MAYO CLINIC

Endocrinology Update

Endocrinology News from Mayo Clinic

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INSIDE THIS ISSUE

Drugs and Environmental Toxins Take on the Thyroid

The interactions between the thyroid and drugs and environmental toxins are many and varied (Figure). Herein, some of the drugs and environmental factors that can affect thyroid function and findings on thyroid function tests are highlighted.

Amiodarone

Approximately 30% of amiodarone is iodine, and approximately half of the 65 mg of iodine in a 200-mg amiodarone tablet is absorbed and delivered to the systemic circulation. Whereas, the daily recommended iodine intake is 0.15 to 0.30 mg.

Amiodarone is lipophilic and gradually deiodinated. Its elimination half-life is 40 to 100 days. Marius N. Stan, MD, of the Division of Endocrinology, Diabetes, Metabolism, and Nutrition at Mayo Clinic in Rochester, Minnesota, says: "A major action of amiodarone regarding thyroid hormone metabolism is to inhibit the conversion of thyroxine (T_4) to triiodothyronine (T_3) in the peripheral tissues. It further blocks T_4 entry into cells and intranuclear T_3 receptor binding. Although most patients are able to compensate for these effects, hypothyroidism develops in about 10% of patients. At the other extreme, about 2% of amiodarone-treated patients have hyperthyroidism."

Dr Stan continues: "Amiodarone-induced thyrotoxicosis (AIT) has 2 types. Type I AIT usually occurs in patients with preexistent goiter, where amiodarone drives increased thyroid hormone production and is associated with increased or normal vascularity. Type II AIT usually occurs in patients with normal pretreatment thyroid examinations who have a destructive process with inflammation and decreased vascularity. Many patients with AIT have mixed features of both types. AIT has important clinical implications because these patients usually have underlying cardiomyopathy, and thyrotoxicosis increases the risk of arrhythmias and hemodynamic instability. In addition, the thyrotoxicosis is resistant to the usual therapies for hyperthyroidism. Typically, type I AIT is treated with methimazole and, in some cases, potassium perchlorate. In contrast, type II AIT is typically treated with corticosteroids. Combined treatment options should be considered when the first option is ineffective. Patients with hyperthyroidism that is unresponsive to combination pharmacotherapy should be referred early for thyroidectomy."

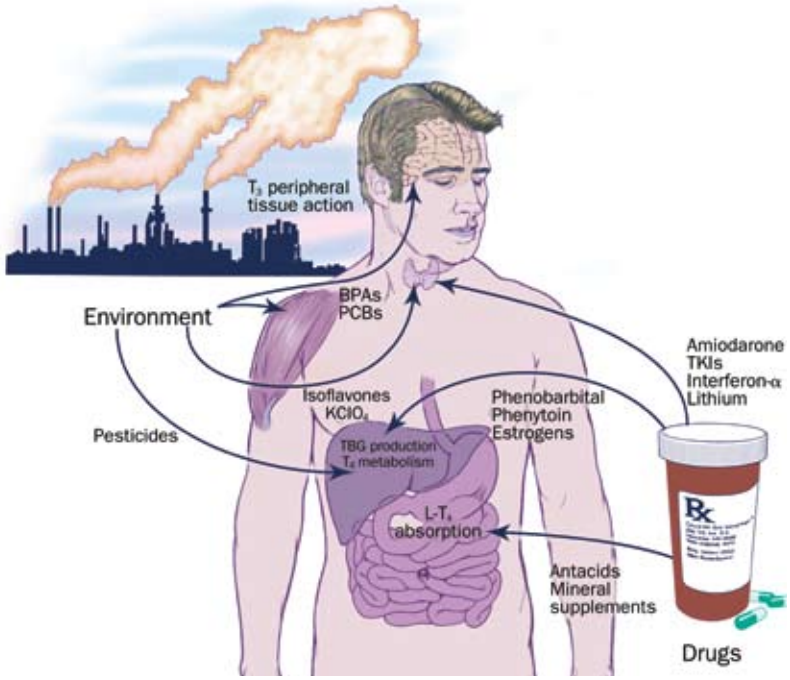

Figure. *Thyroid hormone metabolism and its potential modulation by drugs and environmental toxins. BPA indicates bisphenol A; KClO4, potassium perchlorate; L-T_4, levothyroxine; PCB, polychlorinated biphenyl; TBG, thyroxine-binding globulin; T_4, thyroxine; TKI, tyrosine kinase inhibitor; T_3, triiodothyronine.*

Tyrosine Kinase Inhibitors

Sunitinib and sorafenib can cause transient thyrotropin (TSH) suppression, which is followed by hypothyroidism in patients with an intact


Marius N. Stan, MD

thyroid gland. Dr Stan explains: "Hypothyroidism develops in approximately 40% of patients treated with sunitinib and 18% of those treated with sorafenib. At least 3 hypotheses have been suggested to explain sunitinib-induced hypothyroidism: destructive thyroiditis, inhibition of thyroid peroxidase activity, and decreased thyroid vascularity due to vasoconstriction and vascular endothelial growth factor downregulation. Thyroid function tests should be monitored on days 1 and 28 of the treatment cycles. If the thyroid function tests continue to show reference levels after 3 cycles, then the frequency of monitoring should be decreased to every 3 cycles. If overt hypothyroidism develops or if the serum TSH concentration is increased at the beginning of the cycle, T_4 replacement therapy should be initiated."

Interferon-α

Interferon-α can cause autoimmunity induction resulting in either hypothyroidism (usually subclinical) or Graves' disease. It can also cause a destructive thyroiditis. Dr Stan highlights: "Risks of thyroid dysfunction in patients treated with interferon-α include positivity for thyroid peroxidase antibodies, female sex, and extended duration of therapy."

Lithium

Lithium is used to treat manic-depressive disorder, and when given in high doses it is a goitrogen by blocking thyroid hormone secretion. Dr Stan notes: "Approximately 50% of patients treated with lithium have a goiter. Lithium treatment can also trigger painless thyroiditis or Graves' disease and thus cause hyperthyroidism."

Drugs That Affect Thyroid Hormone Replacement Therapy

Treatment with estrogen and selective estrogen receptor modulators can increase thyroxine-binding globulin. Antacids and calcium and mineral supplements can decrease the absorption of ingested T_4. Treatment with phenobarbital or phenytoin can increase the clearance of administered T_4. Therefore, all of these drugs, along with the tyrosine kinase inhibitors motesanib and imatinib, usually result in a need to increase the T_4 dosage in patients taking thyroid hormone replacement.

Environmental Toxins

Dr Stan highlights: "Many environmental factors have the potential to impact thyroid function." Some of these factors are listed below:

- Potassium perchlorate, which inhibits iodine uptake by the thyroid, is used in rocket propellant, fireworks, and automobile airbags. Potassium perchlorate is stable in the environment and contaminates water throughout the United States. Newborns and infants are most susceptible to this inhibitory effect on iodine transport. The thiocyanates in cigarette smoke can have effects similar to potassium perchlorate.
- Isoflavones (phytoestrogens), found in soy proteins, are thyroid peroxidase inhibitors.
- Pesticides induce glucuronidation of T_4 and reduce T_4 half-life.
- Polychlorinated biphenyls are industrial chemicals that were banned in 1975 but still are routinely detected in the environment. They have been shown to reduce T_4 levels in animals and are neurotoxic. Their effect varies because of partial agonist effect at the thyroid hormone receptor and their varied chemical structure.
- Bisphenol A—used in plastics, as resins for coating food cans, and as dental sealants—antagonizes T_3 activation of the thyroid hormone β-receptor in rats, causing a thyroid hormone resistance–like syndrome.

Bisphosphonate-Associated Jaw Osteonecrosis

Osteonecrosis of the jaw is an uncommon, but severe, adverse event associated with oral and intravenous bisphosphonate therapy. A confirmed case of bisphosphonate-associated jaw osteonecrosis is defined as an area of exposed bone in the maxillofacial region that does not heal within 8 weeks of identification by a health care provider in a patient who currently receives or has been exposed to a bisphosphonate and has not had radiation therapy to the craniofacial region. Letters, case reports, and small case series of jaw osteonecrosis have been published in the oncology, dental, maxillofacial surgery, and general medical literature during the past 7 years. Patients with jaw osteonecrosis typically present with jaw pain—more often in the mandible than the maxilla—and associated exposed bone (Figure 1).

Clinical Setting

Of jaw osteonecrosis cases, 60% occur after dental extraction, root canal surgery, dental implantation, or other dentoalveolar surgery, whereas all other cases appear to occur spontaneously. To date, 94% of cases have occurred in patients treated with intravenous bisphosphonates, and 85% of these patients were being treated for cancer with 1 or more of the potent nitrogen-containing intravenous bisphosphonates, usually once a month for several years. The highest risk of jaw osteonecrosis appears to be associated with frequent—typically monthly—infusions of intravenous zoledronic acid, which has been used widely in patients with multiple myeloma or breast or prostate cancer.

Presentation

Sreenivas Koka, DDS, PhD, of the Department of Prosthodontics at Mayo Clinic in Rochester, Minnesota, explains: "Jaw osteonecrosis usually appears as an intraoral lesion with areas of exposed yellowish-white hard bone. It sometimes is associated with extraoral or intraoral sinus tracts and has a delayed healing response—that is, for more than 8 weeks, the bone stays exposed rather than being covered with gingival or mucosal tissue. Painful ulcers may be present in the soft tissues adjacent to the bony margins of the lesion. Dental radiographs are typically not helpful in early cases, but advanced cases may present with areas of moth-eaten radiolucencies with or without radiopaque bone sequestra [Figure 2]. Dental

Bart L. Clarke, MD, and Sreenivas Koka, DDS, PhD

or surgical trauma sites are commonly associated with development of jaw osteonecrosis. In advanced cases, pathologic jaw fractures may occur or part of the mandible or maxilla may need to be removed."

Risk Factors and Prevalence

Bart L. Clarke, MD, of the Division of Endocrinology, Diabetes, Metabolism, and Nutrition at Mayo Clinic in Minnesota, says: "The main risk factors include cancer, frequent intravenous infusions of nitrogen-containing bisphosphonates, and dentoalveolar trauma. Risk factors have not been identified for patients receiving oral bisphosphonates, such as alendronate, risedronate, and ibandronate, for postmenopausal osteoporosis without cancer because only a small number of cases have been published. Most of these cases were associated with alendronate therapy, likely because of its

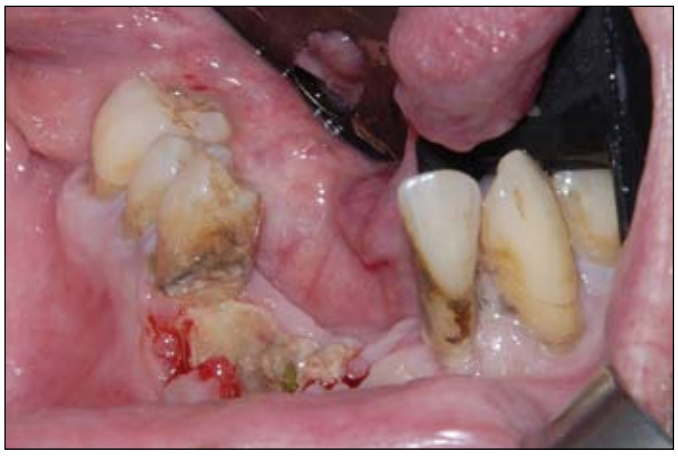

Figure 1. *Osteonecrosis of the jaw in a patient who had poor oral hygiene and generalized periodontal disease and recently underwent routine dental extractions in the mandible. This patient had undergone monthly intravenous bisphosphonate therapy for treatment of multiple myeloma during the previous 12 months.*

wider use than other oral bisphosphonates."

Dr Clarke continues: "Unless the number of cases has been greatly underreported, the prevalence of oral bisphosphonate–associated jaw osteonecrosis appears to be low—estimated in 1 European database to be on the order of 0.00038% (3.8 cases per 1 million persons treated). Intravenous bisphosphonate–associated jaw osteonecrosis in cancer patients is much more common, with prevalence estimates ranging between 0.8% and 10% and with most studies reporting estimates from 1% to 4%."

Pathophysiologic Factors

No pathophysiologic mechanism has been established by which oral or intravenous bisphosphonate treatments cause jaw osteonecrosis. It is hypothesized that suppressed bone turnover caused by potent bisphosphonate therapy leads to accumulation of fatigue damage in the form of microcracks, which may lead to microfractures. Also, bisphosphonates are potent inhibitors of angiogenesis, leading to a decreased ability to heal. Dental trauma or infection increases the demand for bone microdamage repair, which may lead to localized osteonecrosis, although it is not yet clear how this occurs.

Prevention

Dr Koka explains: "No randomized clinical trials have been published describing interventions to prevent or treat jaw osteonecrosis. Patients should have potentially traumatic dental treatment, such as tooth extractions, root canals, or dental implantations, before starting oral or intravenous bisphosphonate therapy. The optimal time for withdrawal of bisphosphonates before dental surgery in patients already taking bisphosphonate therapy is not yet established, but most specialists advocate withdrawal of therapy 3 months before dental surgery. Nevertheless, the risks and benefits from this form of 'drug holiday' are as yet unproven, particularly because bisphosphonates have a long half-life of several years in the skeleton. It is suggested, however, that if a dental extraction or other form of dental surgery is necessary, a course of pretreatment and posttreatment antibiotics—from 1 day before to 7 days after surgery—be used because this course may reduce the risk of osteonecrosis of the jaw. Encouragingly, retrospective analyses indicate that dental implants placed in individuals receiving bisphosphonate therapy for osteoporosis or osteopenia are successful."

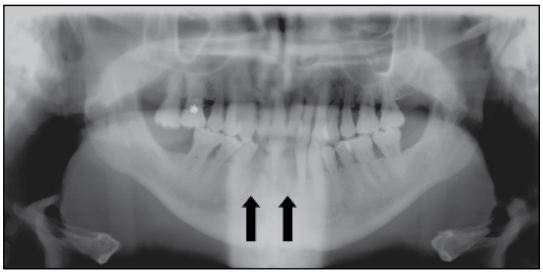

Figure 2. *Dental radiograph showing nonhealing of extraction sites (arrows) in the anterior mandible—findings consistent with jaw osteonecrosis in this patient, who was treated with monthly intravenous bisphosphonate therapy.*

Treatment

No effective therapy has been established for jaw osteonecrosis in patients receiving oral or intravenous bisphosphonate therapy. Some dental specialists recommend supportive management, starting with withdrawal of oral or intravenous bisphosphonate therapy, avoidance of further dentoalveolar trauma, appropriate use of oral antibiotic rinses, use of hyperbaric oxygen therapy, and adequate time for healing. In some instances, surgery to debride dead bone may exacerbate the condition; however, debridement and local, pedicled soft tissue flaps have been reported to stimulate healing in selected patients.

Recommendations

Dr Clarke suggests: "Until further relevant clinical data become available, it is reasonable to begin or continue oral or intravenous bisphosphonate therapy in patients with appropriate indications, unless jaw osteonecrosis is present or develops. Physicians should review with each patient the decision to continue treatment with frequent infusions of potent intravenous bisphosphonates. Patients contemplating starting therapy with oral or intravenous bisphosphonate for prevention or treatment of osteoporosis should be informed of the rare risk of jaw osteonecrosis with oral bisphosphonates and the relatively infrequent risk of jaw osteonecrosis with intravenous bisphosphonates. Patients should undergo dental evaluation and treatment before starting intravenous bisphosphonate therapy and be regularly evaluated to ensure optimal oral health. It is appropriate to encourage patients who express concern about jaw osteonecrosis and who are taking, or about to start taking, oral bisphosphonates to visit their dentist for more information."

Endocrine Reflections

Michael D. Brennan, MD, of the Division of Endocrinology, Diabetes, Metabolism, and Nutrition at Mayo Clinic in Rochester, Minnesota, was President of the Officers and Councilors of Mayo Clinic staff in 2010. Dr Brennan was asked to reflect on endocrinology and Mayo Clinic. What follows are some of his comments.

Michael D. Brennan, MD

Many of us reflect back to when we bade a reluctant farewell to our carefree teenage years and began to face a succession of decisions that would serve as determinants of our future life's work. They ran the gamut: will I go to college, if so which one, and which major, and then what about graduate training, and if so, what kind? Those who chose medical school could still keep their options open, for the medical profession evolved in a manner that provided a wide range of possibilities. For me, there was never much doubt but that my future would be in internal medicine—but which, if any, subspecialty? As I progressed through medical residency, I found each discipline held appeal. We were trained to be clinical detectives capable of piecing together little bits of evidence in order to unravel medical complexity. Advanced imaging techniques had yet to make their impact. I was intrigued by the wealth of information cardiologists and pulmonologists could glean from chest radiographs and gastroenterologists from plain abdomen and barium studies and of the evidence gathered by nephrologists from the intravenous pyelogram.

My endocrine attendings showed me what could be learned from clinical observations combined with what we would now consider rudimentary technologies. Plain films of the hands could, to the trained eye, yield telltale evidence of the subperiosteal resorption characteristic of hyperparathyroidism while subtle clues to the presence of sellar tumors could be picked up from skull radiographs. Those years were notable, too, for the advent of radioimmunoassay, which revolutionized the discipline of endocrinology. It was a tipping point for endocrinology that resulted in the specialty becoming a leader in the new scientific era.

The Mayo Clinic Division of Endocrinology was in the vanguard of the new science. It was a heady experience for a young aspiring medical resident to see the masters at work as they combined the new scientific evidence with clinical observations and mature judgment. During morning rounds, they shared the new knowledge generously and with palpable excitement. My choice of specialty was clear. I would be an endocrinologist while continuing to embrace the broader field of internal medicine.

In the decades that followed, I never questioned my decision. Our specialty has reached heights that, back then, were beyond our wildest expectations. We use precise diagnostic tools and have added numerous therapeutic arrows to our quiver. The understanding of the genetic substrates of endocrine disease has grown exponentially. So, too, has our appreciation of the biological determinants of disease. Such

William J. Mayo, MD, (left) and Charles H. Mayo, MD, (right) in operating rooms at St Mary's Hospital in July 1922.

Henry S. Plummer, MD, the "architect of modern medical practice."

advances have led to more targeted and individualized treatments. Our patients have benefitted enormously, and our generation of endocrinologists has been along for a very exciting ride.

While hormones serve to integrate and coordinate human physiology and biochemistry, the specialty of endocrinology contributes similarly to clinical medicine. Our specialty deals with diseases and disorders that are expressed in every organ system. The good endocrinologist is also the good internist.

This year, Mayo Clinic celebrates an important event in its history. It marks the centenary of the 1910 commencement address of William J. Mayo at Rush Medical College in Chicago. In his speech, he reminded the graduating class that "the best interest of the patient is the only interest to be considered, and in order that the sick may have the benefit of advancing knowledge, union of forces is necessary"—in other words, teamwork.

When completed in 1928, the Plummer Building was the tallest building in Minnesota.

No discipline depends more heavily on teamwork than endocrinology. The diagnosis and treatment of the diseases we encounter require it. The precision of laboratory investigation, the often subtle imaging expressions of the abnormal endocrine gland, and the finer points of endocrine pathology and cytology all contribute. The arrival at a firm diagnosis is frequently followed by collaboration of endocrinologist and surgeon. Mayo endocrinologists, and the patients we care for, enjoy the combined expertise of pathologists, radiologists, and surgeons who have been schooled in and deeply understand endocrinology principles. It is in the best tradition of the union of forces.

When the Mayo brothers, William and Charles, identified what would be needed for an academic and integrated group practice, they turned to Dr Henry S. Plummer, internist and endocrinologist. Henry, one of the early partners of the Mayo brothers, had grown up within a short distance of Rochester, Minnesota. He was a skilled physician whose careful and meticulous clinical research greatly expanded the endocrinology knowledge base. Among his observations were the beneficial effects of preoperative iodine administration in Graves' disease and his description of hyperthyroidism in multinodular goiters, a condition that bears his name.

Henry Plummer's skill set involved what today we would associate with systems engineers. He developed a unitary medical record, a system to transport it around the campus, and a building to support the processes of care. Generations of visitors to Mayo Clinic have marveled at the towering beauty of the 14-story Plummer Building, for which he was a contributing architect. It is located across the street from where endocrine researcher and Nobel laureate Edward Kendall worked on the chemical structure of thyroxine and subsequently described and synthesized Compound E, cortisone.

Endocrinologists continue to have key roles in the success and evolution of Mayo Clinic. I believe that endocrinology training prepares us to be systems thinkers. We think in terms of servo mechanisms that are key elements in the "milieu intérieur" of Claude Bernard. Similarly, systems thinking holds the key to the homeostasis of an integrated clinical practice, such as that of Mayo Clinic.

Ananda Basu, MBBS, MD, received the 2010 Department of Medicine Laureate Award. Rebecca S. Bahn, MD, received the 2010 Mentor of the Year Award from the Center for Translational Science Activities. Matthew T. Drake, MD, PhD, received the 2010 Department of Medicine New Investigator Award.

Michael D. Jensen, MD, was named the Thomas J. Watson, Jr, Professor in Honor of Dr Robert L. Frye and was selected to be the director of the Obesity, Weight Management, and Nutrition Research Program in the Department of Medicine at Mayo Clinic in Rochester, Minnesota. In 2010, Dr Jensen received the TOPS (Take Off Pounds Sensibly Foundation) Research Achievement Award from The Obesity Society. K. Sreekumaran Nair, MD, PhD, received the 2010 Sir David Cuthbertson Award and Lecture from the European Society for Clinical Nutrition and Metabolism. In July, 2011, Dr. Nair will become the new Editor-in-Chief for the journal *Diabetes*.

Robert C. Smallridge, MD, was named the Alfred D. and Audrey M. Petersen Professor in Cancer Research. Victor Bernet, MD, was appointed to the American Thyroid Association Board of Directors.

Johannes D. Veldhuis, MD, received the Teacher of the Year Award for 2010 from the Department of Internal Medicine, Mayo Fellows Association, Mayo Clinic, Rochester, Minnesota. Dr Veldhuis also received the 2010 Penn State Distinguished Alumnus Award. William F. Young Jr, MD, was named the Tyson Family Endocrinology Clinical Professor in Honor of Vahab Fatourechi, MD, and will be given the 2011 Distinguished Physician Award from The Endocrine Society. Michael D. Brennan, MD, was conferred with an honorary fellowship of the Royal College of Surgeons in Ireland. Seven Mayo staff have been so honored, previously all surgeons, beginning with William J. and Charles H. Mayo.

John C. Morris III, MD, was elected Secretary and Chief Operating Officer–Elect for the American Thyroid Association. Vahab Fatourechi, MD, (seated) received the 2010 Department of Medicine Henry S. Plummer Distinguished Physician Award. Geoffrey B. Thompson, MD, was the 2010 Distinguished Invited Lecturer for the Royal Australasian College of Surgeons, and he was appointed the section head of Endocrine Surgery, Department of Surgery, Mayo Clinic, Rochester, Minnesota.

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Endocrinology Update

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CME Opportunities

Mayo Clinic Nutrition in Health and Disease

September 15-16, 2011, Seattle, Washington

This course—designed for physicians, nurse practitioners, physician assistants, dietitians, and health and wellness staff—will provide a full-spectrum, in-depth overview of challenging nutritional issues that clinicians encounter in the ambulatory setting. An additional course objective is to discuss wellness programs that include nutrition, physical activity, and other lifestyle behaviors. The course will be held at the Hyatt at Olive 8. For more information about this course, please call 800-323-2688 or visit mayo.edu/cme/endocrinology.

15th Mayo Clinic Endocrine Course

April 16-21, 2012, Palma, Mallorca, Spain

This course, created for endocrinologists and interested internists and surgeons, will present the latest material on the diagnosis and treatment of endocrine disorders. The course will span the full spectrum of endocrinology. For more information about this course, please visit mayo.edu/cme/endocrinology.

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