. Parving.

He continued with a discussion of prevention, beginning with a primary prevention study by Ruggenenti et al. (N Engl J Med. 2004;351:1941-1950). Type 2 diabetic patients with normal albuminuria were randomized to receive either conventional treatment or combined treatment with an ACE inhibitor and a calcium-channel blocker (trandolapril plus verapamil). Patients in the treatment arm had a reduced occurrence of microalbuminuria.

Dr. Parving also described a study he and his colleagues conducted, which evaluated the renoprotective effect of the angiotensin-II-receptor antagonist.
Peter A. McCullough, MD, MPH, Consultant Cardiologist and Chief, Divisions of Cardiology, Nutrition, and Preventive Medicine, William Beaumont Hospital, Royal Oak, Michigan, described the “deadly triangle” of kidney disease, cardiovascular disease, and anemia. “Anemia is a treatable condition, but it also is a novel cardiovascular risk state,” he said.

Anemia and cardiac complications in patients with diabetic nephropathy is associated with micro- and macrovascular complications. This also is an independent risk factor for hospitalization, congestive heart failure, left ventricular hypertrophy (LVH), and ischemic heart disease. “Anemia and CKD together become risk multipliers for adverse cardiovascular outcomes,” said Dr. McCullough.

CKD are more likely to die of CV disease than to develop ESRD requiring dialysis,” he said. Even patients with stage 4 kidney disease are more likely to die before they require dialysis.

In terms of risk for developing ESRD, Dr. McCullough pointed out that among patients with an eGFR of 30 to 60 mL/min, those with the lowest level of hemoglobin are at highest risk for progression to ESRD (Levin A. Nephrol Dial Transplant. 2002;17:8-13). “For some reason, anemia or hemoglobin is a reflection of underlying worsened renal disease, or it may contribute to the progression of CKD,” he said.

Among patients who have macrovascular disease (i.e., CV disease) who have diabetic nephropathy, there is an increased prevalence of anemia, Dr. McCullough continued. “Chronic kidney disease itself is a cardiovascular risk factor,” he said.

While the exact causes of anemia in CKD are not known, a likely explanation is erythropoietin deficiency. Other possible explanations include epoetin alfa resistance, hemodilution, other chronic diseases, shortened RBC lifespan from 120 to 64 days, iron deficiency, malnutrition, and anemia related to ACE inhibitors/ARBs. “CKD is a state where there is an inadequate erythropoietic response, which causes inappropriately low erythropoietin production and reduced level of RBCs,” said Dr. McCullough.

He cited a study showing that once the eGFR is below 60 mL/min, there’s a higher rate of anemia in diabetics com-

**From this study, it’s clear that earlier detection and more aggressive multifactorial treatment aimed at renal and vascular protection are urgently needed,” said Dr. Parving.**
pared to nondiabetics. “Something about diabetes and its relationship to erythropoietin response causes a greater degree of anemia,” he said.

Among patients who have both heart and kidney failure, there appears to be a vicious cycle where anemia and a subtle degree of tissue hypoxia cause peripheral vasodilation, which drops blood pressure, increases sympathetic nervous system activity and regulatory hormone output, reduces renal blood flow, further activating the renal angiotensin system and creating a degree of plasma volume expansion. These factors cause LVH and dilation, further fibrosis within the heart and the kidney, and worsening ejection fraction and glomerular filtration rate. According to the American Heart Association, CV risk factors in patients with CKD include both anemia and diabetes.

“Anemia causes reduced hemoglobin tissue hypoxia, ultimately causing a greater degree of cardiac work, which triggers LVH that further worsens ischemia and ultimately can cause congestive heart failure, stable angina, and unstable coronary syndromes,” said Dr. McCullough.

According to the American Heart Association, CV risk factors in patients with CKD include both anemia and diabetes.

He described the following pathophysiologic consequences of untreated anemia: decreased cardiac function, cognitive function, exercise and physical performance, and health-related quality of life, and increased cardiac output, transfusion requirements, hospitalization, mortality, and expenditures.

Dr. McCullough referred to a study of patients with diabetic nephropathy and anemia that stratified mortality rate based on diabetes alone, anemia alone, CKD alone, and all three combined (Collins. Adv Stud in Med. 2003;3:S14-S17). The highest mortality rate occurred in the group with all three. It’s also been shown that both all-cause and cardiac death rates are higher among dialysis patients who are persistently anemic on dialysis compared to those who are not anemic (Li et al. Kidney Int. 2004;65: 626-633).

Dr. McCullough described a study of angiotensin receptor blockers in patients with new onset heart failure or large myocardial infarction (Aguilar et al. Circulation. 2004;110:1572-1578). “Diabetes, whether previously known or newly diagnosed, was associated with a higher unadjusted and adjusted relative risk for death over time and a higher composite outcome of CV death, reinfarction, heart failure, resuscitated sudden death, and stroke,” he said (Figure 1).

The ARIC Study looked at stable outpatient populations and found that individuals who are anemic over time have a higher rate of CV disease than those that are non-anemic (Sarnak et al. J Am Coll Cardiol. 2002;40:27-33). Anemia has also been found to be an independent risk factor for mortality in patients with heart failure (Mozaffarian et JACC. 2003;41:1933-1939). In the TIMI Study, anemia (Hb <13g/dL) was found to be a predictor of adverse outcomes in patients following acute coro-

A
g

Figure 1

Mortality by Diabetic Status

- Previously known diabetes
- Newly diagnosed diabetes
- No diabetes

![Figure 1](https://via.placeholder.com/150)

Anemia has also been shown to increase relative risk of stroke in CKD patients. “There appears to be no aspect of CV disease that is immune from the risk of anemia,” said Dr. McCullough.

LVH is present in 74% of patients at dialysis initiation and LVH is an independent predictor of CV disease. For every 1 g/dL decrease in hemoglobin there is a 6% increased risk of LVH; therefore, a 3% decrease in hematocrit predicts a 7% increase in risk of death.

A study by Gurm et al. found that declining kidney function and declining hemoglobin levels are independent predictors of mortality in patients undergoing PCI (Am J Cardiol. 2004;94: 30-34). When the two are combined, the effect is potentiated (rather than additive).

Dr. McCullough concluded: “CKD is an independent CV disease risk state. Diabetes is the most common cause of chronic kidney disease and is an important risk factor for adverse CV outcomes. Treating anemia may reduce the risk of mortality and CV events, especially in CKD patients.”
Management of Anemia in Patients with Diabetic Nephropathy

“C”hronic kidney disease leads to erythropoietin deficiency and anemia, that goes on to cause CV disease,” began Brian J.G. Pereira, MD, Professor of Medicine, TUSM, Tufts-New England Medical Center, Boston. “For a long time we focused on ESRD and dialysis,” he continued. “We now know that even mild degrees of kidney dysfunction are associated with an increased likelihood of death and an increased risk for cardiac events.”

Conventional CV risk factors do not explain all of the CV risk in CKD patients, almost 38% of whom have non-traditional risk factors. Traditional risk factors include older age, hypertension, high LDL, low HDL, diabetes, smoking, inactivity, menopause, and family history of CV disease. Non-traditional risk factors include albuminuria, high homocysteine, lipoprotein(a) isoforms, lipoprotein remnant, and anemia, among others (Sarnak et al. Circulation. 2003;108: 2154-2169).

Dr. Pereira noted that anemia begins early in CKD, the prevalence of anemia of CKD is high, and anemia is a predictor of progression of CKD. It also is an important predictor of CV disease in CKD. Anemia during CKD is a risk factor for death in the general population, in patients with CV disease, in patients with CKD, and in patients with ESRD.

“Anemia is as big a risk factor for LVH as blood pressure,” said Dr. Pereira. A drop in hemoglobin of 0.5 g/dL is associated with the same increased risk as a 15 mmHg increase in blood pressure. “The bad news is CKD patients tend to have both anemia and hypertension,” said Dr. Pereira. He pointed to seven studies in which patients were treated with erythropoietin agents, which resulted in a rise in hemoglobin and an improvement in left ventricular mass index. “To some extent, the dysfunction from anemia is reversible,” he said.

Dr. Pereira pointed out that anemia is an important predictor of resource utilization. A study by Khan et al. found that a 1% increase in hematocrit was associated with an 8% reduction in hospitalizations and a 13% reduction in hospital days (Kidney Int. 2002;62: 229-236). “The question is, does correcting anemia reduce hospitalizations?” said Dr. Pereira. A study by Silverberg et al. in both diabetics and nondiabetics found that when hemoglobin was corrected hospitalization rates dropped significantly while the NYHA class improved significantly (Nephrol Dial Transplant. 2003;18: 141-146).

“Despite all of the evidence that anemia, CKD, and diabetes are a bad combination, anemia of CKD is under recognized and under treated,” said Dr. Pereira. He cited a study by Obrador et al. that showed that the majority of patients starting dialysis are already severely anemic (J Am Soc Nephrol. 1999;10:1793-1800). In a separate study, Obrador et al. showed that significant progress has been made in the treatment of anemia in dialysis over the past 10 years. Ten years ago, the average hematocrit was 29% six months into dialysis, while today it is close to 36%. However, no progress has been made in managing anemia prior to dialysis. Ten years ago, the average hematocrit at the start of dialysis was 27.5% and today it is 28.5% (Kidney Int. 2001;60: 1875-1884).

“Darbepoetin effectively corrects anemia and maintains hemoglobin similar to erythropoietin,” said Dr. Pereira.

“By the time patients come to see a nephrologist, 60% of them have anemia, and only one-third of those with a hematocrit less than 28% have gotten a dose of an erythropoietic agent,” said Dr. Pereira, citing data from Kazmi et al. (Am J Kid Dis. 2001;38: 803-812).

Dr. Pereira went on to discuss the new generation of long-acting erythropoietin agents, which includes darbepoetin alfa. Darbepoetin binds to the same receptor as erythropoietin and has the same mechanism of action. The difference is the addition of sialic acid chains that prolongs the in-vivo activity. This means it has a three-fold longer half-life compared to erythropoietin. “Darbepoetin effectively corrects anemia and maintains hemoglobin similar to erythropoietin,” said Dr. Pereira.

An important advantage of darbepoetin is less frequent dosing. Erythropoietin must be administered two to three times per week, Varenterghem and colleagues showed that in patients converted from erythropoietin to darbepoetin, 97% maintained hemoglobin levels with once-a-week administration (Kidney Int. 2002;62: 2167-2175). A study by Ling et al. showed that 85% of CKD patients maintained hemoglobin levels with once-a-month administration (Clin Nephrol. 2005;63: 327-334).

So far, the evidence showing that treating anemia can reduce risk for CV disease and mortality comes from retrospective analyses. Dr. Pereira concluded by describing the first large prospective randomized studies looking at treatment of anemia versus no treatment. The first is the Trial to Reduce Cardiovascular Events with Darbepoetin Alfa Therapy (TREAT), which includes 4,000 type 2 diabetes patients with eGFR of 20 to 60 mL/min and hemoglobin less than 11 g/dL, who are randomized to receive darbepoetin or placebo. The primary endpoints are all-cause mortality and nonfatal CV events. The study will run for four years.

The second study is the Anemia Correction in Diabetes Trial (ACCORD), which is testing the hypothesis that treatment of anemia with recombinant erythropoietin reduces CV risk in patients with diabetic nephropathy and mild-to-moderate CKD.
Understanding Female Sexual Dysfunction and the Role of Testosterone

At a symposium held May 21, 2005, during the American Association of Clinical Endocrinologists’ Fourteenth Annual Meeting and Clinical Congress, a panel of experts reviewed causes and consequences of female sexual dysfunction, discussed the endocrinology of female sexuality, and examined treatment strategies for menopausal women with hypoactive sexual desire disorder, including a review of testosterone safety and efficacy data.

Sex and the Menopausal Woman: Psychological and Interpersonal Considerations

“While there are no predictable and definite changes in sexuality that occur to all postmenopausal women, menopause is associated with a variety of hormonal and psychological concomitants,” said Sandra R. Leiblum, PhD, Professor of Psychiatry and Obstetrics/Gynecology, UMDNJ-Robert Wood Johnson Medical School, Piscataway, New Jersey. “To understand and treat the sexual problems of mid-life women, it is necessary to be cognizant of the particular historical, biological, and current factors affecting their lives,” she added.

Dr. Leiblum outlined some of the factors that contribute to women’s sexual problems, beginning with changes in hormones at menopause. There is a diminution of estrogen, but also a reduction in androgen, which starts to change in a woman’s mid-30s. One of the biggest culprits, she said, is medications. For example, SSRIs, given for depression, can diminish sexual interest. Other factors include a past history of disappointing sex, lack of privacy, history of sexual abuse or other physical trauma, problems with the current relationship, and lack of adequate partner stimulation. Dr. Leiblum also noted that postmenopausal women may be self-conscious about their weight, shape, and size.

“The odds of having a sexual problem increase with both anxiety and depression,” said Dr. Leiblum. For example, Dunn et al. found that the odds ratio for depressed women having problems with sexual arousal was six times higher than it was for nondepressed women (J Epidemiol Community Health. 1999;53:144-148). Both depression and the medications used to treat depression can negatively impact all aspects of a woman’s sexual response—desire, arousal, and orgasm.

The most prominent sexual function concern of postmenopausal women is loss of sexual interest and desire, which affects about 35% to 50% of postmenopausal women. Another concern relates to sexual arousal, which includes inability to become physically (genitally) aroused, inability to become subjectively (mentally) aroused, and a newly diagnosed complaint, persistent sexual arousal, which refers to genital arousal that persists despite one or more orgasms. Postmenopausal women may also complain that their orgasms are muted (or absent), that they are experiencing discomfort or pain before, during, or after coitus, and that they have begun to experience stress incontinence.

The most prominent sexual function concern of postmenopausal women is loss of sexual interest and desire, which affects about 35% to 50% of postmenopausal women.

The degree to which these issues are distressing to women was assessed in the Women’s International Study of Health and Sexuality (WISHeS), a self-administered mail survey of 2,050 surgically and naturally postmenopausal women aged 20 to 70. One-third of each of the following three groups reported decreased sexual interest: surgical menopause aged 20 to 49, surgical menopause aged 50 to 70, and natural menopause aged 50 to 70. “About 72%

This program was supported by an unrestricted educational grant from Procter and Gamble Pharmaceuticals.
of the younger surgically menopausal women reported considerable distress about the loss of sexual desire,” said Dr. Leiblum, adding that “44% of the older surgically menopausal women and 33% of naturally menopausal women reported distress.” This study extrapolated that 26% of young surgically menopausal women would meet the DSM-IV definition of hypoactive sexual desire disorder (HSDD), as would 20% of older surgically menopausal women, and 10% of naturally menopausal women.

Participants in the study reported that the emotional consequences of loss of sexual desire included feeling less feminine (47%), inadequate (39%), like a sexual failure (39%), ashamed (35%), insecure (33%), and having low self-esteem (37%).

Dr. Leiblum noted that another sexual concern of postmenopausal women is a discrepancy between the woman’s sexual script (the “who, what, when, where, how of sexual exchange”) and that of her partner. “She wants seduction, romance, lingering foreplay, darkness, sex at night. He wants spontaneity, visual stimulation and variety, sex in the morning.” Relationship dynamics can also influence sexual dysfunction. “It can be hard to know if relationship problems lead to sexual problems or if the sexual problems lead to the relationship problems,” she said. But clearly sexual problems in one partner contribute to problems in the other.

Dr. Leiblum listed the following categories of women at high risk for sexual dysfunction: surgically menopausal women (or women with hormonal insufficiency), women with comorbid conditions (especially depression, diabetes, hypertension, neurological disease, or cancer treatment), and women with relationship problems.

In conclusion, Dr. Leiblum stated: “There are many psychological and interpersonal factors that can affect postmenopausal sexual functioning. There is rarely a single etiological cause for any woman’s sexual complaints. The best treatment is one that includes attention to the precipitating, maintaining, and contextual factors contributing to a woman’s sexual health and well-being, as well as attention to biological and interpersonal considerations.”

Testosterone and Female Sexual Function

Glenn D. Braunstein, MD, Chair, Department of Medicine, Cedars-Sinai Medical Center, and Professor of Medicine, David Geffen School of Medicine at UCLA, Los Angeles, discussed sources of androgens, androgen metabolism, how testosterone is measured, and the syndromes associated with low androgen production in women.

In the premenopausal state, 25% of testosterone comes from the ovaries, 25% from the adrenals, and 50% from peripheral conversion in a variety of tissues. In the postmenopausal state, only about 10% of testosterone comes from the adrenals, 50% from the ovaries, and 40% from peripheral conversion. A study by Zumoff et al. showed that mean testosterone levels in the circulation decreased by about 50% between ages 20 and 40, with a further reduction until age 50 (J Clin Endocrinol Metab. 1993;80:1429-1430).

“There is an age-related reduction in testosterone and adrenal androgen precursor production,” said Dr. Braunstein.

Women. Testosterone dynamics indicate that levels of testosterone are higher in the morning, and therefore levels should be measured in the morning. There is also a midcycle peak of testosterone in women of reproductive age that coincides with the LH peak. “To measure the highest level of testosterone in a woman of reproductive age, the blood sample should be obtained in the morning at mid-cycle,” he said.

He next addressed the question of which moiety should be measured—total, free, or bioavailable testosterone? Total testosterone refers to the total amount of testosterone in the circulation, taking into account that about two-thirds of the testosterone is bound to sex hormone-binding globulin, and is unavailable to the tissues. About one-third of the total testosterone is bound to albumin. Albumin has a high capacity but low affinity for testosterone and therefore the testosterone may diffuse off the albumin and enter peripheral tissues. About 2% of total testosterone is in the free state (Figure 1). The combination of free and albumin-bound testosterone makes up the bioavailable testosterone. In addition to these three molieties, there are several testosterone metabolites that can be measured.

There are a variety of methods for measuring testosterone. The gold standard for measuring total testosterone is either liquid chromatography or gas chromatography followed by tandem mass spectroscopy. However, the direct method is used most often because it is fast and relatively inexpensive, but it can be inaccurate for measuring testosterone in women, Dr. Braunstein said. He described a study showing that the direct method overestimated the amount of total testosterone present in the circulation of women (Taieb et al. Clin Chem. 2003;49:1381). Free testosterone is best measured by equilibrium dialysis, which
is expensive. Therefore, it is most often measured by direct assays. Dr. Braunstein cited another study showing that using a direct assay results in an underestimation of the amount of free testosterone in women (Miller et al. J Clin Endocrinol Metab. 2004;89:525).

The free androgen index is a calculation done by measuring total testosterone and sex hormone binding globulin to approximate free testosterone levels. Sex hormone-binding globulin measurements are easy to perform and are consistent.

Dr. Braunstein noted that few normal ranges of testosterone levels for women have been published. “It’s currently not possible to differentiate women who have low libido from women who have normal libido based on testosterone results,” he said. He doesn’t believe there’s any value in measuring testosterone in women who are complaining of hypoactive sexual desire disorder or low libido because almost all have low testosterone levels.

Dr. Braunstein next reviewed the conditions associated with androgen insufficiency, which include hypothalamic-pituitary abnormalities, bilateral oophorectomy, adrenal insufficiency, glucocorticoid therapy, and exogenous oral estrogens.

A study by Arit et al. found that women with either primary or secondary adrenal insufficiency had low levels of DHEA, DHEA sulfate, androstenedione, testosterone, dihydrotestosterone, and androstenediol (N Engl J Med. 1999;341:1013-1020). “When these women were treated with DHEA their levels of all the androgens increased into the low normal range,” said Dr. Braunstein. They had decreased sexual function before DHEA therapy, which improved after therapy.

Some, but not all, studies have correlated testosterone with overall sexual drive, arousability, masturbation, and coital frequency. “Antiandrogen administration decreases libido, and testosterone replacement improves libido in women who have had oophorectomy and are placed on estrogens, as well as for women who undergo natural menopause,” said Dr. Braunstein. In a study by Buster and colleagues, the change in total, free, and bioavailable testosterone were correlated with change in the frequency of sexual activity, change in desire, and a decrease in distress (Obstet Gynecol. 2005;105:944-52).

Dr. Shifren noted that it’s important to first determine the causes of sexual concerns, which can relate to relationship issues, partner performance, psychology, sociocultural issues, and physiology. “In many cases, sex therapy can be very effective,” said Dr. Shifren. She cited a study of 365 married couples with a range of sexual dysfunctions, which produced a 65% success rate (Sarwer & Durlak. J Sex & Marital Therapy. 1997;23:87).

Several pharmaceutical drugs have been investigated for sexual dysfunction in women. Sildenafil, the drug for male erectile dysfunction, was found to be effective for women with arousal disorder, but no more so than placebo (Basson et al. J Women’s Health & Gender-Based Med. 2002;11:367). The antidepressant bupropion was found...
Understanding Female Sexual Dysfunction and the Role of Testosterone

Case #1
52-year-old woman with three children who is active in community service.
• Her spouse is the CEO of a large company; he gets home late and travels often.
• There is increased tension in the marriage, and she has decreased interest in sex over the past year.
• She has infrequent sexual relations with minimal pleasure.

Recommendation: “The most appropriate therapeutic approach for this couple is relationship counseling and sex therapy.”

Case #2
61-year-old retired teacher with five grandchildren.
• She had onset of mild depression four years ago, which was successfully treated with an SSRI.
• Her spouse of many years has hypertension and diabetes and intermittent erectile dysfunction.
• The marriage is stable and happy.
• For several years, she has had decreased interest in and pleasure from sex.

Recommendation: “Switch her antidepressant to bupropion and treat her husband’s erectile dysfunction.”

Case #3
49-year-old architect who had a right salpingo-oophorectomy at age 23 for large endometrioma.
• She underwent complete hysterectomy and left salpingo-oophorectomy at age 47 for persistent endometriosis.
• She has no interest in sex and few sexual thoughts or fantasies since her surgery.
• All sexual activity is partner initiated and she has decreased orgasmic response.

Recommendation: “This patient is a candidate for testosterone therapy.”

to improve sexual function in premenopausal women (Masand, et al. Am J Psychiatry, 2001;158:805). Bupropion is associated with several side effects, so it may be most appropriate for women already taking an antidepressant.

Dr. Shifren explained that while hormonal levels do not predict sexual function, hormonal interventions may still be effective. For example, vaginal estrogen can be very helpful. “In addition to nonhormonal lubricants, you should encourage your menopausal patients to use low-dose vaginal estrogen therapy,” she said. Vaginal estrogen creams, tablets, and rings all reduce vaginal dryness and discomfort with intercourse. The vaginal ring raises plasma estradiol levels slightly when initially inserted, but levels then return to baseline for the remainder of the three months the ring stays in place (Schmidt et al. Gynecol Obstet Invest. 1994;38:253).

Testosterone for sexual dysfunction in menopausal women was examined in a study by Sherwin and Gelfand, in which surgically menopausal women were treated with injections of estradiol, testosterone plus estradiol, or placebo. The women receiving the combination had statistically significant improvements in all aspects of sexual function: desire, fantasies, arousal, and coitus (Psychosom Med. 1987;49:397). “This was a great test of the concept, but the blood levels of testosterone achieved in this study were in the low male range, and we’re interested in discovering the effect of providing testosterone in the physiologic range,” said Dr. Shifren.

A study by Davis et al. looked at surgically and naturally menopausal women without sexual concerns who were given implants of estradiol or testosterone plus estradiol for three years (Maturitas. 1995;21:231). There were significant improvements in all measures of sexual function in the combination group compared to the estradiol alone group.

Dr. Shifren addressed the potential delivery systems for testosterone, noting that injectables are “uncomfortable and difficult to dose in women,” and implants aren’t available in the United States. The FDA-approved oral androgen product, which is a combination of esterified estrogens and methyltestosterone, was shown to improve sexual desire and frequency of desire in a randomized trial (Lobo et al. Fertil Steril. 2003;79:1341). However, this drug contains fixed doses of estrogen (0.625 mg) and methyltestosterone (1.25 mg), and oral androgens have an adverse effect on HDL due to the first-pass hepatic effect.

Testosterone transdermal patches and gels are available for men, but Dr. Shifren does not recommend using these in women because women’s testosterone levels are about one-tenth those of men; consequently, women are at risk for overdose and side effects with these products.

“Unfortunately, we currently do not have a way of giving testosterone appropriately dosed for women, delivered in a non-oral form,” said Dr. Shifren. She explained that a transdermal testosterone patch for women has been developed and is currently being tested in Phase III trials.

In clinical trials, 1,110 surgically menopausal women and 530 naturally menopausal women with HSDD received the testosterone patch (300 mcg per day) or placebo, with concurrent estrogen therapy. Among those in the treatment arm, free testosterone levels were in the middle to upper limit of normal for premenopausal women. In addition, women in the treatment group had statistically significant improvement in satisfying sexual activity and sexual desire compared to placebo. “Every measure of sexual activity that was assessed had a statistically significant increase in women treated with testosterone compared to placebo-treated women. Significant decreases in personal distress also were seen,” said Dr. Shifren.

In terms of adverse effects, there was a slight increase in facial hair and acne in testosterone-treated women.

Dr. Shifren concluded: “Androgens should be used in very carefully selected women. There should be a physiologic reason for decreased testosterone, and alternative etiologies and treatments should be considered and treated first. More research on testosterone patches and gels appropriately dosed for women is needed.”
Insulin resistance together with β-cell dysfunction leads to the appearance and gradual progression of type 2 diabetes. At a symposium held May 20, 2005, during the American Association of Clinical Endocrinologists’ Fourteenth Annual Meeting and Clinical Congress, a panel of experts discussed the risk factors disposing patients to type 2 diabetes, cardiovascular disease, and other complications, and they evaluated data supporting combination therapy which includes agents such as thiazolidinediones.

Insulin resistance and Hypertension: Synergistic and Opposing Effects

“Insulin resistance is associated with significant clinical abnormalities that are associated with increased cardiovascular risk,” began Vivian Fonseca, MD, Professor of Medicine and Chief of Endocrinology, Tulane University Medical Center, New Orleans. In the average cardiology office, 15% of patients have diabetes and another 15% have impaired glucose tolerance. “Hypertension is an independent risk factor for developing type 2 diabetes,” he said.

Targeting insulin resistance is important because over 90% of patients with type 2 diabetes are insulin resistant. Insulin resistance comes from visceral obesity and it contributes to hypertension, disordered fibrinolysis, complex dyslipidemia, endothelial dysfunction, systemic inflammation, and atherosclerosis.

The treatment of most cardiac risk factors in patients with diabetes and coronary artery disease do not meet goals. In particular, hemoglobin A1C, HDL cholesterol, blood pressure, and obesity are poorly controlled. Sixty-two percent of patients with type 2 diabetes have inadequate glycemic control. According to Dr. Fonseca, combination therapy is needed to control hyperglycemia and hypertension. He described the ongoing Action to Control Cardiovascular Risk in Diabetes (ACCORD) study, which is the first study attempting to normalize blood pressure, normalize blood glucose, and address lipids as well. The results of this study should be reported in 2010.

Insulin Resistance, Hypertension, and Their Effects on the Vasculature Devastation

“The decline in coronary events rates seen in the 1970s, 1980s, and 1990s has ended,” began Andrew Selwyn, MD, Professor of Medicine, Harvard Medical School, and Associate Chief, Cardiovascular Division, Brigham and Women’s Hospital, Boston. It’s predicted that coronary event rates will increase, largely due to the aging population but also because of the increase in the body mass index and the explosive increase in type 2 diabetes.

The early phases of insulin resistance are characterized by hyperinsulinemia, which is followed by poor insulin secretion. “Macrovascular disease develops 7 to 10 years before the onset and diagnosis of overt diabetes,” said Dr. Selwyn.

Microvascular disease tends to develop a little later.

Dr. Selwyn noted that the same risk factors that trigger coronary artery disease characterize the metabolic syndrome. He summarized the characteristics of metabolic syndrome, calling it “a malignant family of cardiovascular risk factors.” These include hyperglycemia; hypertension; hyperglyceridemia; small, dense LDL-C; low HDL-C; impaired fibrinolysis; and hypercoagulability. These factors cause oxidant stress, endothelial dysfunction, inflammation, and proliferation, all of which lead to atherosclerosis. “These pathologic features are initiated and propagated by all the well-known risk factors that characterize the
metabolic syndrome,” explained Dr. Selwyn. And there is a direct correlation between the level of CRP and the number of risk factors for metabolic disorder. “It is fair to say that this inflammation associated with atherosclerosis is highly triggered by the metabolic syndrome,” he added.

Basic research has illuminated the mechanism of insulin resistance. As excess glucose enters cells, the enzymes in the glycolytic pathway are overwhelmed, leading to the release of toxic byproducts that alter the potential of the mitochondrial membrane. With an altered membrane potential, the respiratory chain is impaired at stage 3 and produces oxygen-free radicals instead of ATP. The oxygen free radicals are highly damaging and affect a number of different systems.

“Early in the development of type 2 diabetes, there is an association with a failure of endothelium-dependent vasodilation compared with matched controls,” explained Dr. Selwyn. As patients progress from insulin resistance, to impaired glucose tolerance, to diabetes and hypertension, there is an associated impairment in the behavior of the endothelium.

Dr. Selwyn cited a study that examined insulin resistance in non-diabetic patients who had recently been diagnosed with essential hypertension (Hypertension. 2004;44:127-133). Following glucose load, virtually all of the patients displayed hyperinsulinemia and evidence of insulin resistance. In addition, MRI scan results demonstrated that these patients had a significant increase in visceral fat. “Patients with essential hypertension commonly have insulin resistance,” he said.

He summarized the results of several studies on the prevention of diabetes and management of metabolic syndrome. In one study, lifestyle modification resulted in a 58% reduction in the onset of new diabetes (Knowler WC, et al. N Engl J Med. 2002;346(6):393-403). The results of the CARD study demonstrated that atorvastatin, as an adjunctive treatment in diabetics, caused a striking reduction in all-cause cardiovascular disease. In another study, patients with metabolic syndrome benefited from treatment with a statin. “These patients had a greater benefit than those patients in the trial who did not have metabolic syndrome,” added Dr. Selwyn.

A review of studies on thiazolidinediones (TZDs) concluded that this class of drugs decreases glycosylated hemoglobin in type 2 diabetes by about 1.5%. “The benefit of TZDs is not lost in combination with metformin,” he added. On a background of metformin, the TZDs will produce a substantial fall in blood pressure and, on the background of sulfonylureas, TZDs will still produce a measurable drop in systolic blood pressure. “The administration of TZDs will produce a drop in small, dense LDL, a rise in HDL, some drop in triglycerides, and a marked fall in circulating free fatty acids,” explained Dr. Selwyn. In addition, TZDs will improve insulin resistance in combination with metformin and decrease PAI-1, CRP, microalbuminuria, and circulating matrix metalloproteinases.

In summary, Dr. Selwyn concluded: “Treating the components of the metabolic syndrome has already been shown to improve cardiovascular outcomes and we are still looking at aggressively lowering LDL and blood pressure.”

The Latest Data for the Treatment of Hypertension and Insulin Resistance: What We Learned from the GEMINI Trial

“Diabetic patients are exquisitely sensitive to blood pressure lowering,” began David Bell, MD, Professor of Medicine, Endocrine Division, University of Alabama School of Medicine in Birmingham, AL. The HOT study reported a 51% decrease in cardiac events in diabetic patients who were receiving hypertension treatment (Hansson L. Lancet. 1998;351:1755-62). Because of this and other studies, the target blood pressure in diabetics should be 130/80 mm Hg. “Fewer than 10% of diabetic patients with hypertension in this country are actually treated to that level,” said Dr. Bell. This is because not enough antihypertensive therapy is being utilized, he added.

Dr. Bell said that three to five medications need to be used to treat hypertension in the diabetic patient. The first three should be an ACE inhibitor, a thiazide diuretic, and a beta-blocker. Additional agents may be required to reach goal. Reports of meta-analyses of studies on the effects of beta-blockers on survival post-myocardial infarction (MI) concluded that in diabetic patients, who typically have poor outcomes following MI, treatment with beta-blockers can improve the outcome almost to the level of nondiabetic peers (Kjekshus J. Eur Heart J. 1990;11:43-50). Another study found that diabetic patients with coronary artery disease had a 41% reduction in total mortality when they were treated with beta-blockers.

“As diabetologists, we don’t like to use beta-blockers because of the increased insulin resistance and hyperglycemia,” said Dr. Bell. New-onset diabetes is increased by 25% to 30% when some beta-blockers are used in nondiabetic subjects (Gress TW. N Engl J Med. 2000;342:905-12). However, the beta-blocker carvedilol actually lowers insulin resistance. In a study comparing carvedilol and metoprolol, carvedilol was associated with 22% less new-onset diabetes (Bell DSH. Am J Cardiol. 2004;93:49-52B).

The effect of beta-blockers on insulin sensitivity in hypertensive patients was studied by Jacob et al. (Am J Hypertens. 1998;11:1258-1265). Their comparison of seven beta-blockers is shown in Figure 1.

Dr. Bell described the GEMINI study, a six-month, double-blind,
randomized comparison of the effects of metoprolol and carvedilol in the treatment of diabetic hypertensive patients (Bakris GL. JAMA. 2004; 292:2227-36). They studied 1,235 diabetic hypertensive patients taking an ACE inhibitor or an angiotensin II receptor blocker. The primary endpoint was the A1C change from baseline, and secondary endpoints were amelioration of microalbuminuria, effects on lipids, and nuisance side effects. The patients were treated with increasing doses of either carvedilol (12.5, 25, and 50 mg) or metoprolol (100, 200, and 400 mg) daily in two divided doses. Both groups achieved an equal lowering of blood pressure; in fact, nearly 70% of the patients got below the goal of 130/80 mm Hg. During the study, approximately 43% of the patients required a thiazide diuretic, 24% needed a dihydropyridine calcium channel blocker, 2% needed more alpha blockade, and only 45% received a statin.

Unlike metoprolol, carvedilol caused a significant reduction in total cholesterol and an insignificant increase in triglycerides. There were no significant changes in LDL or HDL, most likely because three times more patients in the metoprolol group were started on statins than the carvedilol group. There was a trend towards less fatigue with carvedilol.

Also, patients taking carvedilol did not have the weight gain associated with beta-blockers like metoprolol. The quality-of-life assessment favored carvedilol due to less hyperglycemia and less hypoglycemia.

The major finding of the GEMINI study was the decrease in microalbuminuria associated with carvedilol treatment, presumably due to the antioxidant activity of this drug. Microalbuminuria is a manifestation of endothelial dysfunction since the glomerulus is an arteriole, and when endothelial dysfunction is present not only does albumin leak into the urine but lipoproteins leak into the subintimal space. In the Islington Diabetes Survey, microalbumin was not only associated with diabetes but also with coronary artery disease and peripheral vascular disease. After 3.5 years, mortality was increased by over 16-fold in those with microalbuminuria (Yudkin J. Lancet. 1998;2:530-533).

To treat diabetic hypertension the first choice should be an ACE inhibitor, the second a diuretic, and the third a beta-blocker. Based on the GEMINI study, the beta-blocker of choice in the diabetic patient should be carvedilol.

“After that whatever else is needed to get the blood pressure to goal should be added,” concluded Dr. Bell.

**Relationship Between Insulin Resistance and Hyperglycemia**

“We need to be in the game early because insulin resistance appears to reach its peak at or before the time we diagnose diabetes,” began Peter Weissman, MD, Assistant Clinical Professor of Medicine and Endocrinology, University of Miami School of Medicine. “The difference between simply being insulin resistant and having diabetes is β-cell function,” he explained. In addition, it is the insulin resistance that appears to be correlated with the macrovascular risk; therefore, treatment regimens for diabetics should include insulin-sensitizing strategies.

According to the UK Prospective Diabetes Study group, with all therapies for diabetes—lifestyle intervention, insulin, metformin, insulin secretagogues, sulfonylureas—there was an inexecutable decay of glycemic control that was shown to be due to a decrease in β-cell function. Factors that may drive the progressive decline of β-cell function include hyperglycemia (glucose toxicity), insulin resistance, and lipotoxicity from elevated free fatty acids and triglycerides. “Perhaps there is a direct connection
between insulin resistance and the β-cell,” Dr. Weissman added.

The data that suggest thatTZDs may help β-cell function come from many sources. In a study of rodents who are predisposed to diabetes, there was a progressive death and disintegration of the islet and β-cells throughout the animal’s lifespan (Finegood DT et al. Diabetes. 2001;50:1021-1029). In animals pretreated with rosiglitazone, the β-cells were preserved fairly closely to the lean nondiabetic control. This positive action on the β-cell has also been demonstrated in humans. In three clinical trials using rosiglitazone alone or in combination with metformin or sulfonylurea, there was significant improvement in β-cell function compared with baseline and the comparator. Studies with troglitazone, which has been withdrawn from the market, have demonstrated the ability of TZDs to prevent disease progression from pre-diabetes to diabetes.

“I am most impressed by studies that compare the effects ofTZDs and sulfonylureas on pancreatic β-cell function,” said Dr. Weissman. Sulfonylureas have always been the quintessential β-cell drugs because they stimulate insulin release. TZDs seem to improve β-cell function more than the sulfonylureas. In addition, in studies that have looked at TZDs alone, or TZDs in combination with other agents, the initial improvement in A1C persists (Figure 2). This durability of glycemic control is due to the improvement and maintenance of β-cell function.

TZDs do to free fatty acids. In one study, rosiglitazone caused a dose-dependent reduction in free fatty acid levels in comparison with gliburide. “This effect may be, and probably is, independent of glycemic control,” added Dr. Weissman. Also, rosiglitazone treatment is associated with a decrease in the small, dense LDL particles and an increase in the larger, more buoyant fraction. “TZDs are not primary lipid agents; however, it is reassuring to know that there is a very good lipid profile for TZDs,” he explained. The two available TZDs do not impair the ability of statins to reduce LDL.

To treat type 2 diabetes, clinicians frequently use regimens that involve a TZD plus other standard agents. The combination of metformin plus TZD is preferred because of the numerous benefits for the patient, including reduced insulin resistance, cardiovascular protection, potential preservation of β-cells, minimal hypoglycemia, less weight gain, and high patient compliance. “Although I prefer the metformin/TZD combination, TZD plus sulfonylurea is also quite good,” added Dr. Weissman.

AlthoughTZDs are an ideal choice for diabetes control, only about 18% of diabetics are treated withTZDs. One barrier to the broad use ofTZDs is weight gain, which can be substantial. To counteract this side effect, patients should be warned and instructed to institute strategies to prevent weight gain. Another barrier to TZD utilization is the incidence of edema. “We need to be alert to the appearance of edema, but it doesn’t occur in the majority of patients,” Dr. Weissman explained. He also noted that edema is not synonymous with congestive heart failure, occurring in only 10% of that minority of patients who develop edema, and it is not an overriding issue for most patients.

Dr. Weissman concluded: “Dual mechanisms of disease pathophysiology require combination therapy that addresses both insulin resistance and β-cell dysfunction. Maximizing monotherapy instead of adding a second agent is generally not as effective for long-term control. Earlier intervention with combination therapy provides durable glycemic control, may reduce disease progression, and reduces side effects from higher doses of individual drugs. Clinical trials have supported the use ofTZDs with either metformin or sulfonylureas at submaximal doses.”

In studies that have looked at TZDs alone, or TZDs in combination with other agents, the initial improvement in A1C persists.
Hot Topics in Thyroid Disease

At a symposium held May 18, 2005 during the American Association of Clinical Endocrinologists Fourteenth Annual Meeting and Clinical Congress, a panel of experts discussed three challenging problems in clinical thyroidology: amiodarone-induced thyroid disorders, serum thyroglobulin test interpretation in the monitoring of patients with previously treated thyroid cancer, and postoperative radioiodine ablation of remnant thyroid tissue.

Amiodarone-Induced Thyroid Disorders

Amiodarone is a drug commonly used to treat cardiac tachyarrhythmias. “Due to its large iodine content and its induction of inflammatory changes in many organ systems, amiodarone can cause thyroid dysfunction,” said Lewis Braverman, MD, Professor of Medicine, Boston University School of Medicine, and Chief, Section of Endocrinology, Diabetes and Nutrition, Boston Medical Center.

The major metabolite of amiodarone is desethylamiodarone, which is extremely rich in iodine. Amiodarone is 37% iodine by weight and 10% of the molecule is deiodinated every day, resulting in 7 to 20 mg of iodine in the serum daily. The recommended daily intake of iodine is 150 mcg. Amiodarone is widely distributed in fat and other tissues and is released slowly, so the effects of amiodarone may persist for months after it is withdrawn.

“Amiodarone is a fascinating drug. Not only is it loaded with iodine, it is a potent inhibitor of the outer ring and inner ring deiodinases,” said Dr. Braverman. Amiodarone also decreases the entry of T4 into hepatocytes, decreases T3 receptor binding, and increases T4 conjugation. “In an animal model, hypothyroidism and amiodarone effects on the heart are relatively similar,” he explained.

Patients receiving amiodarone and who remain euthyroid have serum thyroid stimulating hormone (TSH) values that are essentially normal; however, there is a significant increase in the serum T4 levels, significant decrease in serum T3 levels, and a marked increase in reverse T3 levels.

Amiodarone-induced hypothyroidism is due to the excess iodine and is more common in women and in countries with iodine sufficiency. It usually occurs 2 to 40 weeks after starting amiodarone and frequently develops in patients who have Hashimoto’s thyroiditis. To treat amiodarone-induced hypothyroidism, patients should be continued on amiodarone and levothyroxine should be added to normalize the TSH. It is often necessary to give higher levothyroxine doses in patients who develop hypothyroidism due to the decreased generation of T3.

Another thyroid condition caused by amiodarone is thyrotoxicosis, which is more prevalent in countries with a higher prevalence of nontoxic nodular goiter and marginal iodine intake. Thyrotoxicosis has an unpredictable onset and may occur as long as three years after amiodarone treatment, even after withdrawal of the drug. Thyrotoxicosis occurs more frequently in men. Patients may be asymptomatic because T3 levels are not as high as they would be in ordinary thyrotoxicosis, or patients may present with recurrent tachycardia.

There are two types of amiodarone-induced thyrotoxicosis: Type 1 (Jodbasedow disease), which is secondary to excess iodine, and Type 2 (throiditis). Making a differential diagnosis between the two can be difficult. Painful or subacute thyroiditis is associated with elevations in C-reactive protein and IL-6; however, the differences in amiodarone-induced thyrotoxicosis

This program was supported by an unrestricted educational grant from Genzyme Corporation.
Postoperative Radioablation of Thyroid Remnants in Thyroid Cancer Management

Another thyroid condition caused by amiodarone is thyrotoxicosis, which is more prevalent in countries with a higher prevalence of nontoxic nodular goiter and marginal iodine intake.

In a near total or total thyroidectomy, it’s often necessary to decide whether to proceed directly to thyroxine suppressive therapy or ablate the remnant tissue,” said Paul Ladenson, MD, Director of the Division of Endocrinology and Metabolism, The Johns Hopkins University School of Medicine, Baltimore. “Retrospective and nonrandomized prospective studies have shown there to be lower risk of recurrent cancer in patients who underwent ablation if they were a Stage 3 or 4 papillary or follicular thyroid cancer patient,” he said. These arguments haven’t yet been well supported in a randomized, prospective trial.

Dr. Ladenson summarized a systematic review of studies on remnant ablation. By analyzing pooled data of 8,000 patients, the authors found that, at 10 years, there was a significant treatment effect of ablation for local recurrence of cancer and a reduction in distant metastasis. “They concluded that radionuclide ablation can be beneficial in reducing recurrence, but there is some inconsistency among the reports,” he said. While an argument against ablation has been lack of a randomized clinical trial, the feasibility of such a trial has been examined and found to require 1,000 patients followed for more than 25 years to detect a 20% difference in disease-specific mortality. Other arguments against ablation include sialadenitis resulting in xerostomia and altered taste; psychological impact; a low, but real risk of radiation-induced malignancies; and until recently, hypothyroidism caused by thyroid hormone withdrawal.

Patients for whom remnant ablation is most clearly indicated include those with the following: tumors that have invaded adjacent soft tissues; more than a minimal cervical or any extracervical metastasis; tumor histologies with a higher risk of recurrence (particularly columnar and tall cell variant and insular variants of papillary cancer and angioinvasive follicular cancer). Possible future indications for remnant ablation are related to new molecular criteria. One relates to molecular markers of clonality of tumors that are multifocal and the other is the BRAF oncogene.

Dr. Ladenson and colleagues examined the clonality of papillary thyroid cancer in 10 women with multifocal disease (Shattuck TM, et al. New Engl J Med. 2005;352:2406-2412). Using an androgen receptor gene assay, they could define the clonality of tumors based upon their X-inactivation. “The distinct X-inactivation patterns in at least one-half of patients with multifocal papillary thyroid cancer support the notion that many patients with multifocal papillary cancer have independent tumor foci rather than intrathyroidal metastasis,” he explained. This suggests that patients with multifocal papillary cancer have a susceptibility to developing de novo papillary cancers and is an indication for remnant ablation.

The BRAF oncogene is a member of the mitogen-activated protein (MAP) kinase signaling pathway that is important in thyrocyte proliferation. In a study of more than 200 patients with papillary thyroid cancer, examination of recurrence-free survival suggests that BRAF positivity was associated with cancer recurrence (in press). “I think that BRAF and markers like it may also tell us in the future which patients warrant this addi-
tional step of radioiodide remnant ablation,” said Dr. Ladenson.

When considering remnant ablation, it’s important to consider the following: how to prepare the patient for TSH stimulation, what radioiodine dose to use, the phenomenon of stunning, use of a low iodine diet, and lithium therapy to augment the ablative potency of the radioiodine. “Traditionally, we’ve asked patients after surgery to either not take the thyroid hormone or use temporary T3 therapy to allow them to drift down into the hypothyroid state and take advantage of endogenous TSH stimulation for remnant ablation,” he explained.

Dr. Ladenson summarized a study which sought to demonstrate that thyroid remnant ablation with radioiodine after recombinant TSH in euthyroid patients results in an ablation rate comparable to hypothyroidism after withholding thyroid hormone. The success of remnant ablation was assessed eight months later and 100% of the patients in both the traditional withdrawal arm and the recombinant TSH arm were successfully ablated. “These are remarkable and reassuring results,” he said.

One concern about remnant ablation in patients who are continuing to take thyroxine therapy has been the administration of cold iodine in the thyroxine. “Would this thyroxine-related iodine be enough to diminish the radioiodine uptake with the therapeutic dose?” asked Dr. Ladenson. Apparently not because there was no statistically significant difference in urinary iodine concentrations between the two groups right before they underwent remnant ablation. Also, recombinant TSH-stimulated ablation preserved quality of life based upon fewer symptoms and signs of hypothyroidism. Interestingly, the radioiodine kinetics differed in the two groups: there was significantly less whole body exposure to radiation in the rhTSH group, potentially reducing the risk of second cancers in the long-term. “Recombinant TSH-stimulated ablation appears to be as effective as withholding thyroid hormone therapy and results in less morbidity,” concluded Dr. Ladenson.

**Interpretation of Thyroglobulin Levels in Thyroid Cancer Monitoring**

“Serum thyroglobulin is a specific and sensitive monitoring tool for patients with differentiated thyroid carcinoma who have been treated with surgery and radioiodine,” said Bryan Haugen, MD, Associate Professor of Medicine and Pathology Assistant Head, Division of Endocrinology, Metabolism and Diabetes, University of Colorado at Denver and Health Sciences Center, Aurora. In a study published in 1975, treated thyroid cancer patients who had no metastasis had low serum thyroglobulins, whereas those with metastasis had high serum thyroglobulins. “This was a landmark paper that told us we could use serum thyroglobulin as a marker for thyroid disease,” said Dr. Haugen.

There are several technical considerations: these include the thyroid status, presence of thyroglobulin antibody, assay standardization, and TSH level. “About 20% to 25% of patients with differentiated thyroid cancer have antithyroglobulin antibodies,” he said. If the antibody is positive or unknown, it is difficult to interpret thyroglobulin assay result because in the commonly used immunoradiometric assay technique, endogenous antibodies can falsely lower the thyroglobulin level. Establishment of international standards has improved reproducibility, but it is still recommended that patient samples taken over time be run in a single assay to help reduce interassay variability.

Another technical consideration is the lower limit of the reference range. “If it is not possible to define the lower end of the reference range, the assay is likely to have poor functional sensitivity or precision,” explained Dr. Haugen. Also, it is important to know whether the thyroglobulin is obtained from a patient in whom the TSH is suppressed by exogenous thyroid hormone or has been stimulated by endogenous or exo-
higher sensitivity if thyroglobulin is measured following thyroid hormone withdrawal or recombinant TSH; identification of an elevated thyroglobulin at baseline, after rTSH, or after thyroid hormone withdrawal is specific for the presence of residual or recurrent disease. This meta-analysis also found that the diagnostic accuracy of thyroglobulin testing was higher in patients who had previously undergone radioiodine remnant ablation. “We do have reasonable sensitivity with a TSH-suppressed thyroglobulin but it’s much better if we use a TSH-stimulated thyroglobulin for detecting disease,” explained Dr. Haugen.

Recommendations for the use of thyroglobulin measurements in disease management were published in 2003. In a low- to moderate-risk patient, if serum thyroglobulin is undetectable while the patient is taking thyroxine, then recombinant TSH should be used to stimulate the thyroglobulin level. If the stimulated thyroglobulin level is low (< 2 ng/mL), then the patient can be followed without extensive further evaluations. If the stimulated thyroglobulin level is > 2 ng/mL, imaging studies, such as neck ultrasonography and chest x-ray, should be performed. A recent study suggested that measurement of thyroglobulin while on thyroid hormone-mediated TSH suppression combined with a negative sensitive neck ultrasound, performed by a technician experienced at imaging postsurgical necks, may provide adequate surveillance. Unfortunately, the thyroglobulin level remained below the cutoff that would signal concern (2 ng/mL) in 10 of 122 patients, despite the fact that these patients had metastases. Neck ultrasonography had a reduced specificity due to a high false-positive rate. An accompanying editorial said that stimulating thyroglobulin with rTSH remains useful, in line with published U.S. and European guidelines. Thus, the same set of data has generated two different opinions. “There have been a number of studies looking at this that have not specifically asked the question using imaging studies,” said Dr. Haugen. If a neck ultrasound is performed, the utility of stimulated thyroglobulin can be ascertained. Between 7% to 12% of the cases examined were thyroglobulin positive and imaging study negative. Most of the disease was detected in the neck; very little metastatic disease was identified in patients with elevated rTSH-stimulated thyroglobulin measurements.

Do thyroglobulin levels at the time of radioactive iodine ablation have any predictive value? Several studies found an association between high pretreatment thyroglobulin and persistent thyroglobulin positivity or documented disease recurrence, although the diagnostic accuracy of this approach has not yet been shown to be as good as the standard follow-up schedules. “The positive predictive value of a low thyroglobulin is quite good,” said Dr. Haugen. Most studies use between 2 to 5 ng/ml as a negative value, but the positive value was highly variable.

The positive predictive value of a low thyroglobulin is quite good,” said Dr. Haugen.

Assays for thyroglobulin include radioimmunoassay, immunoradiometric assay, immunochemiluminescence assay, and the ELISA. The second-generation assays, which many labs are using now, usually have a functional sensitivity of between 0.5 and 1 ng/ml. “We are going to see more third-generation assays that have very low functional sensitivities,” he added.

“I think that we can identify patients in complete remission and provide reassurance without performing a number of other studies; it is also possible to identify patients in need of close follow-up (those who are thyroglobulin positive and imaging negative),” Dr. Haugen concluded.
Advancing Care and Compliance in Diabetes: New Evidence, Tools, and Techniques

At a symposium held May 20, 2005, during the American Association of Clinical Endocrinologists’ Fourteenth Annual Meeting and Clinical Congress, a panel of experts discussed the clinical challenges for clinical endocrinologists and healthcare professionals in managing diabetes.

Evidence Supporting the Need to Control Mealtime Glucose Excursions

In January 2005, the American Association of Clinical Endocrinologists held the Implementation Conference for Outpatient Management of Diabetes Mellitus to reinforce the stringent goals established at the 2001 ACE/AACE Glycemic Control Consensus conference. These goals include hemoglobin A1C less than 6.5%, preprandial glucose levels less than 110 mg/dL, and two-hour postprandial glucose levels less than 140 mg/dL.

The thirty experts concluded that type 2 diabetes is not detected early enough. “We need to detect and treat impaired glucose tolerance for the purpose of preventing type 2 diabetes,” said Paul S. Jellinger, MD, Professor of Medicine, Voluntary Faculty, University of Miami, and President, American College of Endocrinology. The experts recommended using currently recognized profiles to identify patients at risk for type 2 diabetes and to perform a two-hour oral glucose tolerance test in these patients. Education and appropriate therapy should be started promptly. They also recommended adopting an uncompromising “treat-to-target” approach to achieve and maintain glycemic control, including the following: treat early and titrate persistently to achieve and maintain glycemic targets; address postprandial and fasting glucose to achieve target A1C; minimize glucose excursions throughout the day; and combine treatment (medications as well as nutrition therapy and other lifestyle interventions).

Dr. Jellinger presented the evidence supporting the need to control meal time glucose excursions. “The mean A1C among normal nondiabetic individuals in the United States is 5.2%,” he said. The mean A1C in people with type 2 diabetes treated with insulin is 8.3%, and only 26% of insulin users achieve goals. Only 37% of diabetics using oral agents achieve goals.

Because most of the day is spent in the postprandial state, Dr. Jellinger emphasized that it’s not sufficient to focus only on fasting blood sugar. The true fasting state lasts only about four to six hours in the morning. The next 12 to 15 hours are postprandial. He cited two studies that showed discordance between fasting glucose and A1C (Gerich JE. Arch Intern Med. 2003;163:1306-1316; Lancet. 1998;352:837-853). “Patients with an A1C of 6.5% can still have a disturbingly high post-meal glucose,” said Dr. Jellinger (Figure 1).

A study by Monnier et al. showed that postprandial glucose has a considerably greater influence over A1C when it is 8.4% or less. But when control is poor (8.5% and higher), fasting glucose has the greater influence (Diabetes Care. 2003;26:881-885). “This is important since there is increasing recognition for the need to ‘fine tune’ glucose control to target the low-end A1C range,” said Dr. Jellinger.

He noted that in normal patients, an IV glucose test infusion results in an almost simultaneous 10-fold increase in plasma insulin, while patients with type 2 diabetes get almost no early-phase insulin release.

Dr. Jellinger cited the Diabetes Control and Complications Trial (DCCT), which showed that A1C and retinopathy relate to each other in a curvilinear fashion. “If you reduce A1C from 11 to 9, it’s still poor but you reduce retinopathy by 50%,” he said. Furthermore, the DCCT demonstrated that reducing A1C to the same level by intensive therapy rather than conventional therapy is more effective in preventing retinopathy. This would suggest that prandial (regular) insulin, by reducing post-meal glucose as well as possible other effects, may have a unique contribution to minimizing complications.

The continuation of the DCCT—the Epidemiology of Diabetes Interventions and Complications Research Group (EDIC)—found that in diabetic patients treated intensively (which included pre-meal regular insulin) the intima-media thickness readings for the
Dr. Jellinger again raised the possibility that this may be due to the use of pre-meal fast-acting insulin, which limited post-meal excursions.

He addressed the question of the prevalence of isolated postchallenge hyperglycemia in undiagnosed diabetics (ages 50 to 89). A study by Barrett-Connor et al. of 133 men and 125 women who were unaware of their diabetes found that 72% of the women and 48% of the men had isolated postchallenge glucose (Diabetes Care. 1998;21:1236-1239). Over the next seven years, the women in this group had a significant increase in fatal cardiovascular disease and heart disease compared to nondiabetic women.

The Honolulu Heart Study looked at the effect of one-hour postchallenge glucose levels on risk of coronary heart disease (Donohue RP, et al. Diabetes Care. 1987;36:689-692). A high one-hour postchallenge reading correlated in a linear fashion with high risk for CHD, even 12 years later. A study by Tominaga et al. showed that a high two-hour glucose reading increases risk of cardiovascular death, even in patients with impaired glucose tolerance (Diabetes Care. 1999;22:920-924).

The DECODE study showed that for every fasting glucose level the risk for coronary artery disease death was increased, but the two-hour postchallenge elevation added a new amplitude of risk that significantly exceeded fasting glucose (Lancet. 1999;354:617-621).

Dr. Jellinger drew the following conclusions from these and other studies: “Even in nondiabetic individuals, postprandial hyperglycemia carries higher risk of death than elevated FPG. Since 1980, robust epidemiologic evidence originating from diverse geographic regions and varied populations has shown that elevated postchallenge and postprandial glucose increases the risk for cardiovascular disease. Earlier detection and management of postprandial hyperglycemia is crucial.”

Dr. Jellinger cited the STOP-NIDDM study, which demonstrated a 49% reduction in probability of cardiovascular events when acarbose, which selectively targets post-meal glucose, was used (JAMA. 2003;290:486-494). In a study comparing repaglinide to glyburide, the postprandial peak was lower with repaglinide and patients taking repaglinide had reduced carotid intima-media thickness over time (Esposito K, et al. Circulation. 2004;110:214-219). Repaglinide lowered post-meal glucose considerably more than glyburide did, but the change in A1C for both groups was essentially the same. “Interestingly, there was a greater lowering of C-reactive protein in patients on repaglinide,” said Dr. Jellinger. Possible effects of acute hyperglycemia include endothelial dysfunction, increased oxidative load, pro-inflammatory effects, protein glycosylation, and altered coagulation.

Dr. Jellinger concluded: “As the EPIC-Norfolk study demonstrates, even within the normal range, the higher the A1C the greater the risk for all-cause and cardiovascular mortality. Targeting postprandial glucose is an important strategy in achieving the lowest possible A1C and in reducing the adverse physiologic effects resulting from an acute rise in blood sugar.”
Practical Use of Blood Glucose Data: Management for the Endocrinologist

It’s clear that achieving the goals established by the Implementation Conference for Outpatient Management of Diabetes Mellitus are desirable and achievable. Irl B. Hirsch, MD, Professor of Medicine, University of Washington, School of Medicine, Seattle, described some tools that can be used by practitioners to attain better glucose control in their patients. For example, computer-generated downloads for home blood glucose data have been available for the past 15 years. However, few endocrinologists are taking advantage of this useful tool.

Downloaded blood glucose meters provide a variety of assessments for both patients and providers that are not available otherwise, and they may lead to improved A1C outcomes and improved glycemic variability outcomes. Perhaps, most importantly, they serve to motivate patients. “If you have data, you can take action on the data,” said Dr. Hirsch.

He noted that the standard deviation (SD) is the preferable approach to assessing glycemic variability with large amounts of data. He gave the example of two patients, both of whom had A1C of 6.5%. Joe was on CSII with insulin aspart and Mary was on HS insulin glargine and prandial insulin lispro. Joe’s SD was 51, while Mary’s was 63. “You can’t figure this out in your head; you need the computer to do it,” said Dr. Hirsch.

The calculation to determine the SD target is as follows: SD x 2 should be less than the mean. “Ideally, the SD times three should be less than the mean; but this is difficult with type 1 patients,” said Dr. Hirsch. Two examples of the application of this calculation are in Table 1. A high SD indicates insulin deficiency (especially good with fasting blood glucose), poor matching of calories (especially carbohydrates) with insulin, giving mealtime insulin late (or missing shots completely), erratic snacking, poor matching of basal insulin, or possibly a need for insulin pump therapy.

“Glycemic variability can cause increased oxidative stress and endothelial dysfunction, which can lead to diabetes complications,” said Dr. Hirsch. “The A1C is a crude measurement of average glycemia and it doesn’t give you the full story,” he added. “The downloaded blood glucose meters give you a better picture.”

Diabetes Case Studies: How to Optimize Glucose Control with Insulin and Insulin Delivery Systems and Glucose Sensing

Bruce W. Bode, MD, Atlanta Diabetes Associates, Atlanta, Georgia, discussed various therapeutic options when trying to achieve an A1C of 6.5% in patients with type 2 diabetes. “Insulin is the most powerful tool we have to normalize glucose control,” he said. “When used appropriately, glucose control can be optimized in almost any individual with diabetes.” He presented five case studies of how to initiate and use insulin effectively in patients with poorly controlled type 2 diabetes.

Case 1
40-year-old African-American male diagnosed with diabetes six months ago with an admission for MI. He is currently not being treated for diabetes. Weight is 201 lbs., height is 69 inches, and BMI is 29. A1C is 13%, blood glucose is 497, creatinine is 1.3, and ketones are negative. He is...
being treated for hyperlipidemia and has had a stent placed for coronary artery disease. The goal for glucose in this patient should be 80 to 110 mg/dL premeal and less than 140 mg/dL postmeal, according to the AACE guidelines discussed by Dr. Jellinger. Dr. Bode asked the audience what treatment in addition to diet an exercise should be started in this patient, with no clear consensus. He said that he started the patient on basal bolus therapy. Because the patient refused insulin, Dr. Bode put him on two oral agents and the patient quit drinking sweet tea, colas, and orange juice. A1C at three months was 6.8%.

"Insulin is the most powerful tool we have to normalize glucose control," he said. "When used appropriately, glucose control can be optimized in almost any individual with diabetes."

Case 2
46-year-old Indian man with diabetes since age 33, on maximum doses of rosiglitazone, glyburide, and metformin. His diet is balanced and he exercises daily. Weight is 167 lbs., height is 69.5 inches, and BMI is 24. His A1C is 8%, creatinine is 1.1, C-peptide is 2.6 mg/mL. Complications include vitreotony in right eye, proteinuria, and hyperlipidemia. His daily self-monitored blood glucose averages 110 mg/dL fasting. His random blood glucose is 300 post-breakfast.

The treatment Dr. Bode chose for this patient was bolus insulin (6 units) with the largest meal (supper). He added 4 units prebreakfast at the end of the first week based on self-monitored blood glucose taken four times a day. All blood glucose measurements were normal by one month.

"Bolus insulin with the meal does work," said Dr. Bode. He cited a study showing insulin aspart with the meal plus oral agents got patients’ A1C to under 7%, while those on human NPH or 70/30 did not change (Diabetes Care. 2003;26:3273-3279). He noted that basal insulin should be started when fasting glucose is above 140 mg/dL.

"Advantages of basal insulin are that it’s one shot a day; it’s slow, safe, and easy," said Dr. Bode.

Case 3
80-year-old white man with diabetes since age 60, on repaglinide 4 mg three times a day. He has a history of congestive heart failure. He has a supportive daughter and wife. Weight is 175 lbs., height is 72 inches, and BMI is 23.5. A1C is 9.2%, creatinine is 2.7, and C-peptide is 5.3 ng/mL. Self-monitored blood glucose is tested 2.7 times per day and averages 246 mg/dL: 178 in the morning, 206 at noon, 247 in the evening, and 271 at bedtime.

"Normally, I would have put a patient like this on basal bolus therapy, but instead I chose premixed insulin," said Dr. Bode. The patient did well; his weight increased and his A1C was 7.2% at three months.

Dr. Bode cited two studies that looked at use of premixed human insulin. In a study by Janka et al. patients with fasting glucose above 120 mg/dL were put on either one dose of glargine per day plus continued metformin and sulfonlurea or human premixed 70/30 insulin without the oral agent (Diabetes Care. 2005;28:254-259). A1C went down from 8.9% to 7.15% with glargine and to 7.5% with premixed insulin. Fewer episodes of hypoglycemia were reported in the glargine group. In the INITIATE study, patients with a fasting glucose above 140 mg/dL were put on glargine 10 units once a day (titrated to 80 to 110 units) plus metformin and, in some cases, a thiazolidinedione or biphasic insulin aspart, 5 or 6 units twice a day, plus metformin (Diabetes Care. 2005;28:260-265). In this study, premixed insulin reduced A1C greater than glargine (6.9% versus 7.4%).

In addition to diabetes training and management by a certified diabetes educator, Dr. Bode added bolus insulin to each meal. She was put on aspart (10 units in the morning, 7 units at noon, and 7 units in the evening) and glargine 40 units at bedtime. After intensive management training in MDI and diet, the patient’s self-monitored blood glucose taken 6.5 times a day was 121 mg/dL and A1C was 6.5%.

"Advantages of basal insulin are that it’s one shot a day; it’s slow, safe, and easy," said Dr. Bode.

Case 4
49-year-old white woman with diabetes since age 37, on glargine insulin at bedtime for three years. Weight is 223 lbs., height is 65 inches, and BMI is 37. A1C is 9.2%, creatinine is 1.2, and C-peptide is 5.3 mg/mL. Current treatment is lispro (25 units morning, 15 units noon, 15 units evening), glargine 85 units at bedtime, and metformin 1,000 mg twice a day. Her diet includes a lot of high-fat food and three colas per day. Four times a day self-monitored blood glucose averages over 300 mg/dL. She gets very little exercise.

Dr. Bode elected to put this patient on an insulin pump. He started her at 75% TDD or 110 units per day. Her pump settings were basal 2.0 units per hour, bolus 25 units, 15 units, and 15 units, and correction bolus: BG—100/15. At three months, A1C was down to 9% from 15.9%.

"People do much better on pumps versus MDI from a quality-of-life perspective," said Dr. Bode. The monitor sends the blood glucose value to the pump via radio waves; the patient enters carbohydrate intake data into the pump, and the "Bolus Wizard" calculates the suggested dose. Advantages of insulin pump therapy include better nocturnal glucose control, ability to alter basal insulin for exercise and stress, and ability to cover all types of meals and snacks with immediate or dual-wave bolus insulin. Insulin pump therapy is also more convenient and easier for most patients.
Vitamin D Today: Reducing the Risk of Falls and Fractures

In an industry-sponsored symposium held in conjunction with the American Association of Clinical Endocrinologists’ Fourteenth Annual Meeting and Clinical Congress and moderated by Michael F. Holick, PhD, MD, three leaders in biophysics, epidemiology, and nutrition presented the latest information on vitamin D and bone health. Topics included the role of vitamin D in neuromuscular and bone health and function, the diagnosis and treatment of osteoporosis, and the definition and measurement of vitamin D levels for bone and overall health.

“Current evidence indicates a key role for vitamin D in ensuring not only neuromuscular and bone health, but also regulation of cell growth, immune function, and overall health and functioning,” said Michael F. Holick, PhD, MD, Professor of Medicine, Physiology and Biophysics, Section of Endocrinology, Diabetes, and Nutrition, Boston University School of Medicine. According to Dr. Holick, vitamin D supplementation may provide a significant benefit in optimizing bone/neuromuscular health and reducing the risk of diabetes, hypertension, cardiovascular events, and certain cancers.

Vitamin D: Source and Metabolism
Vitamin D may be found in some foods; however, much of the body’s vitamin D requirement is derived through casual exposure to sunlight. “While overexposure to sunlight should be avoided due to skin cancer risk, casual exposure of 5 to 15 minutes two times per week of arms and legs or hands, face, and arms between 10 am and 3 pm should be adequate to meet the body’s need for vitamin D,” Dr. Holick explained.

Once exposed to sunlight, the skin responds to the ultraviolet (UV) rays to make vitamin D, and the liver metabolizes vitamin D to 25-hydroxyvitamin D [25(OH)D], which is further metabolized in the kidney to its active form, 1,25-dihydroxyvitamin D [1,25(OH)2D] vitamin D. This form of vitamin D interacts with the vitamin D receptor, which is present in every tissue and cell of the body. “This includes the calcium-regulating tissues, with 1,25(OH)2D acting to maintain bone health, regulate the efficiency of intestinal calcium absorption, and mobilize calcium from the skeleton,” Dr. Holick explained. “Not only is vitamin D itself essential to bone health, but only 10% to 15% of dietary calcium is absorbed in the absence of vitamin D. With vitamin D, the absorption rate of calcium is approximately doubled,” he added.

Defining Healthy Vitamin D Levels for Bone and Overall Health

Vitamin D Deficiency: Diagnosis and Treatment
Vitamin D deficiency is defined as having blood levels of 25(OH)D of less than 30 nanogram/mL. Deficiency is common, especially in the wintertime and in persons who are elderly, have dark skin, or live in areas of high latitude. Indeed, studies have shown vitamin D deficiency ranging from 30% to 84%. Vitamin D deficiency can cause a number of conditions, including inadequate calcium absorption, osteomalacia, secondary hyperparathyroidism, rheumatoid arthritis, and exacerbation of osteoporosis. Indeed, patients with osteomalacia are often misdiagnosed as having fibromyalgia; an estimated 40% to 60% may be vitamin D deficient. “Current evidence also suggests that approximately 50% of patients with osteoporosis who are receiving a prescription medication to treat osteoporosis had 25(OH)D levels of less than 30 nanograms/mL, regardless of whether or not they are taking a multivitamin,” he said.

With regard to cancer, those living in northern latitudes have been shown to have greater overall mortality rates from cancer. Garland and colleagues demonstrated an inverse association between 25(OH)D levels and risk of colon cancer. Similar findings have been reported for breast, prostate, and other cancers.

In another study, Holick and colleagues treated hypertensive patients with tanning bed therapy with UVB (makes vitamin D3) versus UVA rays (does not make vitamin D3). These results showed not only an 18% increase in 25-OHD levels, but also a 6mm drop in both systolic and diastolic blood pressure, in the group receiving UVB exposure. No change was observed in the UVA group.

Finally, vitamin D deficiency may be associated with heart failure. “We know that cardiac myocytes have receptors for 1, 25(OH)2D, and that vitamin D...
Vitamin D Today: Reducing the Risk of Falls and Fractures

D decreases inflammatory activity, risk of atherosclerosis, and myocardial hypertrophy, thus reducing the risk of heart failure and associated morbidity and mortality,” Dr. Holick said.

Vitamin D: The Assay Conundrum
While vitamin D deficiency is a prevalent condition, the challenge remains in utilizing the appropriate assay to determine 25(OH)D levels accurately. The first 25(OH)D assays used either the vitamin D binding protein in a competitive protein-binding assay, or an antibody to 25(OH)D for a radioimmunoassay. The gold standard, however, was separation of 25(OH)D, and 25(OH)D, from other vitamin D metabolites using high-performance liquid chromatography (HPLC).

There are several commercial assays, including the Diasorin Antibody assay and Nichols Advantage chemiluminescent assay, available to measure 25(OH)D. These assays typically involve taking a serum sample and, after a quick extraction, placing into the assay. The disadvantage is that these assays also detect other hydroxylated vitamin D metabolites including 24, 25-dihydroxyvitamin D. This can lead to an overestimation of 25(OH)D by 10% to 30%.

Holick and colleagues have developed a liquid chromatography tandem mass spectroscopy assay for 25(OH)D, measuring with great specificity and precision 25(OH)D, and 25(OH)D,. In comparison analyses, it was observed that the Nichols Advantage assay underestimated total circulation 25(OH)D levels in patients who received vitamin D treatment by as much as 40%. When almost 300 serum samples were compared by all three assays, a significant correlation was found, and there was good agreement between the assays for determining the prevalence of vitamin D deficiency defined as a 25(OH)D less than 50 ng/mL. However, the prevalence of vitamin D inadequacy (less than 30 ng/mL) was 49% and 50% by the Nichols Advantage and LC-MS/MS assays compared to only 35% with the Diasorin assay. These data suggest that the Diasorin assay had greater specificity, but less sensitivity than the Nichols Advantage assay for measuring serum 25(OH)D concentrations. Thus, most commercial assays are effective in detecting vitamin D deficiency and are useful tools in diagnosing this condition. However, when pharmacologic doses of vitamin D are used to treat vitamin D deficiency, if the 25(OH)D levels do not significantly increase using the Nichols Advantage assay, it is reasonable to have the blood remeasured by another method, such as LC-MS/MS or Diasorin assay.

In closing, Dr. Holick noted, “Based on a wealth of accumulating evidence, the role of vitamin D is now known to be critical not only in calcium regulation, bone health, and fracture risk reduction, but also in the regulation of cell growth, immune function, blood pressure, and overall health.”

New Approaches for the Diagnosis and Treatment of Osteoporosis

The risk of bone fracture increases with advancing age and compromised bone strength. To reduce the risk of such fractures, clinicians need to be vigilant of the risk factors and screening recommendations for osteoporosis, said Robert A. Adler, MD, Professor of Internal Medicine, Professor of Epidemiology and Community Health, Virginia Commonwealth University, Richmond. According to Dr. Adler, “Importantly, we must also understand that both decreased bone mass [density] and bone quality play a role in the pathophysiology of osteoporosis.”

Diagnosis: Bone Mass and Bone Quality
“The definition of osteoporosis now includes not only decreased bone mass, but also decreased bone quality,” Dr. Adler explained. In terms of bone mass, accumulation of bone occurs during growth, and loss of bone increases with aging. Bone mass may also be related to bone size, and new DXA measures may allow for enhanced evaluation of bone size and mass,” he noted. With regard to bone quality, important factors include bone architecture, bone turnover, damage accumulation, mineralization, bone matrix (protein), and bone cell health. “In evaluating patients, indicators of bone quality may include bone turnover markers, fracture history, and presence of fracture on VFA or spine x-ray,” Dr. Adler said.

One early study of women age 50 and older clearly demonstrated that fracture risk increases significantly as bone mineral density (BMD) decreases, but also as age advances. “Even in women with the same BMD, those who were age 75 to 79 years old had significantly higher bone fracture rates than those age 50 to 54,” Dr. Adler said (Hui et al. J Clin Invest. 1988;81:1804). In another study of women taking calcium, the presence of vertebral fractures was shown to predict the incidence of future vertebral fracture (Lindsay et al. JAMA. 2001;285:320). “These and other studies clearly show the impact of both BMD and bone quality on risk of fracture,” Dr. Adler noted.

Currently, BMD is measured by DXA (Table 1). For every standard deviation below the normal BMD, risk of fracture increases by a factor of two. “While DXA is helpful in screening for and diagnosing osteoporosis, it has limitations,” the speaker said. “For example, while

<table>
<thead>
<tr>
<th>Table 1 Bone Mineral Density Definitions</th>
</tr>
</thead>
<tbody>
<tr>
<td>• T-score compares patient with young (30 year old) normals of same sex and ethnic group</td>
</tr>
<tr>
<td>• T &gt; -1 is called normal</td>
</tr>
<tr>
<td>• T between −1 and −2.5 is called osteopenia</td>
</tr>
<tr>
<td>• T &lt; −2.5 is called osteoporosis</td>
</tr>
<tr>
<td>• Established for white post-menopausal women only</td>
</tr>
</tbody>
</table>
Sites commonly used for DXA measurement include the spine, hip, and forearm (especially in those who cannot undergo spinal scan). Interestingly, Adler and colleagues showed that, in older men identified by an osteoporosis screening program, only BMD of the forearm was reduced compared with younger counterparts.

According to ISCD guidelines, DXA screening should be performed using male and female databases (currently not adjusted for race/ethnicity). Women without risk factors should begin screening at age 65; men without risk factors should begin screening at age 70. If DXA of the spine is not available, the distal one-third radius may be used (Leib et al. J Clin Densitom. 2004;7:1). Risk factors that may necessitate screening at a younger age include early menopause, weight < 127 pounds, and family history of osteoporosis in women; and hypogonadism or EtOH excess in men. In men and women, smoking, fracture after age 45, poor nutrition, weight loss, small frame, chronic obstructive pulmonary disease, and vitamin D deficiency are risk factors for osteoporosis.

### Treatment of Osteoporosis

Numerous interventions are available for the treatment of persons with osteoporosis (Table 2). In one bisphosphonate study, alendronate was shown to increase BMD over a treatment period of 1, 2, and 3 years compared with placebo. In another study, women with PMO and vertebral fracture were treated with alendronate or placebo for 3 years. These results showed a 47% reduction in new vertebral fracture with alendronate therapy. Similar findings were found on hip measurements (Black et al. Lancet. 1996;348:1535). Alendronate therapy has also been shown to increase BMD in men (Orwoll et al. N Engl J Med. 2000;343:604). Both agents were tolerated well, with few side effects and no difference in gastrointestinal side effects (Rosen et al. J Bone Miner Res. 2005;20:141).

According to Dr. Adler, in persons who do not show a response to bisphosphonate therapy after 1 to 2 years’ treatment, several key factors warrant consideration. “First, after 1 year of bisphosphonate therapy, general adherence rates are only approximately 30%, so frequent education is key in this patient population,” he noted. Second, is the patient receiving adequate amounts of calcium and vitamin D? Third, does the patient suffer from malabsorption? If these issues are addressed and the patient continues not to respond, it may be that DXA measurements are not accurately reflecting bone changes. In the FIT trial, for example, women who were taking alendronate and had lost 0% to 4% in spine or hip BMD after 1 year still had lower vertebral fracture risk than those taking placebo (Chapurlat et al. Osteo Int. 2005;16:842). “These findings suggest that DXA may not be an adequate measurement to determine changes in BMD and/or bone quality with bisphosphonate treatment,” Dr. Adler explained.

With regard to bisphosphonate therapy options, both alendronate and risedronate have been shown to be effective and well tolerated. A recent meta-analysis utilizing an adjusted indirect comparisons method suggested that alendronate produced a greater decrease in non-vertebral fracture risk than risedronate (Wehren et al. Curr Med Res Opin. 2004;20:525). The FACT study—the only head-to-head trial of alendronate and risedronate—showed a greater increase in BMD and greater resorption marker effect with alendronate. Both agents were tolerated well, with few side effects and no difference in gastrointestinal side effects (Rosen et al. J Bone Miner Res. 2005;20:141).

“Current evidence suggests that patients should receive bisphosphonate intervention for a minimum of 5 years to achieve an extended therapeutic effect, as this strategy allows for a plateauing of rather than a decrease in BMD with treatment discontinuation. For this reason, long-term safety is an important area of study,” Dr. Adler said. Ten years of alendronate and 7 years of risedronate research suggest that these agents are generally safe and effective (Tonino et al. JCBM. 2000;85:3109). “Osteonecrosis of the jaw has been documented, usually in the mandible and usually in persons who have had dental extraction or other major procedure that did not heal. While most cases have occurred in persons with cancer undergoing high-dose IV bisphosphonate therapy, this condition has been reported in those being treated for osteoporosis,” Dr. Adler said.

### Future Directions

In closing, Dr. Adler noted that new treatments for osteoporosis—such as new bisphosphonates; anabolic agents used before, after, or with bisphosphonates or other methods to decrease bone resorption—are on the horizon. “Perhaps most importantly, fracture in older persons results in a significant increase in mortality in both men and women. Thus, appropriate screening, diagnosis, and treatment of osteoporosis are critical to reducing not only the risk of fracture, but also the risk of death.” Dr. Adler concluded (Block & Stubbs. Calcif Tissue Int. 1997;61:84).

---

**Table 2**

<table>
<thead>
<tr>
<th><strong>Nutrition/Lifestyle Interventions</strong></th>
<th><strong>Pharmaceutical Agents</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Calcium</td>
<td>• Antiresorptive therapies</td>
</tr>
<tr>
<td>• Vitamin D</td>
<td>– Bisphosphonates</td>
</tr>
<tr>
<td>• Weight-bearing exercise</td>
<td>– Raloxifene</td>
</tr>
<tr>
<td>• Fall risk reduction</td>
<td>– Hormone replacement</td>
</tr>
<tr>
<td>• Hip pads</td>
<td>– Estrogen for young women</td>
</tr>
<tr>
<td></td>
<td>– Testosterone replacement</td>
</tr>
<tr>
<td></td>
<td>– Anabolic therapies</td>
</tr>
<tr>
<td></td>
<td>– Teriparatide</td>
</tr>
</tbody>
</table>
Role of Vitamin D in Neuromuscular Activity, Functionality, and Bone Health

With accumulating evidence in fall (Bischoff-Ferrari et al. JAMA. 2004;291:1999) and fracture prevention (Bischoff-Ferrari et al. JAMA. 2003;293:2257), vitamin D supplementation has become the only treatment to reduce both the risk of falling and risk of non-vertebral fracture,” said Heike A. Bischoff-Ferrari, MD, MPH, Department of Nutrition, Harvard School of Public Health, Department of Rheumatology, Brigham and Women's Hospital, Boston. According to Dr. Bischoff-Ferrari, ensuring optimal vitamin D intake in the older ambulatory and institutionalized population should become a public health priority.


Lower Extremity Function and Fall Prevention
In one study, a NHANES database of ambulatory persons age 60 and older was used to document vitamin 25-OHD levels as well as lower extremity function (Bischoff-Ferrari et al. Am J Clin Nutr. 2004;80:752). These results showed an association between vitamin D levels and increased function, per 8-foot walk test and repeated sit-stand test. “A dramatic improvement was observed from low to approximately 40 nmol/L vitamin D levels, with continued increases to optional function at 90 to 100 nmol/L vitamin 25-OHD,” Dr. Bischoff-Ferrari said (Bischoff-Ferrari et al. Am J Clin Nutr. 2004;80:752). In addition, in a meta-analysis, Bischoff-Ferrari and colleagues analyzed randomized, double-blind, placebo-controlled trials on prevention of falls and vitamin D (Bischoff-Ferrari et al. JAMA. 2004;291:1999). “These findings indicate that vitamin D in any form should reduce an older person’s risk of falling by more than 20% compared with calcium alone or placebo.” The number needed to treat was 15. Dr. Bischoff-Ferrari noted that based on a subgroup analysis, 400 IU vitamin D was not enough to reduce falls (Graafmans et al. Osteoporos Int. 1996;6:427), while evidence from two trials suggested that 800 IU vitamin D per day reduces the risk of falling by 33% (pooled OR = 0.65 [0.40, 1.0]) (Pfeifer et al. J Bone Miner Res. 2000;15:1113. Bischoff et al. J Bone Miner Res. 2003;18:343). “Thus, at least 800 IU cholecalciferol are needed to help prevent falls in older persons. For optimal lower extremity strength in ambulatory men and women, 25-OHD levels of at least 40 nmol/L and as high as 90 to 100 nmol/L may be desirable,” she summarized.

Bone Health and Fracture
In another analysis of NHANES, Dr. Bischoff-Ferrari and colleagues investigated the association between serum 25-hydroxyvitamin D levels and BMD (Bischoff-Ferrari et al. Am J Clin Nutr. 2004;80:752). In persons 30 to 49 and in persons age 50 and older, serum 25-hydroxyvitamin D levels were associated with increased BMD, with 90 to 100 nmol/L 25-hydroxyvitamin D appearing to be most efficacious. “In the older group, this effect was observed among white, Mexican-American, and African Americans. However, in the younger group, the change in BMD with higher 25-hydroxyvitamin D levels was not significant in African Americans. This may be a reflection of the lower vitamin D levels in this population,” Dr. Bischoff-Ferrari explained. In the younger white population, BMD rose beyond 100 nmol/L without reaching a threshold.

In another analysis of randomized, double-blind, placebo-controlled trials, Bischoff-Ferrari and colleagues evaluated the association of vitamin D levels and risk of hip/non-vertebral fracture. These findings showed that 700 to 800 IU vitamin D per day significantly reduced the risk of hip fracture by 26% and any non-vertebral fracture by 23% compared with calcium or placebo. No significant benefit was observed with 400 IU vitamin D per day (Bischoff-Ferrari et al. JAMA. 2005;293:2257).

Conclusions
In closing, Dr. Bischoff-Ferrari emphasized that a growing body of evidence suggests that serum 25-hydroxyvitamin D levels of 80 to 100 nmol/L may be optimal for the reduction of risk of falls and fracture. “Vitamin D supplementation of at least 800 IU per day may be needed to maintain optimal neuromuscular function and bone health in all persons age 60 and older,” Dr. Bischoff-Ferrari concluded.
Individualized Treatment Options: Addressing Unmet Needs for Osteoporosis

At a symposium held in May 2005, during the American Association of Clinical Endocrinologists’ Fourteenth Annual Meeting and Clinical Congress, a panel of experts examined the problem of noncompliance with osteoporosis medication, discussed fracture prevention based on early identification and treatment, identified special patient populations, and discussed novel dosing strategies.

Enhancing Treatment of Osteoporosis: Persistence with Therapy

“Healthcare providers are generally underdiagnosing and undertreating osteoporosis and patients are generally poorly adherent to long-term treatment programs,” began Mark P. Ettinger, MD, Medical Director Emeritus, Radiant Research and The Regional Osteoporosis Center, Stuart, Florida.

He cited evidence showing that in North America, 45% of vertebral fractures were not diagnosed by radiologists in one study (Delmas PD, et al. J Bone Miner Res. 2005;20(4):557-563). A retrospective radiographic study by Gehlbach for admission chest X-rays for women age 60 or older who were hospitalized for various reasons found that 50% of women with vertebral deformities did not have the fractures mentioned in the radiology report. Furthermore, osteoporosis was only mentioned in 17% of fracture patient charts at the time of discharge (Gehlbach SH, et al. Osteoporos Int. 2000;11:577-582).

The prevalence of undertreatment was examined in a study of over 1,000 hip fracture patients in four Midwest hospitals (Harrington JT, et al. Arthritis Rheum. 2002;47:651-654). Only 12% to 24% of these patients received bone densitometry testing with DEXA during hospitalization; 5% to 27% received calcium and vitamin D; 5% to 37% received antiresorptive (antiresorptive) therapy, and 2% to 10% were given bisphosphonates. This low percentage is particularly troubling because “bisphosphonates are the only approved therapy with prospective data showing hip fracture prevention,” said Dr. Ettinger.

As for problems with adherence, Dr. Ettinger began by clarifying the meaning of some terms. Compliance refers to the consistency and accuracy with which a regimen is followed. Persistence relates to the length of time therapy is continued. Adherence comprises both compliance and persistence. Dr. Ettinger suggested that treatment failures may actually be adherence failures.

In general, for all chronic diseases, adherence with long-term therapy is suboptimal. Medications are frequently stopped by 6 to 12 months. Younger patients and those who are less ill are generally less persistent. “Interestingly, the severity of the disease doesn’t always correlate with persistence,” said Dr. Ettinger.

However, good adherence has been shown to improve osteoporosis outcomes. Patients with osteoporosis who took 80% of medications had a 16% lower fracture rate compared to less adherent patients in one two-year study (Caro JJ, et al. Osteoporos Int. 2004;15:1003-1008) and 26% fewer fractures in another two-year study (Siris E. NOF 6th International Symposium Oral Abstract Presentation. April 7, 2005). In addition, one-year adherence correlates with bone mineral density (BMD) changes and with reductions in metabolic markers of bone resorption in women with low bone mass (Clowes JA, et al. J Clin Endocrinol Metab. 2004;89:1117-1123; Yood RA, et al. Osteoporos Int. 2003;14:965-968).

In a study by Emkey et al., BMD was maintained in patients taking chronic glucocorticoids if they were adherent to a bisphosphonate regimen, but patients who discontinued the bisphosphonate early suffered substantial BMD losses in the hip and spine (Arthritis Rheum. 2003;48:1102-1108). An osteoporosis study by McCombs and colleagues found that 95% to 100% adherence for one year was associated with lower risk for hip fracture, lower risk for lumbar-spine fracture, fewer physician services, lower outpatient hospital costs, and lower hospitalization costs (Maturitas. 2004;48:271-287).

Dr. Ettinger noted that patients may never fill prescriptions or stop taking medications for a variety of reasons, including cost, availability, real or perceived adverse effects, and dosing frequency and convenience issues. For example, subcutaneous injections of
Paul D. Miller, MD, Clinical Professor, Department of Medicine, University of Colorado Health Sciences Center, Denver, discussed early identification and treatment options for a group of patients for whom treatment is controversial: those with osteopenia. The questions he raised are: “Should we treat low bone mass?” and “Should postmenopausal women with fragility fractures be treated regardless of the T-score?” He answered yes to both questions.

He described a 71-year-old female patient with no symptoms or fractures whose mother had suffered a hip fracture. The patient’s PA spine T-score was -1.5 and femoral neck was -1.8, which was diagnostic of osteopenia. She had multiple vertebral compression fractures, indicating increased risk and a need for therapy. “Does this woman, with a T-score of -1.5, have osteoporosis?” queried Dr. Miller.

Even though the WHO definition of osteoporosis is based on a T-score below -2.5, Dr. Miller said that the diagnosis can also be made based on the presence of fragility fractures.

Dr. Ettinger emphasized the need for continuous suppression of bone turnover to reduce fractures. He cited a study comparing the once-monthly formulation of ibandronate to the once-daily formulation, which looked at serum C-telopeptides (a marker of bone turnover) (Miller P, et al. J Bone Miner Res. 2005;20(8):1315-1322). “The once-monthly dose was considerably more robust than the once-daily form, with a greater degree of inhibition of bone turnover,” said Dr. Ettinger. Additionally, hip BMD was higher with the once-monthly drug than with once-daily dosing.

A study conducted by Dr. Ettinger and his colleagues compared osteoporosis patients who were taking either once-daily or once-weekly medication (Arthritis Rheum. 2004;50(9S):S513. Abstract 1325). Among the group who were already on therapy at the beginning of the study, only 58.5% of once-weekly patients and 39% of once-daily patients were still taking their medication one year later. Among patients newly started on therapy, only 31.4% of once-weekly patients and 15.7% of once-daily patients were still taking their medication (Figure 1). Some of these discontinuations may have been due to patients switching to a different dosing schedule or switching pharmacies or health plans and no longer being included in the study database; but these persistence rates clearly were suboptimal.

Dr. Ettinger concluded that better patient education may help long-term adherence. Less frequent dosing and increased convenience may also prove helpful.

Fracture Prevention: Early Identification and Treatment Options
Vertebral fractures are a multiethnic problem, and population studies have shown that by age 70, 20% of men and 25% of women have a vertebral fracture.

To demonstrate that existing asymptomatic vertebral fracture predicts future fracture, Dr. Miller showed data from the placebo arm of a risedronate study by Lindsay and associates (JAMA. 2001;285:320-323). Among control subjects who had one morphometrically-defined vertebral fracture, 11% had another fracture within one year if untreated. Among those with two vertebral fractures, 24% had another fracture. “This data is consistent across the placebo arms of clinical trials with all osteoporosis treatments,” said Dr. Miller.

“Vertebral fractures are a multiethnic problem, and population studies have shown that by age 70, 20% of men and 25% of women have a vertebral fracture,” he continued. The Writing Group for the ISCD Position Development Conference established criteria for which patients should be assessed for vertebral deformities (J Clin Densitom. 2004;7:7-12). These include patients who have lost 1.5 inches or more in height, and patients with back pain or known vertebral deformities.

Dr. Miller next raised the question: “In women with low bone mass without a prior fragility fracture, at what T-score should we initiate therapy?” He cited the National Osteoporosis Foundation intervention thresholds, which advise treating postmenopausal women with T-scores of -2.0 or lower without other risk factors, with T-scores of -1.5 or lower with additional risk factors, and with fragility fractures without BMD.

He cited several studies which demonstrated that postmenopausal women with T-scores higher than -2.5 can experience fractures. Untreated osteoporotic women between ages 50 and 64 also have an increased fracture risk, even though their absolute fracture risk is lower than women age 65 and over, since younger age conveys a greater bone strength at equivalent BMD levels. “The challenge is to identify these patients,” said Dr. Miller.

“When people have prevalent vertebral fractures, the data are consistent across all clinical trials that you get a reduction in fracture events, even in the osteopenic population, with treatment,” he continued. Incident fractures can be reduced even in people who do not have T-scores below -2.5.

Dr. Miller concluded: “Postmenopausal women with a prior fragility fracture, especially of the vertebrae or hip, should be treated regardless of their T-scores. Postmenopausal women with T-scores of -2 or lower should be considered for pharmacologic therapy, especially in the presence of additional risk factors. There’s evidence that agents that reduce bone turnover can reduce fracture risk in the osteopenic population.”

Diseases Causing Acute, Rapid, and Severe Bone Loss: Often Unrecognized and Neglected

Acute, rapid, and severe bone loss (ARSBL) is often unrecognized and neglected,” began Solomon Epstein, MD, Professor of Medicine and Geriatrics, and Director of Osteoporosis Research, Doylestown Hospital, Pennsylvania.

ARSBL is a malignant form of osteoporosis accompanied by a high rate of fracture far exceeding that seen with postmenopausal and age-related osteoporosis. It’s usually characterized by over 8% bone loss in the first year after the precipitating event or onset of disease. There are several possible causes of ARSBL, and patients can be divided into two subgroups. The first is those with known fracture data. In this category, possible causes include drug therapy (e.g., glucocorticoids, calcineurin inhibitors), post-transplant bone disease, stroke, immobilization (e.g., spinal cord injury), or prostate cancer treated with anti-sex hormone drugs. The second subgroup includes patients with no fracture data, but with an excessive rate of bone loss. Possible causes of ARSBL in this group include immobilization, space flight, inflammatory bowel disease, celiac disease, chemotherapy (sex hormone deficiency), anorexia nervosa, and treatment with depot progesterone.

Glucocorticoid-Induced Osteoporosis
The most common form of secondary osteoporosis is glucocorticoid-induced osteoporosis. According to the family
practitioner’s database in the UK, 0.5% to 1.7% of postmenopausal women have been exposed to glucocorticoids. The incidence of osteoporosis is about 50% in all patients treated with glucocorticoids for over six months, and the estimated fracture incidence at the spine and ribs in patients on long-term therapy is 15% to 40%. The risk of hip fracture is double in glucocorticoid users.

In glucocorticoid-treated patients, the most rapid bone loss occurs in the first 12 months, but it continues as long as the drug is taken. Loss occurs more rapidly in trabecular bone, and approaches 40% in the lumbar spine, as demonstrated in cross-sectional studies. Bone loss may be partially reversible after steroid withdrawal.

Clinical risk factors for ARSBL include BMD before glucocorticoid therapy, duration and dose of drug, and the underlying disease. For example, patients with rheumatoid arthritis, renal disease, or an autoimmune disease will have bone loss from the underlying condition.

The brunt of the effect of glucocorticoids is on bone formation (osteoblasts) and not on bone resorption (osteoclasts). Dr. Epstein emphasized that “even short courses of relatively small doses of glucocorticoids have an effect on markers of bone turnover, which if continued long term translate into decreased bone mineral density and decreased bone formation.”

The mechanisms of bone loss from glucocorticoid use include decreased calcium absorption, increased renal calcium excretion, secondary hyperparathyroidism, inhibition of sex steroids, and, most importantly, direct and indirect effects on bone cells.

To manage glucocorticoid-induced osteoporosis, intervention often is indicated at a T-score that would be considered normal in the general population. “Patients should receive DEXA bone densitometry, but the results shouldn’t necessarily dictate therapy,” said Dr. Epstein. The underlying disease and the dose and duration of glucocorticoid therapy are more important in determining treatment.


Dr. Epstein cited data indicating that teriparatide is also an option for steroid-induced osteoporosis.

### Transplantation Bone Diseases

There are about 300,000 transplants in the U.S. each year, and these patients are at risk for post-transplantation bone disease from the underlying disease (e.g., liver or renal disease malabsorption, hypogonadism), lifestyle factors (such as smoking, alcohol use, and poor diet), immobilization, and drugs (diuretics, immunosuppressives, anticoagulants).

In patients with kidney transplants, the fracture incidence is about 3% to 10%; in heart transplant patients, it’s 10% to 36%; in liver transplant patients it is up to 65%; and in lung transplant patients it’s 18% to 37%. Risk following renal transplantation does not go down over time, rather it tends to go up as risk factors such as older age, low body mass index, prevalent fractures, menopause, prolonged dialysis, and diabetes come into play.

### Therapeutic options after transplantation include calcium, vitamin D, calcitonin, and bisphosphonates.

To manage post-transplantation bone disease, Dr. Epstein recommended decreasing the dose of immunosuppressants and pretreating with anti-resorptives and calcium and Vitamin D. He cited a study in rats showing that the combination of low-dose cyclosporine plus low-dose rapamycin resulted in no loss of bone.

Therapeutic options after transplantation include calcium, vitamin D, calcitonin, and bisphosphonates. “Bisphosphonates have proven to be the most effective treatment,” said Dr. Epstein. Oral or I.V. bisphosphonates should be started as soon as practical after surgery, he advised.

A study of osteoporosis found that the once-monthly oral bisphosphonate ibandronate at 150 mg was superior to the once-daily formulation (Miller P, et al. J Bone Miner Res. 2005;20(8):1315-1322). Giving bisphosphonates intravenously (either ibandronate or zoledronic acid) also has advantages for this patient population who may be immobilized and who are on several medications. “If you give it intravenously compliance becomes a secondary issue,” he said. He cited the Dosing Intravenous Administration of ibandronate (DIVA) study, which demonstrated an increase in BMD with intravenous administration.

Dr. Epstein concluded by mentioning other potential causes of ARSBL. “Stroke patients can experience rapid demobilization, and the bone loss can be 9% after one year in those who do not relearn to walk,” he said. One study found that fracture incidence increased following stroke, two to four times greater than that of the general population (Rammemark A, et al. Osteoporos Int. 1998;8:92-95).

Androgen deprivation for treatment of prostate cancer also can increase risk of fracture. In a study of 50,613 men diagnosed with prostate cancer, the fracture incidence was 19.4% in those treated with androgen deprivation therapy compared to 12.6% who were not (Shahinian VB, et al. N Engl J Med. 2005;352(2):154-164). “Men receiving this therapy should have BMD monitored and should be prescribed a bisphosphonate,” said Dr. Epstein.

Aromatase inhibitors for treatment of breast cancer can also raise risk for fractures. In a study of 9,336 women with localized breast cancer, incidence of fractures was 340 in the group treated with anastrozole compared to 237 in the tamoxifen group (Howell A, et al. Lancet. 2005;365:60-62).

In summary, Dr. Epstein said: “ARSBL patients need to be identified early and preventive therapy should be initiated to avoid rapid bone loss and fractures. Bisphosphonates are the most effective therapy and we have encouraging data on intermittent dosing and intravenous therapy. The use of anabolic agents, such as intermittent PTH, may also play an increasingly important role in these conditions particularly where bone formation is the major defect.”
Insulin Sensitizers for the Treatment of Type 2 Diabetes: Implications for Cardiovascular Disease Risk Management

In an industry-sponsored symposium held in conjunction with the American Association of Clinical Endocrinologists Fourteenth Annual Meeting and Clinical Congress and moderated by David M. Kendall, MD, three leaders in medicine, endocrinology, and clinical research provided the latest information on insulin resistance, type 2 diabetes, and cardiovascular risk. Topics included insulin resistance and atherosclerotic cardiovascular disease in diabetes, use of insulin sensitizers in persons with cardiovascular disease, and the mechanisms of diabetic dyslipidemia.

This program was supported by an unrestricted educational grant from Takeda Pharmaceuticals North America, Inc.

Relationship of Insulin Resistance to Atherosclerotic Cardiovascular Disease in Diabetes

“T

he most frequent cause of death in people with diabetes is ischemic heart disease. Insulin resistance in type 2 diabetes and with the metabolic syndrome is known to be associated with atherosclerotic cardiovascular disease and a significant increase in related mortality. For this reason, aggressive treatment to achieve glycemic control and reduce cardiovascular risk is needed,” said Burton E. Sobel, MD, E.L. Amidon Professor and Chair, Department of Medicine, University of Vermont, Physician-in-Chief, Fletcher Allen Health Care, Burlington, Vermont. According to Dr. Sobel, it is hoped that ongoing research investigating the effect of insulin-sensitizing regimens on the progression of cardiovascular disease will help to increase our understanding and improve treatment of those with insulin resistance.

Type 2 Diabetes and Metabolic Syndrome

Despite progress in the overall prevention and treatment of heart disease, the risk for cardiovascular events in people with diabetes remains high. “In addition, in women with type 2 diabetes, the risk of cardiovascular mortality appears to be increasing, rather than decreasing,” Dr. Sobel said. According to Dr. Sobel, this may be due to the insulin resistance associated with diabetes and the metabolic syndrome. In the Quebec Heart Study of men with no evidence of ischemic heart disease (Despres et al. N Engl J Med. 1996; 334:952), for example, a single fasting insulin value was a powerful predictor of risk of ischemic heart disease in subsequent years.

“A high risk of cardiovascular disease and associated mortality are also present in those with the metabolic syndrome without diabetes,” Dr. Sobel said. Both the National Cholesterol Education Program and World Health Organization criteria for the diagnosis of the metabolic syndrome include several factors associated with insulin resistance, including: obesity, increased triglyceride levels, decreased high-density lipoprotein (HDL), and hypertension. Insulin resistance may be associated also with numerous other factors that may contribute to increased coronary artery disease, including: impaired glucose tolerance, hypertension, hyperlipidemia, endothelial dysfunction, prothrombotic and hypercoagulable state, impaired fibrinolysis, augmented systemic inflammatory state, and development of atherosclerotic plaques vulnerable to rupture (Figure 1).

Insulin Resistance and Vasculopathy

Insulin resistance in diabetes or with the metabolic syndrome may lead not only to cardiovascular events but also to direct changes to vessel walls underlying macroangiopathy and acute coronary syndromes. In the original BARI trial (Chaitman et al. Circulation. 1997; 96:2162), people with symptomatic coronary artery disease were treated initially either by coronary bypass grafting or by angioplasty. The results showed no differences in mortality, except in persons with diabetes. In those who had diabetes and underwent surgery, mortality was increased twofold over that in the overall population undergoing surgery. “Although the grafts were successful, the patients developed disease in other vessels,” Dr. Sobel explained. In those with diabetes undergoing angioplasty, 5-year mortality was increased fourfold over that in the overall population. “In these cases, the vessel itself reacted adversely to the iatrogenic injury,” he said.

Fibrinolytic System and Plaque Rupture

One factor in increased atherosclerosis in persons with insulin resistance may be that of an abnormal fibrinolytic system and an imbalance in plasminogen activator inhibitor-type 1 (PAI-1)/plasminogen activator concentrations (Sobel. Proc Assoc Am Phys. 1999; 111:313). In one study, persons who had survived acute myocardial infarction, though clinically well and stable, were shown to have a hypoactive fibrinolytic system (Hamsten et al. N Engl J Med. 1985; 313:1557). Obesity and diabetes are
The development of insulin-sensitizing agents, such as the thiazolidinediones (TZDs), represents a significant advance in the treatment of insulin resistance and protection against cardiovascular disease. Indeed, research has indicated that these agents have numerous vasculoprotective effects, derived mainly from their action upon peroxisome proliferator-activated receptor (PPAR)-gamma, said Ronald Goldberg, MD, Professor of Medicine, Division of Endocrinology, Diabetes, and Metabolism University of Miami; and Associate Director, Diabetes Research Institute; Director, Lipid Disorders Unit, Miami.

Dr. Goldberg provided an overview of the current data and future directions investigating the vasculoprotective effects of TZD therapies.

In another study, PAI-1 was found in the internal mammary grafts of persons with diabetes, whereas little or no PAI-1 was observed in those with coronary disease but without diabetes (Pandolfi et al. Arterioscler Thromb Vasc Biol. 2001; 21:1378). “Before gross atheroma had developed in these grafts, an inhibition of the fibrinolytic system had occurred,” Dr. Sobel said. Its unfavorable effect on otherwise protective migration of vascular smooth muscle cells into the developing neointima of evolving coronary atheroma may predispose to development of lipid-laden plaques vulnerable to rupture. “In patients in whom the vessel contains too much PAI-1 but are exposed to an atherogenic drive, plaques can rupture, potentially causing sudden death. Unfortunately, people with insulin resistance—such as those with diabetes or metabolic syndrome—are at increased risk of developing this type of plaque. Even more disconcerting is that this may not be evident by stress test, cardiogram, function tests, or even symptoms,” Dr. Sobel explained. Patients with diseases of insulin resistance, such as diabetes and the metabolic syndrome, are also at increased risk for other manifestations of cardiovascular disease, such as congestive heart failure and, particularly in hypertensive women, diastolic heart failure.

In closing, Dr. Sobel emphasized that treatment should involve aggressive management and control of all aspects of the insulin-resistance phenomenon. “Reduction of insulin resistance, control of blood sugar, management of blood pressure, preservation of endothelial function, cessation of smoking, and implementation of anti-inflammatory regimens are key factors in reducing cardiovascular risk in people with type 2 diabetes or the metabolic syndrome,” he concluded.

Treatment of Patients with Cardiovascular Disease: Impact of Insulin Sensitizers

The development of insulin-sensitizing agents, such as the thiazolidinediones (TZDs), represents a significant advance in the treatment of insulin resistance and protection against cardiovascular disease. Indeed, research has indicated that these agents have numerous vasculoprotective effects, derived mainly from their action upon peroxisome proliferator-activated receptor (PPAR)-gamma, said Ronald Goldberg, MD, Professor of Medicine, Division of Endocrinology, Diabetes, and Metabolism University of Miami; and Associate Director, Diabetes Research Institute; Director, Lipid Disorders Unit, Miami. Dr. Goldberg provided an overview of the current data and future directions investigating the vasculoprotective effects of TZD therapies.
Mechanisms of Vasculoprotective Effect

TZDs act upon the PPAR-gamma receptor located mainly in fat tissue, but also in the liver muscle and vascular cells, exerting an effect on modulation of adipocyte differentiation, lipid metabolism, insulin sensitivity, glucose homeostasis, and inflammation (Table 1). The potential vasculoprotective effects of the TZDs originate not only with their effects on insulin sensitivity, but also on other genes that may affect the process of atherogenesis, Dr. Goldberg said. It is known that PPAR-gamma is present in endothelial cells, vascular smooth muscle cells, and atheroma. Studies have demonstrated that PPAR-gamma inhibits the migration of monocytes, a critical first step for gaining entry to the vascular wall, and then alters cholesterol metabolism. TZD increases CD36, but also turns on the ABCA1 gene pool, which moves cholesterol out of the cell, allowing for removal of pathogenic oxidized low-density lipoprotein while also preventing accumulation of cholesterol in the vascular wall. Together with an effect on interleukin-6, inflammatory cytokines, and matrix metalloproteinases, the actions of TZDs point to a strong vasculoprotective effect, Dr. Goldberg summarized.

Effect on Lipids

In patients with diabetes, the National Cholesterol Education Program recommends a LDL-L goal of < 100, or for those at high risk, a reduction of 30% to 40% of current lipid levels. TZDs have an effect on lipid metabolism, with most evidence indicating an effect on HDL levels, on LDL particle size, and variably on triglyceride levels. Whether the effect is one directed via a dyslipidemic component or LDL cholesterol is an important consideration, Dr. Goldberg noted. In one study, men with coronary artery disease were treated with a PPAR-alpha agonist. While no change in LDL levels was observed, there was a significant increase in HDL and decrease in triglyceride levels. Importantly, the PPAR-alpha agonist may be exerting this effect via non-LDL components of the lipid profile, he said.

The potential vasculoprotective effects of the TZDs originate not only with their effects on insulin sensitivity, but also on other genes that may affect the process of atherogenesis.

In addition, a recent head-to-head comparison trial investigated the lipid-modifying effects of TZD agents, pioglitazone and rosiglitazone. Patients with type 2 diabetes received either pioglitazone or rosiglitazone in addition to standard antihyperglycemic monotherapy. The results showed similar effects on hemoglobin A1c, fasting insulin, PAI-1, free fatty acid, and C-reactive protein levels. However, patients receiving pioglitazone also showed a reduction in triglyceride levels by 12% and increase in HDL by 14.9%; rosiglitazone resulted in an increase in triglyceride levels by 14.9% and lesser increase in HDL of 7.8%. An increase in LDL was observed in both groups, with a 15.7% increase with pioglitazone and 23.3% increase with rosiglitazone. Weight gain was comparable, and prevalence of edema increased only modestly, in both treatment groups. These findings demonstrate significant lipid-modifying effects with these TZD agents, and the ongoing Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROactive) will help in determining the cardiovascular effects of these agents.

Effect on Vasculature

Patients with type 2 diabetes or metabolic syndrome have decreased vasomotor response to stimuli, possibly due to nitric oxide availability and endothelin release. In addition, in one 52-week study, persons with diabetes received either rosiglitazone or glyburide. The results showed no change in systolic and a reduction of diastolic blood pressure with rosiglitazone, compared with increased systolic blood pressure with glyburide. In a similar study, patients receiving pioglitazone had a significant reduction in systolic and diastolic blood pressures versus no change with glimepiride.

Effect on Microalbuminuria

Microalbuminuria, which generally represents the presence of a systemic abnormality of vascular function, is a significant predictor of cardiovascular disease in persons with insulin resistance. In one study, patients with diabetes and microalbuminuria received pioglitazone for 3 months and experienced a significant improvement in microalbuminuria. Similar results were observed in a study of rosiglitazone. In addition, studies of both pioglitazone and rosiglitazone treatment have shown a significant effect on carotid artery intimal medial thickness.

Effect in Coronary Artery Stenting

In patients who have diabetes and have undergone coronary artery stenting, TZD therapy may offer significant benefits. Indeed, studies of this patient population have shown a reduction in intimal hyperplasia and marked reduction in degree of restenosis compared with placebo. These findings suggest a significant vasculoprotective effect with TZDs in patients having coronary artery stents, the speaker summarized.

In closing, Dr. Goldberg noted that TZDs appear to exert multiple vasculoprotective effects in persons with insulin resistance, and continued research is needed to delineate further the cardiovascular and other potential benefits of these potent agents.
Insulin Sensitizers for the Treatment of Type 2 Diabetes: Implications for Cardiovascular Disease Risk Management

Mechanisms of Diabetic Dyslipidemia: Effects of Insulin Sensitizers

One of the central features of insulin resistance and metabolic syndrome is diabetic dyslipidemia. This condition is characterized by blood levels showing elevated triglycerides, reduced high-density lipoprotein (HDL) cholesterol, and normal concentrations of low-density lipoprotein (LDL) that are excessively small and dense, according to Henry N. Ginsberg, MD, Irving Professor of Medicine, College of Physicians and Surgeons at Columbia University; Director, Irving Center for Clinical Research, Columbia University Medical Center, New York. Dr. Ginsberg provided an overview of the mechanisms of diabetic dyslipidemia and the study of the potential effects of thiazolidinedione (TZD) therapies on this syndrome.

Dyslipidemia in Diabetes

Dyslipidemia in patients with diabetes occurs mainly from an increased influx of fatty acids into the liver, where they are synthesized, and efficiently converted back into triglycerides. These triglycerides then remain in the liver, causing hepatosteatosis, or combine with apolipoprotein B (apo B) into very-low-density lipoproteins (VLDL) for secretion. The increased levels of triglycerides, apo B, and VLDL lead to low levels of HDL and the formation of excessively small and dense LDL particles.

The clinical findings of the second-generation Framingham study reflect this process. In men, low HDL levels were present in 20% of normal healthy controls, but more than double that in men with diabetes. High triglyceride levels were present in 70% of non-diabetics, but in approximately 90% of men with diabetes. In women, the impact of diabetes was even more pronounced, with greater differences between non-diabetic and diabetic women in HDL and triglyceride levels. And, unlike the male group, differences in total cholesterol and LDL cholesterol levels were significant in non-diabetic versus diabetic women. “These findings revealed a significant maldistribution of triglyceride and HDL levels among patients with diabetes—and a pronounced gender difference with regard to impact of diabetes on total and LDL cholesterol levels,” Dr. Ginsberg pointed out (Siegel et al. *Metabolism* 1996;45:1267).

Sources of Triglyceride

“The liver makes VLDL to export excess accumulated energy to the periphery for storage in the adipose tissue, with the energy being fatty acid made into triglyceride by the liver. There are several sources of fatty acids, and the effects of insulin resistance play a role in how those sources arrive at the liver, what quantities are in the liver, and how the liver deals with them,” Dr. Ginsberg explained.

Three major sources of triglyceride for assembly with Apo B to be secreted as VLDL are: fatty acid from the periphery, remnant fatty acid triglyceride, and de-novo synthesized lipogenesis. For example, when the body’s insulin is working appropriately, fatty acid is stored in the periphery efficiently because insulin suppresses hormone-sensitive lipase and other lipolytic pathways in the fat cell. In the presence of insulin deficiency or insulin resistance, lipolysis (triglyceride breakdown) and fatty acid release are increased. Another source of triglyceride for VLDL secretion is derived from the endogenous production of fatty acids by de-novo hepatic lipogenesis. De-novo synthesized lipogenesis is controlled by the transcription factor SREBP-1c, which is, in turn, partly regulated by insulin. With hyperinsulinemia, insulin appears to work to drive SREBP-1c and lipogenesis, which is increased in patients who are obese, insulin resistant, or diabetic. However, insulin may also cause the breakdown of apo B in the hepatocyte, inhibiting secretion of VLDL. If insulin is working but also driving lipogenesis, a fatty liver may result. If the liver is insulin resistant, excess apo B and VLDL are secreted.

High levels of blood VLDL and TG play a significant role in reducing blood HDL cholesterol levels and changing LDL size and composition. Much of this is mediated by cholesterol ester transfer protein (CETP). In the bloodstream, VLDL can literally collide with HDL or LDL, and in the presence of CETP, triglycerides can move from VLDL into HDL or LDL. In exchange, cholesterol ester moves from HDL and LDL into VLDL. The breakdown of triglycerides in HDL and LDL then occurs, resulting in cholesterol depletion of these lipoproteins.

Treatment Strategies

Insulin-sensitizing agents, such as the TZDs, have the potential to lower hepatic secretion of VLDL, apo B, and triglycerides by reducing the influx of fatty acids into the liver and perhaps increasing insulin-mediated hepatic degradation of newly synthesized apo B. This effect may also produce an increase in HDL levels and LDL particle size.

In one study, Ginsberg and colleagues added pioglitazone to the treatment of patients with diabetes and high triglyceride levels, who were already taking sulfonylurea and metformin. These patients received placebo for 3 weeks, then pioglitazone for 12 to 16 weeks; sulfonylurea was titrated to lower doses to maintain glycemic control. The results showed improved sensitization to insulin. In addition, fatty acids were decreased by 25%, VLDL triglycerides decreased by 25% to 30%, and HDL increased by about 15% after pioglitazone treatment. Apo B metabolism was unchanged, as was the secretion in to plasma of VLDL. “We did not see a reduction in plasma triglyceride production with pioglitazone therapy, but rather a more efficient removal of VLDL triglycerides from plasma, indicating improved lipolysis,” Dr. Ginsberg explained (Nagashima et al. *J Clin Invest*. 2005; 115:1323).

In closing, Dr. Ginsberg emphasized that “this evidence lends insight into the mechanism of the lipid-modifying properties of PPAR-gamma agonist therapies, and offers promise for the future treatment of insulin resistance and reduction of cardiovascular morbidity and mortality in patients with type 2 diabetes or metabolic syndrome.”
Optimizing Thyroid Hormone Therapy of Hypothyroidism

At a symposium held May 18, 2005, during the American Association of Clinical Endocrinologists’ Fourteenth Annual Meeting and Clinical Congress, a panel of experts presented information on optimizing thyroid hormone therapy in various populations, including reproductive-age women and patients with cardiovascular concerns. They also discussed best practices for the clinical assessment of thyroid function in patients with hypothyroidism.

"S"ymptoms and signs of hypothyroidism are myriad and reflect the numerous organ systems regulated by the thyroid," began Robert C. Smallridge, MD, Director of Research and Professor of Medicine, Mayo Clinic, Jacksonville, Florida. Many of the symptoms are nonspecific and overlap with other common diseases.

During the early stages of hypothyroidism, the T4 level starts to go down but remains within normal limits while the thyroid-stimulating hormone (TSH) level increases above normal. “It’s that period of subclinical hypothyroidism, which may last years or even decades, that causes the most problems in diagnosis,” he explained. Even overt hypothyroidism can be hard to identify clinically. When the thyroid starts to fail, many different systems are involved, including metabolism, neuromuscular, reproductive, integument, gastrointestinal, nervous system, and cardiorespiratory.

Many symptoms are common (e.g., fatigue, weight gain, constipation, depression) but nonspecific. Some unusual presentations of hypothyroidism include pituitary hyperplasia, acquired von Willebrand’s disease, neuromuscular symptoms, and hypophysitis.

Several hypothyroidism clinical scores have been published. Groups of signs and/or symptoms are used to calculate a score to differentiate patients who are euthyroid from those who are hypothyroid. Most of the hypothyroidism scores Dr. Smallridge identified in the literature use symptoms. The Zulewski score was 62% successful and the Billewicz score was 42% successful in patients who were believed to have overt hypothyroidism and 24% and 6% successful, respectively, in patients who were believed to have subclinical disease.

The clinical score generated by Canaris GJ et al. used questionnaires to collect data pertaining to present symptoms and symptoms that had changed over the previous year for hypothyroid patients and controls (J Gen Intern Med. 1997;12:544-550). A large number of symptoms were identified; however, only two of them approached 50%. But, when combinations of changed symptoms were analyzed, most control patients had zero, one, or two symptoms, whereas the hypothyroid patients had several symptoms. “But even with overt hypothyroidism, there had to be seven or more of those symptoms to increase the likelihood that this score would be clinically useful,” said Dr. Smallridge. The use of current symptoms is not as strong statistically as using changes in symptoms.

Patients with overt hypothyroidism clearly need treatment and will benefit from it. “Treating subclinical hypothyroidism is a more vexing issue,” said Dr. Smallridge. He summarized five publications that addressed this issue. Two of these, Cooper (1984) and Nystrom (1988), claimed that patients with subclinical disease got a symptom response. However, a number of the patients in these studies had TSH levels of 30 mIU/L, which is not the type of patient that clinicians typically see today. And, a number of patients described in the Nystrom publication were overtreated and had suppressed TSH levels and elevated free T4. “More recent papers have tried to focus on lower TSH levels; down in the 5 to 10 range is most common,” he explained. But, when patients are divided into those with a TSH of less or greater than 12 mIU/L, it was those with greater than 12 mIU/L who improved with therapy.

The question of whether it would be more beneficial to treat hypothyroid patients with a combination of T3 and T4 instead of T4 alone has been addressed in numerous publications. In a study with 101 patients treated with either T4 alone or T3 and T4, Walsh et al. found that there were no differences in cognitive function, quality of life, or thyroid-specific quality score (J Clin Endocrinol Metab. 2003;88:4543-4550). The general health score was worse and anxiety was higher in patients taking the drug combination. Sawka et al. studied
Cardiovascular Actions of Thyroid Hormones

"T"hroid hormone is an impor-
tant regulator of cardiac function and cardiovascular hemodynamics," said Irwin Klein, MD, Professor of Medicine, NYU School of Medicine, and Chief, Division of Endocrinology, North Shore University Hospital, Manhasset, New York. The thyroid hormone mediated changes to the cardiovascular system may occur via direct effects on the heart or effects on the peripheral circulation which then indirectly causes changes in cardiac function.

Eighty-five percent of endogenous thyroid hormone production is in the form of T4 and 15% is in the form of T3. The majority of serum T3 derives from metabolism in the liver. T3 increases tissue thermogenesis and decreases systemic vascular resistance which leads to a decrease in diastolic blood pressure. In addition, T3 acts directly on the heart by enhancing the rate of beating and the force of contractility. T3, but not T4, is transported into the cardiac myocyte where T3 acts at the level of the nucleus to promote the expression of many proteins which are involved with the regulation of cardiac contractility. "The net effect of this is an increase in cardiac output, which teleologically serves to provide increases in oxygen and substrate delivery to the peripheral tissues," said Dr. Klein. So, in hyperthyroidism, cardiac contractility and cardiac output are enhanced, and systemic vascular resistance is decreased, while in hypothyroidism, the opposite is true.

Dr. Klein reviewed the changes in cardiovascular function in mild hypothyroidism from a study he and his colleagues conducted. In these patients, fractional shortening, cardiac output, and systemic vascular resistance were not significantly different from controls; however, isovolumic relaxation time was prolonged (N Engl J Med. 2001;344:501-509). After thyroid hormone replacement, all measures returned to normal and isovolumic relaxation time was even enhanced. "From an anatomic and hemodynamic point of view, the treatment of mild hypothyroidism can be predicted to improve cardiac function," he said.

The degree of attributable risk from subclinical hypothyroidism clearly rivals that of hypercholesterolemia, diabetes, smoking, and hypertension," said Dr. Klein.

To illustrate this, Dr. Klein summarized a retrospective analysis of hypothyroid patients with coronary artery disease who underwent angiography. Of the 4103 patients with angiography, it turned out that 25 had hypothyroidism (Perk M et al. Can J Cardiol. 1997;13:273-276). It was also determined that coronary artery disease progression was more common in patients with inadequate T4 treatment.

"In an era when cardiovascular risk reduction has been emphasized as an important component of the management of all patients, the cardiovascular risks associated with hypothyroidism are worth reviewing," said Dr. Klein. The cardiovascular risk factors associated with hypothyroidism that respond to treatment include hypercholesterolemia, diastolic hypertension, left ventricular diastolic dysfunction, impaired endothelial mediated vasodilation, hypercoagulable state, and elevated serum homocysteine. C-reactive protein, which is present in hypothyroidism, does not respond to treatment.

Dr. Klein reviewed a population study of nearly 8,000 women, over 1,000 of who were evaluated for lipids, TSH, aortic calcifications, EKG, and myocardial infarction history (Hak AE et al. Ann Intern Med. 2000;132:270-278). When compared with euthyroid controls, patients with subclinical hypothyroidism had a greater than two-fold increased risk of myocardial infarction and almost a three-fold increased risk of myocardial infarction if they also had anti-thyroid antibodies. In addition, aortic atherosclerosis was seen to be present with a two-fold increased risk in subclinical hypothyroidism patients and slightly greater in the presence of antibodies (Figure 1). "The degree of attributable risk from subclinical hypothyroidism clearly rivals that of hypercholesterolemia, diabetes, smoking, and hypertension," said Dr. Klein.

Endothelial function was studied in patients with subclinical hypothyroidism by Taddei and colleagues (J Clin Endocrinol Metab. 2003;88:3731-3737).
Thyroid Hormone Replacement for Women in the Reproductive Years

Pregnancy is associated with increased thyroid hormone production; therefore, it is critical to optimize levothyroxine (L-T4) therapy prior to conception,” began Susan J. Mandel, MD MPH, Associate Professor of Medicine and Radiology, and Associate Chief for Clinical Affairs, Division of Endocrinology Diabetes, and Metabolism, University of Pennsylvania School of Medicine, Philadelphia.

She reviewed the normal physiology of thyroid hormone changes during pregnancy. As estradiol levels increase, there’s an increase in thyroid-binding globulin and an accompanying increase in total T4. Renal iodide clearance is also higher and thyroid hormone metabolism is accelerated because of the placental deiodination of T4. At the end of the first trimester, there is a reciprocal change in hCG and TSH when hCG levels peak and TSH levels reach their lowest. Dr. Mandel explained that there is evidence pointing to the fact that hCG itself serves as a thyroid stimulator. One unit of hCG has thyrotropic activity, but it has a fraction of the strength of TSH. Free T4 levels in pregnant populations are positively correlated with hCG levels in the first trimester. And, studies in cultured thyroid cells indicated that hCG binds to and activates the TSH receptor. A number of authors have coined the term “gestational thyrotoxicosis” to refer to this hCG-mediated increase in thyroid hormone production. About 15% of pregnant women have TSH levels below the nonpregnant reference range and 2% have truly elevated free T4 levels. Gestational thyrotoxicosis improves as hCG levels decrease later in pregnancy so antithyroid treatment is not indicated.

Dr. Mandel cited a screening study of 2,000 pregnant women which found that, at 15 to 18 weeks’ gestation, 97.5% of the patients had TSH levels of less than 6 mIU/L and 2.5% of them had TSH levels of greater than 6 mIU/L, and most of the latter group were antithyroid antibodies positive (Klein RZ et al. Clin Endocrinol (Oxf). 1991;35:41-46). “About 1 in 40 women will be found to have an elevated TSH during gestation,” Dr. Mandel explained. Overt hypothyroidism occurs in 1 in 300 women.

In a case discussion, Dr. Mandel described a 35-year-old woman with mild thyroid failure who had two first trimester miscarriages. “Is there a relationship between hypothyroidism and her miscarriages?” she asked. Dr. Mandel cited a review of six studies that evaluated the miscarriage rate in women with or without antithyroid antibodies. “Having positive antibodies, even if TSH is normal, may be associated with an increased rate of miscarriage in the first trimester,” she said.

“There are no good data to tell us what to do if we see a patient who has miscarried in the past and who has positive antibodies,” explained Dr. Mandel. In practice, Dr. Mandel treats these patients with L-T4 if their TSH levels are greater than 2.5 mIU/L, and closely monitors those patients whose TSH levels are less than 2.5 mIU/L. “This area is ripe for randomized controlled trials to look...
at whether thyroid hormone in these euthyroid women with positive antibodies may affect pregnancy outcome,” she added. In addition, L-T4 therapy should be optimized in women with pre-existing hypothyroidism prior to conception to keep the TSH <2.5mU/L.

Dr. Mandel returned to the case report. The patient was treated with T4 and subsequently became pregnant again. At 9 weeks’ gestation, her TSH level was 8.1 mU/L. Most pregnant hypothyroid women who are being treated with L-T4 require a dosage increase as documented by 9 recent studies. The median time for the dosage increase is at 8 weeks’ gestation (Alexander EK et al, *N Engl J Med*. 2004). Therefore, the TSH level must be checked as soon as a woman finds out that she is pregnant and the L-T4 dosage should be adjusted to keep the TSH level <2.5mU/L.

Dr. Mandel cited a study that looked at pregnancy outcome in 51 patients with an elevated TSH in the first trimester (Abalovich M et al. *Thyroid*. 2002;12:63-68). In 24 of these patients the TSH was never normalized and only about 20% had a term pregnancy. The other 27 patients attained normal levels of TSH and virtually all of them had term deliveries (Figures 2 and 3). “If you don’t get it right and you don’t fix her thyroid function, there’s not a very high likelihood of a term pregnancy,” she explained.

Fetal thyroid production begins at around 12 to 14 weeks’ gestation. Prior to that, all thyroid hormone in the fetus is maternal in origin. Therefore, low levels of maternal thyroid hormones may affect fetal neural development directly and alterations in cardiovascular physiology associated with hypothyroidism may lead to alterations in gravid physiology that could impair placental function and nutrient delivery.

Dr. Mandel reviewed a study that retrospectively measured the TSH in women at 16 weeks’ gestation to identify those who were hypothyroid (Haddow JE et al. *N Engl J Med*. 1999; 341;549-555). The children of 48 women who had undiagnosed and untreated hypothyroidism were more likely to have lower IQ scores, language development, school performance, and motor performance than control children.

Dr. Mandel completed the case study by discussing the need to continually adjust T4 doses during pregnancy. At 8 weeks’ gestation, the patient’s TSH was elevated so her levothyroxine dose was increased. Her TSH levels were normal by 13 weeks; however, by 26 weeks her TSH levels again were elevated.

Possible reasons for the increased L-T4 dosage requirement include: increased serum thyroid-binding protein, increased renal iodide clearance, thyrotropic activity of hCG, placental deiodination of T4, transplacental passage of T4, and effect of altered volume of distribution. Thyroxine dose requirements usually plateau at 20 weeks’ gestation; however, the case patient had anemia and was taking iron supplements, calcium supplements, and was drinking soy milk. “All of these things, if taken at the same time as thyroid hormone, may impair absorption,” she explained. The case patient’s TSH was normalized 3 weeks after she was advised to take the L-T4 separately and she went on to deliver a healthy, term infant. “After delivery, the dose is reduced back to the prepregnancy level and TSH is checked 6 weeks later,” concluded Dr. Mandel.
The Incretin Effect: How a New Class of Pharmacologic Agents May Enhance the Future of Diabetes Management

In an industry-sponsored symposium held in conjunction with the American Association of Clinical Endocrinologists Fourteenth Annual Meeting and Clinical Congress and moderated by Daniel Einhorn, MD, FACP, FACE, three leaders in epidemiology and endocrinology presented the latest data on the pathophysiology and treatment of type 2 diabetes. Topics included glucagon-like peptide-1 physiology and pharmacology, incretin mimetic therapy in type 2 diabetes, and unmet needs in type 2 diabetes management.

Diabetes is the fifth-leading cause of death in the United States, and less than 50% of patients with this disease are achieving the American Association of Clinical Endocrinologists (AACE) recommended hemoglobin A1c levels of < 6.5% on their current treatment regimens. Although the last decade has brought the development of several new classes of drugs for the management of type 2 diabetes, significant treatment gaps remain, according to John B. Buse, MD, PhD, FACE, Chief, Division of General Medicine and Clinical Epidemiology; Director, Diabetes Care Center; and Associate Professor, University of North Carolina School of Medicine, Chapel Hill.

“Issues with current agents include: durability of their effect, hypoglycemia, weight gain, edema, gastrointestinal side effects, and multiple contraindications,” Dr. Buse reported during his presentation. Thus, despite the current availability of numerous agents to treat type 2 diabetes, there is a need for additional agents to achieve improved glucose control.

Pathophysiology of Type 2 Diabetes

“In terms of the classical pathophysiology of type 2 diabetes, it has been recognized for years that there are multiple defects related to glucose metabolism. Perhaps central among them is impairment in insulin secretion which synergizes with insulin resistance,” Dr. Buse explained. A more complete pathophysiology of this disease includes numerous other organs, including the pancreas, stomach, and brain. In the pancreas, not only is there abnormal beta-cell function, but also inadequate alpha-cell action with inappropriate glucagon secretion. In the stomach, gastric emptying is accelerated, contributing to increased postprandial glucose levels.

In persons with type 2 diabetes, glucagon hypersecretion (and therefore, hepatic glucose release) occurs despite the fact that the postprandial glucose rises. Importantly, glucagon hypersecretion cannot be abrogated by the use of insulin therapy alone, Dr. Buse explained.

GLP-1 Physiology and Pharmacology

In one study of non-diabetic subjects, plasma glucose levels were followed for 300 minutes postmeal. “If insulin secretion was suppressed via somatostatin infusion, a substantial increase in glucose levels was observed. If glucagon infusion was provided in combination with insulin suppression with somatostatin, there was an increase in glucose. So, glucagon excess combined with insulin deficiency provides an additive effect to worsen glycemic control,” Dr. Buse noted (Shah et al. Curr Am J Physiol. 1999;277: E283). In addition, other research shows that an increased rate of gastric emptying contributes to increased postprandial glucose levels (Rayner. Diabetes Care. 2001;24:371).

The Incretin Effect

Incretins are peptide hormones secreted by enterendocrine cells in the gastrointestinal tract. These hormones function to modulate pancreatic islet secretions as part of the “enteroinsular axis,” increasing insulin secretion in response to an oral meal. The two major incretins that affect glucose metabolism are glucagon-like peptide (GLP)-1 and glucose-dependent insulinotropic polypeptide (GIP). Indeed, studies of plasma insulin responses show much greater insulin levels in response to oral- than to intravenous- administered glucose. According to Dr. Buse, this “incretin effect” can be demonstrated in persons with diabetes (Perley et al. J Clin Invest. 1967;46:1954).

GLP-1: Sites of Action and Clinical Activity

Importantly, Dr. Buse pointed out, persons with IGT and type 2 diabetes have decreased postprandial GLP-1 levels, indicating moderate GLP-1 deficiency (Toft-Nielsen et al. J Clin Endocrinol Metab. 2001;86:3717). “With respect to glucose lowering, the actions of GLP-1 are glucose-dependent, which is important and different from the effects of sulfonylurea or insulin,” Dr. Buse said. In one study, patients with type 2 diabetes with poor metabolic control were treated with GLP-1 infusion in the fast-
In all patients, insulin and C-peptide increased significantly over basal levels; glucagon was reduced and plasma glucose reached normal fasting concentrations within 4 hours with GLP-1 administration, but not with placebo. The main mechanism of action appeared to be an enhancement of insulin secretion—by leveraging the natural physiologic phenomenon of the “incretin effect.” Since both insulin secretion and glucagon suppression fell back to baseline values as glucose levels approached 90mg/dL, despite GLP-1 infusion continuing, these results demonstrate that these GLP-1 effects are dependent on glucose being elevated (Nauck et al. Diabetologia. 1993;36:741).

"With respect to glucose lowering, the actions of GLP-1 are glucose-dependent, which is important and different from the effects of sulfonylurea or insulin."

According to Dr. Buse, there are multiple sites of action of GLP-1 and thus numerous effects seen. In the central nervous system, GLP-1 may promote satiety and appetite reduction. In the beta cell, GLP-1 stimulates glucose-dependent insulin secretion and perhaps long-term improvement of beta-cell mass (Table 1). In the stomach, GLP-1 may act to slow gastric emptying, thus slowing the absorption of nutrients from the gastrointestinal tract. By inhibiting glucagon secretion in the alpha cells of the pancreas, GLP-1 indirectly helps to reduce hepatic glucose output (Flint et al. J Clin Invest. 1998;101:515. Larsson et al. Acta Physiol Scand. 1997;160:413. Drucker. Diabetes. 1998;47:159. Nauck et al. Diabetologia. 1996;39:1346).

In terms of clinical activity, one study in which patients with type 2 diabetes received a 6-week course of GLP-1 infusion demonstrated numerous effects. Such effects included a decrease in fasting plasma glucose by 77mg/dL, decrease in 8-hour mean plasma glucose by 100mg/dL, decrease in A1c levels by 1.3%, decrease in body weight by 2 to 3kg, and an increase in insulin sensitivity by 77% (Zander et al. Lancet. 2002;369:824). According to Dr. Buse, intestinal GLP-1 is released in response to a meal. It then exists as an active hormone in the plasma, driving GLP-1-related actions in peripheral and brain tissue. However, GLP-1 is inactivated by dipeptidyl peptidase (DPP)-IV, thus most circulating GLP-1 is inactive (Deacon et al. Diabetes. 1996;44:1126).

Because of its broad range of actions in the body, interventions to increase the GLP-1 effect are currently under study. It is hoped that two main treatment strategies—the inhibition of DPP-IV action to degrade GLP-1 and the development of incretin analogues to mimic the effects of GLP-1—will result in additional available treatments and improved glycemic control for patients with type 2 diabetes.

### Table 1

**Effects of GLP-1 on Beta Cells***

<table>
<thead>
<tr>
<th><strong>Acute Effects</strong></th>
<th><strong>Enhances glucose-dependent insulin secretion</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Subacute Effects</strong></td>
<td><strong>Stimulates transcription of proinsulin and biosynthesis of insulin</strong></td>
</tr>
<tr>
<td><strong>Chronic Effects</strong></td>
<td><strong>Stimulates proliferation and neogenesis of beta cells from precursor ductal cells</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Increases expression of Glut-2 and GK</strong></td>
</tr>
</tbody>
</table>

*Source: Drucker. Mol Endocrinol. 2003;17:161
**Demonstrated in vitro or in animal models.

"The clinical development of incretin therapies holds the real promise of enhancing diabetes care—the capacity of these agents to stimulate glucose-dependent insulin secretion, to improve glucagon secretion, to suppress inappropriate postprandial hyperglycemia, and to achieve weight loss when appropriate will undoubtedly improve glycemic control in patients with type 2 diabetes," said David M. Kendall, MD, Chief of Clinical Services and Medical Director, International Diabetes Center; Clinical Consultant in Endocrinology, Park Nicollet Clinic; and Associate Professor of Medicine, University of Minnesota Medical School, Minneapolis. According to Dr. Kendall, the development of incretin mimetic therapies, such as exenatide, has contributed both to the treatment of diabetes as well as our understanding of the pathophysiology of type 2 diabetes.

**Beta-Cell Function**
There are preliminary data that suggest that GLP-1-based therapies may also have a protective effect on beta-cell function. In one study by Fehse and colleagues patients with type 2 diabetes received either a placebo or exenatide infusion, followed by a bolus injection of glucose. “Exenatide infusion significantly improved phasic insulin secretion,” Dr. Kendall said (Fehse et al. Diabetes. 2004;53(suppl 2):A82). In addition, Buse and colleagues found that exenatide treatment improved fasting proinsulin:insulin ratio, an indirect marker of beta-cell health (Buse. Diabetes Care. 2004;27:2628). “This effect is indicative of less demand on the beta cell, suggesting possible improvement in beta-cell function,” noted Dr. Kendall. Further study will be needed to determine the specific impact of GLP-1-based therapy on beta-cell function.

**Body Weight**
Because many of the available therapies for glycemic control in type 2 diabetes are associated with moderate weight gain, the development of agents that may mitigate this weight gain would be a substantial advance in treatment. “GLP-1 and incretin mimetics have been shown to limit appetite and food intake. In each of the three clinical trials of exenatide therapy, treatment was associated with progressive weight loss,” Dr. Kendall said (Buse. Diabetes Care. 2004;27:2628. Kendall et al. Diabetes Care. 2005;28:1083-1091. Defronzo. Diabetes Care. 2005;28:1092–1100).

**Safety and Tolerability**
Overall, exenatide therapy is well tolerated. Common and potential adverse effects include nausea and vomiting, which generally occur at the time of initiation of therapy and attenuate over time. “There is also a risk of hypoglycemia when exenatide is used with sulfonylurea therapy but no increase in hypoglycemia risk when used with metformin,” Dr. Kendall summarized.

**Future Directions**
In closing, Dr. Kendall emphasized that further research will shed further light...
on the use of exenatide in other patient groups, such as those with early or pre-diabetes syndromes, as well as to determine the efficacy and safety of other incretin mimetics and DPP-IV inhibitors in combination with TZDs and insulin. Preclinical data have demonstrated reductions in hemoglobin A1c and modest weight loss with the use of the GLP-1 analogs liraglutide and CJC 1131. The DDP-IV inhibitor, vildagliptin—which increases the levels of native GLP-1—can also lower hemoglobin A1c when used in combination with metformin. “Targeting gut peptides represents a unique opportunity to minimize the treatment gaps in type 2 diabetes—and may lead to treatments that alter the natural history of type 2 diabetes,” Dr. Kendall concluded.

### Unmet Needs in Diabetes Management

**“A**lthough much progress has occurred in the treatment of type 2 diabetes, significant gaps and challenges remain that prevent optimum control,” said Daniel Einhorn, MD, FACP, FACE, Clinical Endocrinologist, Diabetes and Endocrine Associates; Medical Director, Scripps Whittier Institute for Diabetes; and Clinical Professor of Medicine, University of California, San Diego. Dr. Einhorn provided an overview of the unmet needs of current treatment options for type 2 diabetes and suggested where incretin-based therapies might fit in.

**Limitations in Current Treatment**

In the current treatment of type 2 diabetes, a number of factors limit optimal glucose control. “These factors include: limitations in how much any one agent can lower glucose; difficulty targeting postprandial hyperglycemia; wide fluctuations in glucose throughout the day; hypoglycemia; weight gain; nausea; adverse interactions with kidney, liver, or cardiac function; and the seemingly unavoidable progressive decline in beta-cell function that ultimately leads to insulin dependency,” Dr. Einhorn noted.

**GLP-1 Therapy: Advantages and Hurdles**

Incretin mimetics, mimicking the actions of GLP-1, may offer promise in meeting some of these unmet needs in patients with type 2 diabetes. “Indeed, if beta-cell preservation occurs, the natural history of type 2 diabetes may be altered by this new class of compounds,” Dr. Einhorn explained.

Among the potential advantages of incretin mimetics is a unique additive effect when combined with other diabetes treatments. “Because this is an entirely new class of agents, acting by a completely different mechanism of action, this therapy might be added to anything we currently use for type 2 diabetes,” he said. “There is no reason to think there will be any negative interactions with other diabetes medications.”

Another major advantage with this therapy is the reduction in appetite, which allows for weight loss, a unique characteristic among diabetes treatments. This would make it attractive for any type 2 diabetes patient who has been unable to achieve adequate weight loss. Finally, because the incretin mimetic effect is glucose-dependent, hypoglycemia is minimal when used alone or with metformin.

Incretin mimetic therapy is now becoming available as exenatide, which appears to be relatively easy to use and well tolerated, with side effects—such as nausea—being mild and transient.

Despite these benefits, several hurdles exist with this therapy. “The fact that it is first in its class and therefore clinicians have limited experience, is an unavoidable initial limitation,” said Dr. Einhorn. In addition, the idea of twice-daily injections may be an issue for patients who could otherwise benefit from this medication. “Finally, side effects such as nausea—although mild and transient—may be an issue for some patients,” Dr. Einhorn explained.

**Future Directions: Which Patients Would Benefit from GLP-1-Based Therapies?**

Dr. Einhorn stated that, in his opinion and experience, overall potential advantages of incretin mimetic therapy make this attractive in any patient with type 2 diabetes, especially those who would benefit from weight loss. Currently, the incretin mimetic exenatide has been approved by the U.S. Food and Drug Administration as an adjunctive therapy to improve glycemic control in patients with type 2 diabetes mellitus who are taking metformin, a sulfonylurea, or a combination of metformin and a sulfonylurea but have not achieved adequate glycemic control. “Patient acceptance of exenatide therapy is high and it should not be confused with the complexity of using insulin,” said Dr. Einhorn.

Dr. Einhorn emphasized that many research and clinical questions regarding the future treatment with exenatide and other incretin mimetics remain. These include patient selection and where incretin mimetic therapies belong on the continuum of therapies. For example, should select patients begin incretin mimetic therapy before starting insulin therapy—or even before starting a sulphonylurea? Should it be started very early in treatment, or should it be a last resort to achieve target glucose goals? Should all obese patients be offered a GLP-1-based therapy? Should this therapy be used in all those at risk for hypoglycemic complications? Should it be used for beta-cell preservation? “Further study is needed to answer these and other key clinical questions, to optimize the use of GLP-1 and other incretin therapies to ultimately improve glycemic control in patients with type 2 diabetes,” Dr. Einhorn concluded.
The American Association of Clinical Endocrinologists would like to thank the following companies in support of this publication.