Advanced Multidisciplinary Approaches Optimize Care and Outcomes for Patients with Pituitary Tumors

Among few of its kind in the nation, the Pituitary and Neuroendocrine Program at Brigham and Women’s Hospital (BWH) provides expert, coordinated care for patients with pituitary tumors. Led by Medical Director Whitney Woodmansee, MD, and Surgical Director Edward R. Laws, MD, FACS, the Program incorporates subspecialists, including neuroendocrinologists, neurosurgeons, neurologists, neuroradiologists, neuro-ophthalmologists, neuropathologists, radiation oncologists, neuro-oncologists, psychiatrists, and others, to optimize outcomes for patients.

“Our collaborative approach is present in all aspects of the patient’s care, from evaluation through treatment and ongoing care,” said Dr. Woodmansee.

State-of-the-art Evaluation and Medical Management

Patients are initially evaluated by both a neuroendocrinologist and a neurosurgeon in the Program during one visit, and additional specialists participate in each patient’s care as indicated. A full range of diagnostic testing is available to assess pituitary function, including advanced dynamic endocrine testing and inferior petrosal sinus sampling when indicated. These are used in conjunction with imaging and other techniques to aid in treatment planning.

Neuroendocrinologists in the Program use the latest therapies to treat hypersecreting pituitary adenomas and hormonal deficiencies. Therapies include dopamine agonists, somatostatin analogs, growth hormone receptor antagonists, and glucocorticoid receptor antagonists. Neuroendocrinologists in the Program also are participating in a number of clinical trials for acromegaly and growth hormone deficiency, including a Phase III trial, led at BWH by Site Principal Investigator Ursula Kaiser, MD, Chief of the BWH Division of Endocrinology, Diabetes, and Hypertension, that is assessing a long-acting growth hormone formulation delivered by weekly injection compared to the current standard daily injection in patients with growth hormone deficiency. Other upcoming trials will evaluate a new somatostatin analog therapy for acromegaly and a new treatment for Cushing’s disease.

Neurosurgeons and neuroendocrinologists collaborate with many other subspecialists in the Pituitary and Neuroendocrine Program to deliver advanced multidisciplinary care for patients.

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The VITamin D and OmegA-3 Trial (VITAL) at Brigham and Women’s Hospital (BWH) is an ongoing research study in 25,875 men and women across the U.S. investigating whether taking daily dietary supplements of vitamin D3 (2,000 IU) or omega-3 fatty acids (Omacor® fish oil, 1 gram) reduces the risk for developing cancer, heart disease, and stroke in people who do not have a prior history of these illnesses. Funded by the National Institutes of Health, the trial will also assess the nutrients’ effects on diabetes, cognitive function, and other conditions.

VITAL is a randomized, double-blind, placebo-controlled trial of Vitamin D and omega-3 fatty acids that is following a multi-ethnic population for five years. To date, there have been no previous large randomized trials of supplemental vitamin D in high enough doses to produce meaningful changes in circulating vitamin D levels and designed to assess its effects on cancer and CVD.

“Vitamin D and omega-3 fatty acids look promising in observational studies but there’s a great need for large-scale randomized trials that assess cause and effect relationships,” said JoAnn Manson, MD, DrPH, Chief, Division of Preventive Medicine at BWH and the Michael and Lee Bell Professor of Women’s Health at Harvard Medical School.

Participants are divided into four groups: vitamin D (2000 IU/day of vitamin D₃ cholecalciferol) plus omega-3s (1g/day); vitamin D plus placebo omega-3s; omega-3s plus placebo vitamin D; and placebos for both. “We’re looking at the independent effects of vitamin D and omega-3 supplements, and the design allows us to separate the effects of the two interventions,” said Dr. Manson.

The vitamin D dose is based on what was most promising in earlier research and provided the best balance of efficacy and safety. The current Institute of Medicine (IOM) RDA for adults aged 50-70 is 600 IU/day and adults over 70 is 800 IU/day, which is based on strong evidence that this amount is sufficient to maintain bone health in the North American population. However, accumulating data suggest that vitamin D intakes above these RDAs may confer optimal health benefits. For example, systemic reviews and meta-analyses have raised new questions about the effects of supplemental vitamin D alone on fracture risk and bone health outcomes. One review of studies of serum 25-hydroxyvitamin D in relation to various outcomes, including colorectal cancer, falls, fractures, physical functioning, and dental health found that optimal 25(OH)D levels were above 75 nmol/L, rather than the 50 nmol/L level recommended by the IOM.

The omega-3 dose of 1g/day (which includes the marine fatty acids eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA]) is recommended by the American Heart Association (AHA) for people with CVD and has been demonstrated to be beneficial, with minimal side effects, in large secondary prevention trials but has not been previously tested in primary prevention.

Research Demonstrates Vitamin D and Omega-3 Benefits

In some laboratory research, Vitamin D has demonstrated an anti-inflammatory effect that is important in CVD and cancer. When vitamin D is supplemented within the cell culture, it affects the cancer cell’s ability to proliferate and may make the cancer less likely to metastasize. Studies have also shown that vitamin D’s anti-inflammatory properties may lead to favorable effects on blood pressure, cholesterol, and glucose tolerance.

Omega-3 fatty acids have also shown considerable promise for the prevention of CVD in laboratory and observational studies; large randomized secondary prevention trials have also found CVD benefits, including lowering risk of irregular heart
rhythms, as well as decreasing blood clotting and inflammation. The data on omega-3’s effects on the primary prevention of CVD and cancer, however, are inconclusive.

**Study Objectives**

VITAL’s primary aim is to test whether vitamin D or omega-3 fatty acid supplementation reduces the risk for total cancer and major CVD events (myocardial infarction, stroke, and cardiovascular mortality). It is also looking at whether these nutrients reduce the risk for specific cancers, including colorectal, breast, and prostate; total cancer mortality; cardiovascular mortality, and coronary revascularization; and the individual components of the primary cardiovascular endpoint, particularly CVD mortality. Study objectives also include testing whether vitamin D or omega-3 fatty acid supplementation reduces fracture risk and benefits bone structure.

The trial is exploring whether vitamin D3 and marine omega-3 fatty acid supplementation exhibit synergistic or additive effects on the risk for total cancer, major CVD events, and the secondary endpoints, and whether their effects on cancer and CVD risk vary by baseline blood levels of these nutrients, race/skin pigmentation (for vitamin D3), and body mass index (BMI) (for vitamin D3). Testing the effects of vitamin D on African-Americans is particularly important since they are at higher risk of vitamin D deficiency as well as certain cancers, including prostate, cardiovascular events and mortality from cancer and CVD. VITAL is assessing whether supplementation can reduce these health disparities.

With funding from the National Institutes of Health (NIH), the trial is also assessing the effects of these nutrients on diabetes, high blood pressure, respiratory conditions, and other outcomes in a group of 1,050 Boston-area participants who are undergoing detailed testing, including a two-hour glucose tolerance test, and bone imaging to measure body composition, bone mineral density, and bone structure, at Brigham and Women’s. “We are very interested in the question of the effects of supplementation on diabetes, cognitive function, mood/depression, bone health, autoimmune conditions, and other outcomes, which are being addressed in ancillary studies,” said Dr. Manson.

“These studies also will clarify whether high-dose, supplemental vitamin D is effective in the primary prevention of fractures, with major impacts on clinical and public health guidelines,” explained Meryl S. LeBoff, MD, Chief, Calcium Bone Section, Division of Endocrinology, Diabetes and Hypertension and a Professor of Medicine at Harvard Medical School.

**Study May Have Wide-Ranging Influence**

Additional trials of vitamin D and/or omega-3 supplementation are in progress worldwide. If they and VITAL have positive results, “the clinical implications will be substantial if the results demonstrate that 2000 IU/d of vitamin D confers greater benefits than 600 to 800 IU/d, then the population will need supplementation and/or increased food fortification, as current diets do not provide that amount. The findings may influence public policy and nutritional guidelines. Vitamin D could become a standard supplement for CVD and cancer prevention just as folic acid supplementation is recommended during pregnancy to prevent birth defects,” said Dr. Manson.

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The Brigham and Women’s Hospital Video Education Center offers a wide range of educational resources for physicians and other health care professionals. The Center features several videos relating to endocrinology, including:

- Improving Health through Weight Loss – impact on diabetes
- Impact of Sleep on Health – including effect on hormones
- Diagnosis and Management of Pituitary Adenomas
- Female Athlete Triad – Recognition, Treatment, and Prevention
Innovative Surgical Techniques

One of the world’s most experienced neuroendocrine surgeons, Dr. Laws has performed more than 5,700 transsphenoidal operations for pituitary disorders throughout his career. He has been a pioneer in the use of advanced technologies to resect pituitary tumors while preserving the gland. The newest approach combines powerful 3T (Tesla) MRI with the 3D endoscope for maximum clarity and surgical precision and is used with all types of pituitary tumors and cysts, including prolactinomas, that are not responsive to medical therapy. An early adopter of the 3D endoscope, Dr. Laws has performed more than 500 3D endoscopic transsphenoidal pituitary procedures with preservation of the pituitary gland in more than 96 percent of patients.

“The 3D endoscope provides excellent visualization and versatility, enabling us to tailor the procedure to the patient’s tumor,” said Dr. Laws. “Using this tool, we also are able to reduce operative time and minimize the risks of complications. Rates of bleeding, major vessel injury, and meningitis, for example, are extremely low with this technique,” said Dr. Laws.

For challenging cases, the procedure is performed in the Advanced Multimodality Image Guided Operating (AMIGO) suite at BWH, a state-of-the-art medical and surgical research environment that features advanced imaging equipment and interventional surgical systems. All AMIGO procedures are performed under a research protocol and IRB approval. Multidisciplinary teams of specialists use the equipment and the unique design of the suite to efficiently and precisely guide treatment — before, during and after surgery — without the patient or medical team ever leaving the operating room. AMIGO enables real-time imaging to be performed in the suite throughout a surgical procedure.

“We are able to obtain images throughout the procedure, which facilitates removal of the tumor without injuring the normal gland,” said Dr. Laws.

Comprehensive Research

Researchers in the Program are actively involved in a wide range of investigator-led studies designed to advance care for pituitary patients. Dr. Woodmansee has a particular interest in research to optimize medical management of hypopituitarism. In collaboration with colleagues at Dana-Farber Cancer Institute and Boston Children’s Hospital, she has expanded treatment options for these patients and aids in transition from pediatric to adult care. She also has researched the incidence of second neoplasms in GH-treated childhood cancer survivors (Eur J Endocrinol. 2013 Mar 15;168(4):565-73.).

At the 2014 Endocrine Society Annual Meeting in Chicago, Dr. Woodmansee and her colleagues presented research that demonstrated an increased risk of diabetes mellitus in patients with pituitary tumors compared with the general population, after accounting for age, gender, and body mass index (BMI). Neuroendocrinologists and neurosurgeons in the Program also have developed a large clinical pituitary tumor patient database for future research.

Using pituitary tumor tissue in the BWH Tumor Bank, Dr. Kaiser is researching the role of epigenetic factors to better understand pituitary tumor pathogenesis, while BWH neurosurgeon Ian F. Dunn, MD, is analyzing chromosomes and genetic markers to understand the etiology of the disease, prevent recurrence, and uncover ways to manipulate tumor cells.

Access to Our Endocrinology Services

At Brigham and Women’s Hospital, our endocrinologists are available for timely consultations and will work with you to develop treatment plans for your patients. Our Physician Liaison Ellen Steward can provide direct assistance with patient referrals and consultations. Ellen can be reached at (617) 582-4733 or via email at esteward@partners.org.