Throughout most of the 20th century, thyroid carcinoma was considered a rare cancer with a low death rate. During the last 20 to 25 years, however, incidence rates of thyroid cancer have risen exponentially across the world. In combination with the low cause-specific mortality rate of thyroid cancer, this increase has led to huge numbers of living thyroid cancer patients.

Stefan K. Grebe, M.D., Ph.D., of the Department of Laboratory Medicine and Pathology at Mayo Clinic in Rochester, Minn., says, “We predict that by the end of the second decade of the 21st century, thyroid cancer will be the third most common diagnosis in a living cancer patient, just behind carcinomas of breast or prostate, and ahead of colorectal malignancies.”

Dr. Grebe explains, “While most of these thyroid cancer patients will not die of their disease, between 15 and 40 percent will suffer some form of recurrence during their lifetime, creating a growing need for cost-effective and accurate laboratory tests to detect or predict recurrence in order to minimize use of much more costly alternative diagnostic procedures, as well as to reduce morbidity due to delayed therapeutic interventions.”

Fortunately, a good thyroid tumor marker is available. Thyroglobulin (Tg), which serves as a scaffold and substrate for thyroid hormone synthesis and is expressed exclusively in the thyroid gland, should therefore become undetectable in the blood of the majority of thyroid cancer patients, because their gland is usually removed in the course of therapy.

However, M. Regina Castro, M.D., of the Division of Endocrinology, Diabetes, Metabo-

Figure 1. Thyroglobulin (Tg) measurements by liquid chromatography-tandem mass spectrometry (LC-MS/MS) compared with automated immunoassay (IA) measurements (Beckman assay) in Tg-autoantibody-negative samples with Tg concentrations of > 1 ng/mL by Beckman assay. There is a very tight correlation between the two assays, but the LC-MS/MS assay shows approximately a 20 percent downward bias. The inset graph shows that the downward bias is due to miscalibration of the Beckman assay, which becomes apparent when international standard material (CRM457) is run as unknown in the Beckman assay.
Tg is an imperfect tumor marker, chiefly because 15 to 30 percent of patients have autoantibodies to Tg (TgAb) and an additional 0.1 to 3 percent of patients have heterophile antibodies (HAb). These antibodies result in false-low and false-high Tg measurements, respectively, in the current Tg immunoassays. The laboratory routinely tests for the presence of TgAb and alerts the ordering physicians to their presence, but it is usually impossible to determine if, and to what degree, the detected TgAb might affect the serum Tg result. The clinician is basically left to his or her own devices to decide whether to trust the Tg result in such a patient. Moreover, in the case of an HAb interference, the laboratory usually cannot even detect its presence, unless they have been prompted to perform additional investigations because of discrepancies between Tg result and clinical impression.

New Tg assay employs trypsin

“Clearly, this is a suboptimal situation,” says Dr. Grebe. “To address this problem, we have developed a new Tg assay that overcomes the analytical problems caused by TgAb and HAb. Our approach centers on a digestion of the patient’s serum sample with the enzyme trypsin. Trypsin is what I would call an equal opportunity destroyer of all proteins. It will cleave all serum proteins at predictable sites of their primary amino acid sequence, including Tg and any TgAb or HAb, into small peptide fragments. Since all antibodies in the patient’s serum have been digested along with Tg (and all other proteins), all interferences from TgAb or HAb have been eliminated. One can then fish out one or several tryptic fragments that are proteotypic for Tg from the digested sample. This extraction is accomplished by using antibodies generated against the selected fragment(s). The captured Tg fragment(s) are then eluted from the capture antibodies and quantified by liquid chromatography-tandem mass spectrometry (LC-MS/MS).”

Serum Tg measurements with this new method agree closely with those obtained with current immunoassays in patients who have a detectable Tg by immunoassay and do not have...
TgAb. By contrast, in patients with detectable Tg, who do have TgAb, the LC-MS/MS gives results that are 50 to 60 percent higher than those obtained by immunoassay, reflecting the false-low measurement bias of the immunoassay in the presence of TgAb (Figures 1 and 2).

Dr. Grebe continues, “When one tests sera from TgAb-positive patients with an undetectable Tg by immunoassay, around 20 percent will have a detectable Tg by LC-MS/MS measurement (Figure 2). It therefore seems that this new Tg assay, which should be orderable by January 2014, will resolve many of the antibody-related problems of Tg immunoassays.”

However, Dr. Grebe cautions, “The best Tg immunoassays still have slightly better detection sensitivity than the LC-MS/MS Tg assay. They also sport a much faster turnaround time — a few hours versus one to 1.5 days. They should, therefore, currently remain the test of choice in TgAb-negative patients, while patients who are known to be TgAb-positive should be tested, or retested, with the LC-MS/MS assay. Patients with clinically suspected HAb interference (unexplainable or unexpected high serum Tg result) should also be retested by LC-MS/MS.”

Finally, John C. Morris III, M.D., of the Division of Endocrinology, Diabetes, Metabolism, and Nutrition at Mayo Clinic in Rochester, Minn., points out that “the ultimate clinical value of the new LC-MS/MS Tg assay will not be precisely known until several years of use and correlation with clinical outcome data.”

Stefan K. Grebe, M.D., Ph.D., M. Regina Castro, M.D., and John C. Morris III, M.D.

Diabetic Dyslipidemia: An Update

Although cardiovascular disease is still the leading cause of death in the United States, there has been a declining trend of both fatal and nonfatal myocardial infarction in the last decade, thanks to a decrease in the burden of some modifiable risk factors, such as smoking, and an increase in use of medications to lower blood pressure and cholesterol.

John M. Miles, M.D., of the Division of Endocrinology, Diabetes, Metabolism, and Nutrition at Mayo Clinic in Rochester, Minn., cautions: “These heartening trends are likely to be reversed, however, because of the increasing incidence of obesity and type 2 diabetes among adolescent and young children. During this same period, the prevalence of type 2 diabetes increased by more than 1 percent, and the Centers for Disease Control and Prevention now estimates that 11.3 percent of all people older than age 20 have diabetes. The risk of coronary artery disease is two to four times higher in patients with diabetes than in those without diabetes, and unless urgent steps are taken to effectively prevent and manage diabetes and its complications, we are likely to see a rebound increase in incidence of cardiovascular disease.”

Data from the National Health and Nutritional Examination Survey (NHANES) does indicate a modest improvement in control of hemoglobin A1C (HbA1C), LDL cholesterol and blood pressure in patients with diabetes over the last decade, though they were at goal in only approximately 25 percent of the patients. Vinaya Simha, MBBS, M.D., of the Division of Endocrinology, Diabetes, Metabolism, and Nutrition at Mayo Clinic in Rochester, Minn., comments: “While we need to do a better job of targeting these traditional risk factors, it is also important to look beyond LDL cholesterol if we are to make a significant impact on cardiovascular disease in people with diabetes. In fact, LDL cholesterol levels in patients with type 2 diabetes were not increased compared with levels of those without diabetes in both the Framingham study and the NHANES sample.

“It is now well-recognized that type 2 diabetes is characterized by a unique set of lipid abnormalities comprising elevated serum triglycerides, low HDL cholesterol and increased small-dense LDL particles. The core defect is thought to be insulin resistance at the level of adipose tissue, leading to increased lipolysis and delivery of free

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“It is now well-recognized that type 2 diabetes is characterized by a unique set of lipid abnormalities comprising elevated serum triglycerides, low HDL cholesterol and increased small-dense LDL particles. The core defect is thought to be insulin resistance at the level of adipose tissue, leading to increased lipolysis and delivery of free
fatty acids to the liver. Coupled with increased apolipoprotein B production, this defect results in increased hepatic secretion of large triglyceride-rich VLDL particles. Interparticle exchange of triglycerides and cholesterol between these triglyceride-rich VLDL particles and both LDL and HDL particles, mediated by cholesterol ester transfer protein, results in triglyceride-enriched LDL and HDL particles. Subsequent hydrolysis by hepatic lipase and other lipases results in generation of small-dense LDL particles, and small HDL particles that are easily catabolized and excreted by the kidneys, leading to low HDL cholesterol concentration.

“Much progress has been made recently in understanding the subcellular processes linking insulin resistance to this pattern of atherogenic dyslipidemia. While there is much hope that the new information will lead to development of new therapies, current management of diabetic dyslipidemia should focus on both therapeutic lifestyle changes and optimal choice of hypolipidemic and hypoglycemic medications.”

**Lifestyle changes**
Medical nutrition therapy and regular exercise are well-recognized to be the cornerstones of diabetes management, but recent data have reinforced the importance of these measures in ameliorating dyslipidemia as well. Dr. Miles comments: “Analysis of lipid data from the recently concluded Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) study involving 699 obese adolescents with type 2 diabetes showed that, compared to both metformin alone and metformin plus rosiglitazone, the combination of metformin and lifestyle intervention resulted in lower triglycerides and small-dense LDL cholesterol. Further, there was amelioration of the detrimental effect of hyperglycemia on both triglycerides and HDL cholesterol in this group.

“Similarly, a recent subgroup analysis of the Diabetes Prevention Program study revealed that intensive lifestyle intervention led to a decrease in both large VLDL particles and small-dense LDL particles besides raising large HDL particle concentrations. These favorable changes in lipoprotein subfractions, despite minimal to no changes in LDL cholesterol concentration, have the potential to reduce atherosclerosis. It is therefore imperative to emphasize the critical importance of lifestyle intervention to all patients with type 2 diabetes.”

**Hypolipidemic therapy**
The primacy of LDL cholesterol reduction using statin therapy for both primary and secondary prevention of coronary heart disease is well-established, and most, if not all patients with diabetic dyslipidemia will benefit from statin therapy. Dr. Simha adds: “Patients with high triglycerides and low HDL cholesterol, however, are very likely to have a discordance between their LDL cholesterol concentration and LDL particle number. The particle number is a better predictor or cardiovascular risk compared with cholesterol concentration. Despite seemingly normal or at-goal LDL cholesterol concentrations, patients with diabetic dyslipidemia have high residual risk due to elevated LDL particle number, which is reflected by high apolipoprotein B and non-HDL cholesterol concentrations.

“While measurement of LDL particle concentration and apolipoprotein B levels is not widely available or standardized, non-HDL cholesterol can be easily measured and should probably be the primary target in patients with diabetic dyslipidemia. Achieving the non-HDL goal often requires addition of fibrates to statin therapy, as these medications favorably alter LDL particle size and number. However, the enthusiasm for combination therapy has been dampened by the largely negative results of the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) and Action to Control Cardiovascular Risk in Diabetes (ACCORD) Lipid trials.

“Nonetheless, careful analysis of these and other major fibrate trials (Table) show that the subgroup of patients with categorical atherogenic dyslipidemia (high triglycerides and low HDL cholesterol) derives greater benefit than the general population; a meta-analysis showed a 35 percent reduction in relative risk of cardiovascular events. This outcome contrasts rather dramatically with the rather modest incremental effects of doubling statin doses. Thus, combination therapy with statin and fibrates to achieve non-HDL cholesterol goals may be an effective way to reduce cardiovascular risk associated with diabetic dyslipidemia.”

**Anti-hyperglycemic therapy**
The effect of different classes of anti-hyperglycemic medications on lipid profile is also an important consideration in the treatment of diabetic dyslipidemia. Dr. Miles notes: “Unfortunately, studies examining the lipid effects of these medications are few and have generally yielded inconsistent results, partly due to variations in glycemic control. Overall, it appears that metformin, especially in higher doses, causes a modest reduction in both total cholesterol and triglycerides, while sulfonylureas and glinides have minimal effects on lipids.

“Insulin therapy can have significant
triglyceride-lowering effects in people with poor glycemic control. There is little published data on the lipid effects of insulin in people with fair-to-good (HbA1C < 8.0 percent) glycemic control, but anecdotal experience suggests that lipid effects of insulin in these patients are minimal. The alpha-glucosidase inhibitors have been reported to raise HDL cholesterol in some studies, as also the thiazolidinediones. Among this latter class of drugs, rosiglitazone also causes an increase in LDL cholesterol, which is not seen with pioglitazone. Moreover, pioglitazone, which produces beneficial effects on triglycerides and HDL-C that are not demonstrable with rosiglitazone, reduces small-dense LDL particles and increases large, buoyant LDL particle number.

“More recently, metformin has been shown to lower small-dense LDL cholesterol particle concentration and increase both small and large HDL particle concentration, an effect that may contribute to its unique cardiovascular benefit in people with type 2 diabetes. There is also considerable interest in the effect of incretin mimetics on lipid profile. While the DPP-4 inhibitors have only mild and inconsistent effects, GLP-1 receptor agonists have been shown to reduce total and LDL cholesterol, and also both fasting and postprandial triglyceride levels with impressive reciprocal increases in HDL-C. The reduction in postprandial lipemia is particularly significant and postulated to reduce cardiovascular risk. Ongoing trials such as Exenatide Study of Cardiovascular Event Lowering (EXSCEL) and Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) are likely to provide definitive information about the possible cardiovascular benefits of these drugs.”

For more information


<table>
<thead>
<tr>
<th>Study</th>
<th>Drug</th>
<th>Relative risk reduction % (P) whole group</th>
<th>Relative risk reduction % (P) Dyslipidemia group</th>
</tr>
</thead>
<tbody>
<tr>
<td>HHS (1)</td>
<td>Gemfibrozil</td>
<td>34 (&lt; 0.02)</td>
<td>71 (&lt; 0.001)</td>
</tr>
<tr>
<td>BIP (2)</td>
<td>Bezafibrate</td>
<td>9 (NS)</td>
<td>40 (0.02)</td>
</tr>
<tr>
<td>VA-HIT (3)</td>
<td>Gemfibrozil</td>
<td>22 (0.006)</td>
<td>27 (0.01)</td>
</tr>
<tr>
<td>FIELD (4)</td>
<td>Fenofibrate</td>
<td>11 (NS)</td>
<td>23 (&lt; 0.01)</td>
</tr>
<tr>
<td>ACCORD (5)</td>
<td>Fenofibrate</td>
<td>8 (NS)</td>
<td>31 (&lt; 0.05)</td>
</tr>
</tbody>
</table>

Table. Enhanced effect of fibrate therapy on cardiovascular risk reduction in patients with dyslipidemia (elevated triglycerides and low HDL cholesterol levels).
Paget’s disease of bone is a focal disorder of bone remodeling. The disease may involve a single bone or multiple bones and has a predilection for the axial skeleton, such as the pelvis, femur, spine, skull and tibia. The diagnosis of Paget’s disease is usually based on radiographic findings that are characteristic of this disorder. These findings include focal osteolytic lesions, coarsening of the trabeculae, cortical thickening and enlargement of the bone (Figure 1). A whole-body bone scan is frequently performed when Paget’s disease is diagnosed to establish the extent of the disease.

Robert D. Tiegs, M.D., of the Division of Endocrinology, Diabetes, Metabolism, and Nutrition at Mayo Clinic in Rochester, Minn., says: “Individuals with Paget’s disease are usually asymptomatic, but may present with bone pain, bowing deformities of the long bones, fractures or nerve compression syndromes. The clinical features depend on the activity of the disease and the severity and location of the bony deformities. Although much has been learned about the epidemiology, clinical features, natural history and genetics of this disorder since it was described by Sir James Paget in 1877, there is disagreement about the need to treat individuals who have asymptomatic disease.

“In an article that appeared in the New England Journal of Medicine in 2013, Professor Stuart Ralston stated, ‘There is no evidence that asymptomatic patients benefit from anti-resorptive therapy.’ The guidelines published by the Bone Research Society of the United Kingdom reflect this view. According to these guidelines, the only indication for the use of anti-resorptive drugs is pain caused by an increase in the metabolic activity of bone. Treatment of asymptomatic patients was not recommended because treatment has not been shown to prevent complications. The results of the PRISM trial have been cited to support this approach.”

The Paget’s Disease: Randomized Trial of Intensive Versus Symptomatic Management (PRISM) trial studied 1,324 people with Paget’s disease in the United Kingdom. Dr. Tiegs explains, “This trial did not show a difference in fracture, the need for orthopedic surgery or hearing loss when comparing the outcomes of patients who received intensive therapy to patients who received symptomatic therapy during the two to five years that patients were monitored.” In an editorial in the same journal, Professor Ian Reid outlined the limitations of the study:

- Most patients had been treated with bisphosphonates prior to enrollment in the study.
- More than half of the participants had normal serum alkaline phosphatase values at the time of entry into the trial.
- The difference in disease activity between the two groups was small (78.8 percent of the patients in the intensive treatment group had normal serum alkaline phosphatase levels at the end of the study, compared with 61.2 percent of the patients in the symptomatic treatment group).
- Zoledronic acid, which has been shown to be more effective than risedronate for the treatment of Paget’s disease, was not available when the study was designed.
- The study was not designed to assess the effect of the different treatment approaches on fractures through pagetic bone.
- The duration of the study was short relative to the time required for complications to develop.

“The PRISM trial contributed to our understanding of Paget’s disease and its treatment.
but did not address the question of whether treatment early in the course of the disease reduces the risk of long-term complications,” says Dr. Tiegs.

An alternative approach is to treat asymptomatic patients who have active disease involving skeletal sites where complications are likely to develop, such as the skull, spine and long bones (Figure 2). Dr. Tiegs argues that the support for this approach is based on several observations. First, bone deformities progress in untreated patients with Paget’s disease and can cause serious complications. These complications include:

• Bowing of the long bones, which predisposes to secondary arthritis and fracture
• Softening and enlargement of the skull
• Neurologic compression syndromes, including spinal stenosis

Second, treatment with the new generation of nitrogen-containing bisphosphonates has been shown to:

• Promote healing of osteolytic lesions
• Restore bone remodeling to normal levels in a majority of patients
• Improve bone histology through the formation of lamellar rather than woven bone

The adverse reactions to the nitrogen-containing bisphosphonates (Table), such as atypical femur fractures and jaw osteonecrosis, also need to be considered when prescribing these agents. The frequency of these complications may be less in patients with Paget’s disease, because:

• Treatment is intermittent
• Doses used to treat patients with Paget’s disease are less than the doses used to treat patients with skeletal metastases
• Based on our knowledge of the pharmacokinetics of bisphosphonates, the drug is preferentially delivered to areas that have the highest rate of bone remodeling — pagetic bone

Dr. Tiegs concludes: “We do not have evidence that treatment with anti-resorptive agents alters the natural history of the disease, prevents skeletal deformities or reduces the risk of complications that result from these deformities. Until we have better data, the decision to treat or not treat asymptomatic patients should be based on clinical judgment and patient preferences.”

For more information

Table. Bisphosphonates approved for the treatment of Paget’s disease of bone.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
</tr>
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<tbody>
<tr>
<td>Oral</td>
<td></td>
</tr>
<tr>
<td>Etidronate*</td>
<td>400 mg/day for 6 months</td>
</tr>
<tr>
<td>Tiludronate*</td>
<td>400 mg/day for 3 months</td>
</tr>
<tr>
<td>Risedronate</td>
<td>30 mg/day for 2 months</td>
</tr>
<tr>
<td>Alendronate</td>
<td>40 mg/day for 6 months</td>
</tr>
<tr>
<td>Intravenous</td>
<td></td>
</tr>
<tr>
<td>Pamidronate</td>
<td>30 mg/day for 3 days†</td>
</tr>
<tr>
<td>Zoledronic acid</td>
<td>5 mg infused over 15 minutes</td>
</tr>
</tbody>
</table>

* Etidronate and tiludronate are less potent than the nitrogen-containing bisphosphonates.
† A more commonly used regimen is 60 or 90 mg infused over two to four hours.

Figure 2. Paget’s disease involving the third lumbar vertebra (arrow). Paget’s disease involving the lumbar spine can cause spinal stenosis, cauda equina syndrome and sciatica.
Education Opportunities

For more information or to register for courses, visit www.mayo.edu/cme/endocrinology, call 800-323-2688 (toll-free) or email cme@mayo.edu.

17th Mayo Clinic Endocrine Update

Designed for endocrinologists and interested internists and surgeons, the 17th Mayo Clinic Endocrine Update will address gaps in medical knowledge and barriers in clinical practice in order to improve the outcomes of patients with endocrine and metabolic disorders. This course will span the full range of endocrinology, through lectures, debates, panel discussions, clinicopathologic sessions, clinical pearls sessions, informal breakfast round-table discussions and small-group discussions with experts. Attendees will have plenty of opportunity for interaction with the course faculty, who are selected from Mayo Clinic for their expertise and clinical acumen.

Mayo Clinic Nutrition and Wellness in Health and Disease
Sept. 18-19, 2014, in San Francisco

Nutrition, physical activity and other healthy lifestyle behaviors are vital components in the promotion of health and the treatment of disease. This course — designed for physicians, advanced practice clinicians, dietitians, nurses, and health and wellness staff — will provide a full-spectrum, in-depth overview of situations that clinicians encounter in the ambulatory setting, including obesity in adults and children, weight management strategies, healthy diets, obesity-associated medical conditions, bariatric surgery and pre- and post-surgery medical management, dietary supplements, effective ways to provide coaching, principles of adult learning, nutrition for selected groups (patients with diabetes mellitus, women with cardiac disease and individuals who are malnourished), in addition to physical activity and wellness. Current clinical topics will be highlighted through presentations, interactive case studies and panel discussions.

Ray A. Kroc Visiting Professor

Patrick J. O’Connor, M.D., M.P.H., senior clinical investigator, HealthPartners Institute for Education and Research, and members of the Mayo Clinic Diabetes Core Group. Left to right: Yogish C. Kudva, MBBS, Robert A. Wermers, M.D., Steven A. Smith, M.D., Patrick J. O’Connor, M.D., M.P.H., Roger L. Nelson, M.D., M. Regina Castro, M.D., Pankaj Shah, M.D., and Vinaya Simha, MBBS, M.D.