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Endocrinology Update

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The Knowledge Synthesis Program

The Knowledge Synthesis Program, part of the Knowledge and Evaluation Research (KER) Unit of the Division of Endocrinology at Mayo Clinic in Rochester, Minnesota, is an active research program providing methodologic support to the Endocrine Society Clinical Practice Guidelines Subcommittee. Victor M. Montori, MD, MSc, of the Division of Endocrinology, Diabetes, Metabolism, and Nutrition at Mayo Clinic in Rochester, says: "The Knowledge Synthesis Program has supported numerous clinical practice guidelines over the past 5 years, assisting task force members with formulating evidence-based recommendations for the care of patients with diabetes mellitus, congenital adrenal hyperplasia, male hypogonadism, osteoporosis, vitamin D deficiency, pituitary incidentalomas, growth hormone deficiency, hyperaldosteronism, pediatric obesity, hirsutism, Cushing syndrome, hyperprolactinemia, and transgender care."

The KER Unit team is led by M. Hassan Murad, MD, MPH, of the Division of Preventive Medicine at Mayo Clinic in Rochester, and Dr Montori. The team includes experienced reference librarians, endocrinology staff, clinical and research fellows, research assistants, and collaborators who provide additional expertise in research or guideline methods or in endocrinology. Dr Murad explains: "The program follows rigorous procedures that start with developing protocols for the systematic reviews needed to support guideline panels. Systematic reviews seek

The KER Unit team. Standing, left to right: Juan Pablo Domecq Garces, MD, Gabriela J. Prutsky Lopez, MD, Victor M. Montori, MD, MSc, Kasey R. Boehmer, Tarig A. Elraiyah, MBBS, and Rim R. Hasan, MD. Seated, left to right: Mohammed Nabhan, MD, M. Hassan A. Murad, MD, MPH, and Belal M. Firwana, MD.

to provide summaries of the existing research evidence, identifying best estimates of association, diagnostic test performance, or treatment effect, and explanations for between-study differences in results. Extensive discussion leads to the definition of the population target of the recommendations and the interventions and outcomes that need to undergo formal synthesis. Librarians conduct comprehensive literature searches that span multiple databases. The team of investigators selects the relevant studies on the basis of strict criteria and extracts data from the individual studies, which are often reanalyzed as a whole body of evidence, in a process called *meta-analysis*. The team evaluates the quality of the evidence following a state-of-the-art framework—the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) approach—and presents the results to the guidelines panel. The systematic reviews are usually published alongside the guidelines."

The Knowledge Synthesis Program supports several other professional societies and organizations (all not-for-profit; the KER Unit does not receive funding from for-profit pharmaceutical or device corporations). The program has secured multiple grants to maintain its operations, infrastructure, and goals since 2005. Dr Murad highlights: "Our fundamental goal is to provide an unbiased summary of the best available evidence to decision makers (clinicians and guideline developers) and assist them in incorporating this evidence into recommendations that are useful and clear."

Dr Montori explains: "The Knowledge Synthesis Program has an important secondary goal: education. The tasks of developing reviews and assisting in the formulation of useful and clear recommendations offer opportunities for highly motivated individuals. Through a formal mentorship program, many such individuals—from premed students to experienced faculty—have gained the insights and knowledge that can help them form a better understanding of evidence-based endocrinology. Over the years, several Mayo Clinic residents, fellows, and consultants have participated in the program and fulfilled this educational goal."

He continues: "The knowledge synthesis exercises also expose our investigators to the complicated situation of intellectual interest and financial relations that cloud the objectivity of our field's experts. For example, our group reported that many of the expressed expert opinions regarding the safety of rosiglitazone were strongly associated with their financial relations with the relevant drug company. Whether this association resulted from or led to the opinion of the expert can only be speculated. We have also uncovered challenges with the credibility of research assessing the effect of treatments on biochemical measures that, while objective, bear unclear relation with the effect of these treatments on outcomes that matter to patients, such as living longer, feeling better, or being able to pursue one's goals without hindrance from health or health care."

Dr Murad concludes: "Much more work lies ahead. With many reviews identifying that the evidence base to answer many common endocrinology questions remains at high risk of bias and very sparse, the KER Unit reviews offer a virtual list of important research questions that must be answered to better the value of care for our patients. Also, much education work remains to promote practices that reflect not only the state of the evidence, but also the context, values, and preferences of the informed patient. Indeed, many practices appear to reflect physician training or the effects of product marketing. Finally, endocrinologists must come to terms with the resource implications of their recommendations."

Type 2 Diabetes and Cardiovascular Disease: Managing One to Prevent the Other

The prevalence of type 2 diabetes mellitus (T2DM) is increasing inexorably in Western countries and developing nations. Epidemiological studies indicate that one-half to three-quarters of people with T2DM are destined to die of cardiovascular events and their sequelae. However, considerable controversy exists concerning the mediators of this increased risk and whether treatment can reduce the risk. John M. Miles, MD, of the Division of Endocrinology, Diabetes, Metabolism, and Nutrition at Mayo Clinic in Rochester, Minnesota, says: "Although early scientists assumed that hyperglycemia was the mediator of all of the complications of diabetes, many studies undertaken over the past half century have cast doubt on this notion. This research indicates that many factors, including hypertension, dyslipidemia, and a prothrombotic state, contribute to the increased cardiovascular risk of type 2 diabetes."

The nonischemic cardiomyopathy that occurs in T2DM is an area of increasing interest to investigators. Ananda Basu, MD, of the Division of Endocrinology, Diabetes, Metabolism, and Nutrition at Mayo Clinic in Rochester, explains: "The

notion that fatty heart (the accumulation of lipid in the heart muscle, analogous to fatty liver) is a common occurrence in obesity and type 2 diabetes and mediates diastolic dysfunction leading, in some cases, to overt heart failure has gained credence in recent years on the basis of results from animal and human studies. There is virtually no information on the effect of diabetes pharmacotherapy on this phenomenon."

Before 1995, pharmacological treatment of T2DM in the United States was limited to insulin and sulfonylurea agents. Dr Miles notes: "Since that time, numerous new agents with unique and disparate mechanisms of action have become available. It is now clear that there are marked differences among agents in their nonglycemic effects, with potential implications regarding cardiovascular risk reduction." The differences among these agents are summarized in the Table.

The UK Prospective Diabetes Study demonstrated that insulin provision therapy in the form of either insulin or sulfonylureas produced a statistically significant (*P*=.01), but somewhat disappointing (~15%), reduction in the incidence of myocardial infarction, durable over 20 years of follow-up. Dr Miles explains: "The same study showed a one-third reduction in myocardial infarction with metformin over 20 years. The differences between the modest benefit of insulin provision and the more robust effect of metformin could not be explained by differences in glycemic control. What, then, is the explanation? Metformin produces modest weight loss, whereas insulin provision therapy is associated with weight gain. A number of studies have shown favorable effects of metformin on high-density lipoprotein cholesterol and triglycerides; in contrast, the effects of sulfonylureas on lipids are modest to negligible. Metformin is associated with lowering of the plasminogen activator inhibitor-1 (PAI-1) level. Insulin and sulfonylureas, on the other hand, produce no change (in some instances, they have been shown to result in an increase in PAI-1). Metformin does not appear to be associated with an increase in blood pressure, whereas several studies have shown an increase in blood pressure during insulin treatment that appears to be related to weight gain. In addition, insulin is an underrated regulator of renal tubular sodium metabolism, promoting sodium retention. These observations explain, in part, why the American Diabetes Association recommends metformin as first-line therapy for type 2 diabetes."

Ananda Basu, MD, and John M. Miles, MD

Dr Basu says: "Other classes of diabetes agents, such as thiazolidinediones (TZDs) and α-glucosidase inhibitors, have been shown to have favorable effects on cardiovascular outcomes in some clinical trials, although results are inconsistent. TZDs (specifically, pioglitazone) lower blood pressure and decrease PAI-1, improve dyslipidemia and endothelial function, and induce a favorable redistribution of body fat. α-Glucosidase inhibitors lower blood pressure and decrease low-density lipoprotein cholesterol (and in some studies also lower triglyceride levels), improve endothelial function, and promote modest weight loss. Although improvements in forearm endothelial function have been shown with acute administration of glucagonlike peptide 1 (GLP-1) and GLP-1 agonists, hard outcome data are not yet available with long-term exposure to these agents. In addition, GLP-1 agonists lower blood pressure and triglycerides levels, raise high-density lipoprotein cholesterol levels, and produce significant weight loss. This result stands in contrast to sulfonylureas, which are associated with weight gain and do not have favorable effects on blood pressure, lipid levels, or endothelial function."

Table. Nonglycemic Effects of Diabetes Medications

Agent	Effects on Weight	Effects on Lipids	Lowered Blood Pressure	Improved Endothelial Function
Insulin	Increase	Mild	No	+/-
Sulfonylureas	Increase	Negligible	No	No
Metformin	Decrease	Moderate	No	Yes
TZDs	Increase[a]	Large[b]	Yes	Yes
α-Glucosidase inhibitors	Decrease	Mild to moderate	Yes	Yes
GLP-1 agonists	Decrease	Large	Yes	Not known

Abbreviations: GLP-1, glucagonlike peptide 1; TZDs, thiazolidinediones.
[a] Occurs with favorable redistribution of body fat.
[b] Occurs with pioglitazone therapy only.

Dr Miles concludes: "Thus, there are many roads to Rome and it matters how you get there. It should be acknowledged that insulin and sulfonylureas remain important and necessary tools for the treatment of hyperglycemia in type 2 diabetes. However, in the presence of difficult-to-manage dyslipidemia, hypertension, and a generally increased risk profile, the nonglycemic effects of diabetes agents should be taken into consideration when selecting therapy. Metformin should be prescribed as monotherapy or in combination with other agents, including insulin and sulfonylureas, for most overweight and obese patients unless there is a specific contraindication to its use."

Multifactorial Basis for Age-Associated Hypoandrogenemia in Men

The Institute of Medicine recommended in 2004 that mechanistic studies be pursued to elucidate why testosterone (Te) availability declines with age, noting that neither the long-term safety nor the therapeutic benefit of androgen supplementation in healthy older men is established. The World Health Organization has projected that both the absolute number and the proportion of men aged 60 years or older will increase substantially during the next 50 years in certain countries, such as the United States.

Johannes D. Veldhuis, MD, of the Division of Endocrinology, Diabetes, Metabolism, and Nutrition at Mayo Clinic in Rochester, Minnesota, says: "Investigations of the causes of aging-associated hypogonadism have been stymied by major technical and paradigmatic hurdles. Technical challenges include the facts that a) neuroendocrine adaptations unfold gradually and subtly as individuals age; b) unobservable changes in the hypothalamic release of gonadotropin-releasing hormone (GnRH) influence pituitary luteinizing hormone (LH) secretion, which in turn affects testicular Te synthesis; and c) concentrations of Te and estradiol (E_2) feed back negatively on both GnRH and LH signaling, thus creating a dynamic system. However, GnRH outflow and Te and E_2 feedback are not directly observable, thus necessitating validated analytical tools to quantify the interlinked dynamics of the GnRH-LH-Te axis." Figure 1 illustrates the analytical construct of GnRH-LH-Te axis.

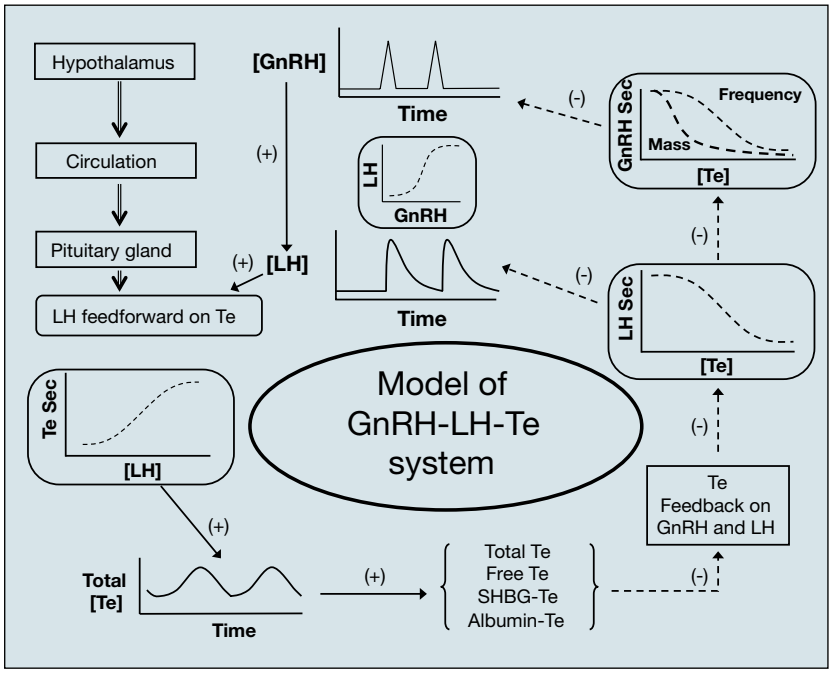

Figure 1. *Ensemble model of interlinked regulation of gonadotropin-releasing hormone (GnRH), luteinizing hormone (LH), and testosterone (Te) by mathematically estimable dose-response functions. Sec indicates secretion; SHBG, sex hormone binding globulin; [ ], concentration of.*

One successful approach comprises biomathematical constructs. Dr Veldhuis explains: "Such models predict concomitant reductions in all three—GnRH secretion, LH-induced Te secretion, and Te negative feedback. Together, these factors may explicate the tetrad of low-amplitude and high-frequency LH pulses, irregular LH secretion patterns, and hypoandrogenemia in older men. More particularly, clinical investigations at Mayo Clinic and elsewhere now suggest that advanced age results in the following:

- Diminished amount of hypothalamic GnRH secreted in each pulse
- Reduced stimulatory efficacy (maximal effect) of endogenous LH pulses and exogenous recombinant human LH pulses in driving Te secretion
- Impairment of estrogen's feedback at the pituitary level while accentuating androgenic

feedback on the hypothalamus

Low Te availability typically accompanies acute illness and chronic disease, which are further associated with increased cortisol and reduced insulinlike growth factor 1 (IGF-1) concentrations. Thus, changes in all 3 axes may confound interpretation of aging effects. Dr Veldhuis notes: "An unstudied possibility is that metabolic, inflammatory, and lifestyle (sleep-deprivation) stressors inhibit GnRH-LH-Te secretion to a greater extent in older than young men. This unifying concept would link age-related failure of stress adaptations of the LH-Te, growth hormone–IGF-1, and cortiotropin-cortisol axes."

Implications of Testosterone Deficiency in Aging Men

Impoverished Te production in older men has been documented by a) direct sampling of the spermatic vein, b) meta-analysis of cross-sectional data, and c) longitudinal investigations in healthy cohorts. Dr Veldhuis highlights: "Cross-sectional data collected in healthy men in Olmsted County, Minnesota, verify the age-associated decrements in Te concentrations measured by tandem mass spectrometry [Figure 2]. Interest is motivated by epidemiological associations among hypoandrogenemia and muscle weakness, sarcopenia, osteopenia, diminished physical stamina, erectile dysfunction, systolic hypertension, carotid-artery thickness, increased abdominal visceral-fat mass, insulin resistance, reduced high-density lipoprotein cholesterol concentrations, postprandial somnolence, impaired quality of life, depressive mood, diminished working memory, and decreased executive-cognitive function [Figure 3]."

Dr Veldhuis continues: "Among such postulated relationships, low Te availability correlates best with reduced grip strength, decreased lean-body mass, and increased visceral adiposity in meta-analyses. Moreover, these 3 pathophysiological features are markedly reversed by Te supplementation. Of note, certain medications, stress, diabetes mellitus, inflammation, sleep deprivation, acute illness, systemic disease, and other comorbidities exacerbate androgen deficiency in aging populations. What is unknown is how such factors repress the GnRH-LH-Te axis in older men."

Dr Veldhuis concludes: "Decreased Te and E_2 concentrations accompany long-term institutionalization, critical illness, trauma, cardiovascular disease, human immunodeficiency virus and other infections, rheumatoid arthritis, systemic lupus erythematosus, lymphoproliferative disorders, surgery, burns, stroke, myocardial infarction, and sepsis. They also accompany chronic alcoholism, systemic inflammation, diabetes mellitus, the metabolic syndrome, malignancy, acute hypoglycemia, sleep deprivation, and aging. An emerging thesis is that aging disrupts joint neuroendocrine adaptations among GnRH, LH, and Te and that multiple systemic illnesses exacerbate ensemble disruption."

Johannes D. Veldhuis, MD

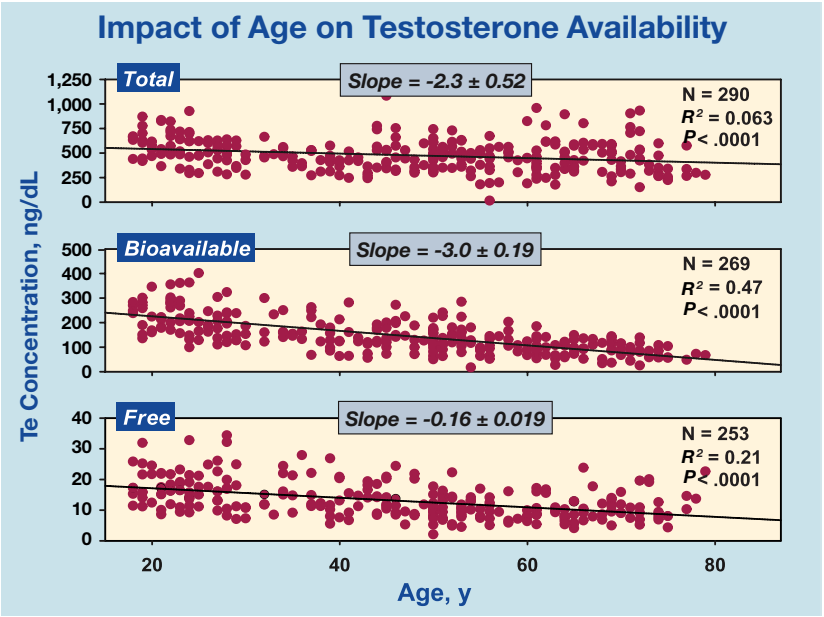

Figure 2. *Associations between each of total, bioavailable, and free testosterone (Te) concentrations and age in healthy men in Olmsted County, Minnesota (unpublished data).*

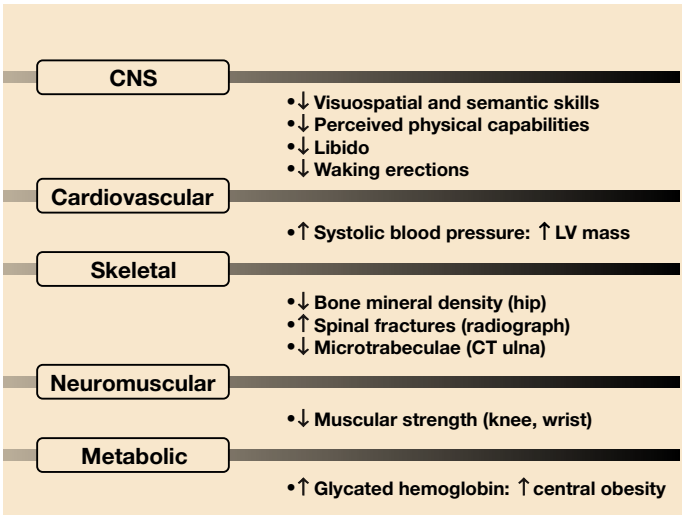

Figure 3. *Associations with androgen deficiency. CNS indicates central nervous system; CT, computed tomography; LV, left ventricle.*

Clinical Guidelines for Hyperthyroidism

Evidence-based practice guidelines for the treatment of patients who have hyperthyroidism and other forms of thyrotoxicosis were recently developed by a task force of expert clinicians jointly appointed by the American Thyroid Association (ATA) and the American Association of Clinical Endocrinologists (AACE). The guidelines—consisting of 100 recommendations, the supporting evidence, and a rating of the quality of the evidence and the strength of each recommendation—were published simultaneously in the journals of the 2 associations (Bahn et al. *Thyroid*. 2011;21[6]:593-654 and Bahn et al. *Endocr Pract.* 2011;17[3];456-520). The guidelines are also available on the Web sites of the 2 associations.

Rebecca S. Bahn, MD, of the Division of Endocrinology, Diabetes, Metabolism, and Nutrition at Mayo Clinic in Rochester, Minnesota, and chair of the Guidelines Task Force, says: "Clinical topics addressed in the guidelines include the initial evaluation and management of thyrotoxicosis; management of Graves' hyperthyroidism using radioactive iodine (RAI), antithyroid drugs, or surgery [Table]; management of toxic multinodular goiter or toxic adenoma using RAI or surgery; Graves' disease in children, adolescents, or pregnant patients; subclinical hyperthyroidism; hyperthyroidism in patients with Graves' ophthalmopathy (GO); and management of other miscellaneous causes of thyrotoxicosis. The guidelines were constructed to be useful to the practicing physician. To this end, 14 detailed tables are included in the text. In addition, many technical details are discussed relative to medication selection, dosage, and timing; administration of RAI; interval monitoring of thyroid function; and differential diagnosis, as well as others. The overall content is indexed for ease of access, and a listing of the recommendations without text is included as an Appendix." A few of the topics from the hyperthyroidism guidelines are highlighted below.

Graves' Disease

Marius N. Stan, MD, of the Division of Endocrinology, Diabetes, Metabolism, and Nutrition at Mayo Clinic in Rochester and a member of the Guidelines Task Force, explains: "The ATA/AACE hyperthyroidism recommendations center on the patient and her or his individual needs and preferences. This focus is manifest in the guidelines pertaining to Graves' disease, in that no general recommendation is given to use 1 particular treatment option (RAI, thyroidectomy, or an antithyroid medication) over the others. Rather, the guidelines state that patients with overt

Marius N. Stan, MD, and Rebecca S. Bahn, MD

Graves' hyperthyroidism 'should be treated' with one of these 3 modalities. In addition, the treating physician and the patient 'should discuss each of the treatment options, including the logistics, benefits, expected speed of recovery, drawbacks, potential side effects, and cost. This sets the stage for the physician to make recommendations based on best clinical judgment and allows the final decision to incorporate the personal values and preferences of the patient.' This recommendation is followed by a detailed section describing the medical factors that favor each modality, the contraindications to each, and the factors that may impact patient preference of one over another."

An area where the guidelines are more proscriptive is concerning which particular antithyroid drug to use. Dr Bahn comments: "In the past, both methimazole (MMI) and propylthiouracil (PTU) were thought to be appropriate as first-line therapy for Graves' disease. However, recent evidence has come to light that PTU can cause fulminant hepatic necrosis that may be fatal. Liver transplantation has been necessary in some patients taking PTU. For this reason, the guidelines state that 'MMI should be used in virtually every patient who chooses antithyroid drug therapy for Graves' disease, except during the first trimester of pregnancy, when PTU is preferred; in the treatment of thyroid storm; and in patients with minor reactions to MMI who refuse RAI or surgery.' Because the onset of PTU-induced hepatotoxicity is rare and the hepatotoxicity may be acute and rapidly progressive, routine monitoring of liver function in all patients taking this medication has not been found to prevent severe hepatotoxicity."

Dr Bahn continues: "Both MMI and PTU can produce transient cholestatic abnormalities, with the latter causing increases in serum alanine aminotransferase and aspartate aminotransferase

in up to one-third of patients. Hyperthyroidism can itself cause mildly abnormal liver function test results. Therefore, 'a liver profile including bilirubin and transaminases should be measured prior to initiating either drug,' and 'liver function and hepatocellular integrity should be assessed in patients taking PTU who experience pruritic rash, jaundice, light-colored stool or dark urine, joint pain, abdominal pain or bloating, anorexia, nausea, or fatigue.' Similarly, because routine monitoring of white blood cell counts is not likely to identify cases of agranulocytosis associated with either medication, routine monitoring of white blood cell counts is not recommended. However, because patients are typically symptomatic, 'a differential white blood cell count should be obtained during febrile illness and at the onset of pharyngitis in all patients taking antithyroid medication.' This approach is, of course, predicated on the recommendation that patients be informed of the adverse effects of antithyroid drugs and be alerted to stop the medication immediately and call their physician should they note symptoms suggestive of either hepatic injury or agranulocytosis."

Specific recommendations are given in the guidelines regarding the prevention of GO and the treatment of hyperthyroidism in patients with established GO. Dr Stan explains: "Because smoking is a significant risk factor for GO, the guidelines emphasize that 'smokers with Graves' disease should be advised to stop smoking and be referred to a structured smoking cessation program.' In patients who have no clinically apparent GO and do not smoke, 'RAI, MMI, or thyroidectomy are equally acceptable therapeutic options.' In contrast, 'patients with mild active GO who choose RAI should be considered for concurrent treatment with corticosteroids,' depending on the risk-benefit ratio relative to the patient's overall health. This recommendation is based on several studies showing that RAI therapy is a risk factor for progressive disease in patients with established mild active GO—a risk that can be essentially negated by the concurrent use of oral corticosteroids. However, if the patient with mild active GO is a smoker, 'RAI should not be given without concurrent corticosteroids.' Finally, the guidelines assert that 'patients with active moderate-to-severe or sight-threatening GO should not be treated with RAI but should instead either receive MMI or undergo surgery.'"

Table. Graves' Disease Topics Covered in the Clinical Guidelines for Hyperthyroidism

Background

How should clinically or incidentally discovered thyrotoxicosis be evaluated and initially managed?
- Assessment of disease severity
- Biochemical evaluation
- Determination of etiologic factors
- Symptomatic management

How should overt hyperthyroidism due to Graves' disease be managed?
- If ^{131}I therapy is chosen, how should it be accomplished?
- Preparation of patients with Graves' disease for ^{131}I therapy
- Administration of ^{131}I in the treatment of Graves' disease
- Patient follow-up after ^{131}I therapy for Graves' disease
- Treatment of persistent Graves' hyperthyroidism following radioactive iodine therapy

If antithyroid drugs are chosen as the initial management of Graves' disease, how should the therapy be managed?
- Initiation of antithyroid drug therapy for treatment of Graves' disease
- Monitoring of patients taking antithyroid drugs
- Management of allergic reactions
- Duration of antithyroid drug therapy for Graves' disease

If thyroidectomy is chosen for the treatment of Graves' disease, how should it be accomplished?
- Preparation of patients with Graves' disease for thyroidectomy
- The surgical procedure and the choice of surgeon
- Postoperative care

How should thyroid nodules be managed in patients with Graves' disease?

How should thyroid storm be managed in patients with Graves' disease?

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Upcoming Education Opportunity

15th Mayo Clinic Endocrine Course

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

Designed for endocrinologists and interested internists and surgeons, the 15th Mayo Clinic Endocrine Course 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 5-day course will span the full spectrum of endocrinology through lectures, debates, panel discussions, clinicopathologic sessions, "clinical pearls" sessions, informal breakfast roundtable discussions, and small-group discussions with experts. There will be plenty of opportunity for interaction with the course faculty, who are selected from Mayo Clinic for their expertise and clinical acumen. An optional thyroid ultrasound course will also be offered. For more information about this course, please visit http://www.mayo.edu/cme/endocrinology.

12th Annual Mayo Clinic Nutrition and Wellness in Health and Disease

September 20-21, 2012, Scottsdale, Arizona.

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, obesity-associated medical conditions, effective ways to provide nutrition counseling, and other common nutrition issues, in addition to physical activity and wellness. Current clinical topics will be highlighted through presentations, interactive case studies, and panel discussions. The course will be held at the Westin Kierland Resort & Spa, Scottsdale, Arizona. For more information about this course, please call 800-323-2688 or visit http://www.mayo.edu/cme/endocrinology.

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