



## Multiple Endocrine Neoplasia Type 2: A Case Report

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### Introduction

H.G. is a 46-yr-old Hispanic male who presented to Mount Sinai's Emergency Department with a 2-d history of nausea, nonbilious vomiting, watery diarrhea, and midepigastric abdominal pain. His past medical history included anxiety and a long-standing seizure disorder. His outpatient medications consisted of two antiepileptics, neuronin and lamictal. He had no known drug allergies, no tobacco or recreational drug history, and drank alcohol only socially. He emigrated from Mexico in the early 1980s and had a family history notable for diabetes and early coronary heart disease in both parents. In addition, H.G. reports that his father had a goiter but is uncertain about the details surrounding his thyroidal illness.

Initial vital signs revealed a temperature of 37.9, blood pressure of 150/90, and pulse of 90. The patient's abdomen was soft with normal bowel sounds and no palpable masses. There was some voluntary guarding with midepigastric tenderness to palpation, but the rest of his exam was unremarkable. Initial laboratory data demonstrated a leukocytosis of 14,000 with no left shift. The rest of his blood counts, chemistries, liver function tests, amylase, and lipase values were all normal. An abdominal/pelvic computed tomography (CT) scan (Fig. 1A) was obtained in an attempt to elucidate the etiology of the patient's symptoms, and as a result, three large adrenal masses were discovered: 2.5 × 2.5 cm on the left, 7.3 × 5.8 cm on the right, and an additional 4.7 × 4.1 cm mass abutting the right adrenal gland.

At this point, an endocrinology consult was obtained for what appeared to be bilateral large adrenal incidentalomas. Upon further questioning, H.G. admitted to having episodic "spells" for the past 20 yr consisting of sweats, palpitations, pallor, shortness of breath, chest tightness, and a sensation of his head squeezing. These episodes would occur two to three times a week, last 3–4 h in duration, and spontaneously resolve. He could identify no specific trigger factors. Of note, as this history was being obtained, H.G. had one of his classic spells with an associated dramatic elevation in his blood pressure to 190s/100s. Review of systems was also notable for a 20-lb unintentional weight loss over the past year, a several-year history of intermittent midepigastric abdominal pain and watery diarrhea, and stable two- to three-pillow orthopnea.

Further examination revealed a firm, palpable, nontender 2- × 2-cm right upper lobe thyroid nodule without any associated lymphadenopathy. This finding was subsequently confirmed by thyroid ultrasound (Fig. 1B). No mucosal neuromas, moon facies, buffalo hump, abdominal striae, proximal muscle weakness, thinning of the skin, abnormal reflexes, or abnormal hair growth were identified. Skin exam, however, was remarkable for several café au lait spots on his trunk.

Additional laboratory tests were ordered and returned as follows with reference ranges in parentheses: plasma normetanephrines 7125 (18–111 pg/ml),

plasma metanephrines 2105 (12–60 pg/ml), 24-h urine metanephrines 23,900 (110–1050 ng/dl), 24-h urine dopamine 190 (65–610 μg), 24-h urine epinephrine 196 (0–24 μg), 24-h urine norepinephrine 614 (0–140 μg), chromogranin A above 800 (0–160 ng/ml), calcitonin 194 (0–8.4 pg/ml), PTH 128 (16–87 pg/ml), corrected calcium 9.7 (8.5–11 mg/dl), gastrin 123 (0–115 pg/ml), pancreatic polypeptide 530 (0–418 pg/ml). Serum thyroid function tests, plasma aldosterone to renin ratio, random morning cortisol, prostate-specific antigen, Ca 19-9, and carcinoembryonic antigen were all found to be normal.

Given the likely diagnosis of pheochromocytoma based on clinical presentation, markedly elevated urine and plasma neuroendocrine markers, and adrenal imaging, the patient was started on twice daily phenoxybenzamine for adequate α-blockade. After 3 d of oral therapy, he was transferred to the intensive care unit and given iv phentolamine, esmolol, and fluids for 24 h in preparation for surgery the following day. He underwent a bilateral open adrenalectomy with adrenal cortical-sparing technique without complications, and both pathology (Fig. 1C) and histology (Fig. 1, D–F) returned consistent with bilateral pheochromocytomas. H.G. was discharged home on postoperative d 4 with replacement doses of both prednisone and florinef. He was to follow up with outpatient endocrine and ear, nose, and throat surgery for thyroid fine needle aspiration followed by likely total thyroidectomy, subtotal

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## LETTER FROM THE CHAIR

The Endocrine Fellows Foundation welcomes all new Endocrinology Fellows to its ranks as well as those of you who are in your second or third years of training. EFF is the only professional group dedicated solely to furthering the education and training of fellows in endocrinology. We have always held that training in endocrinology is ideally broad and deep and that programs that are training you are not always able to cover this waterfront completely. To help meet this challenge, the EFF provides venues that help you in your quest to receive the most complete training in endocrinology possible.

Our web site contains valuable educational materials such as streaming videos of preceptorships and lectures given by eminent authorities in several disciplines. The scientific forums that are regularly held contribute to our mission, as do preceptorials in subspecialties and research workshops. *EndoTrends* is also a valuable repository of information for you.

We are hopeful that our efforts will meet with your approval and that we will be able to continue to provide first-rate experiences that complement those that you are gaining in your own program. We are always available to hear from you if you think there are additional ways in which we can be helpful to you.

Sincerely,  
John P. Bilezikian, M.D.  
Chair, The Endocrine Fellows Foundation



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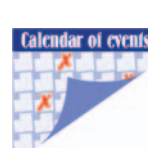
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## EndoTrends

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## Multiple Endocrine Neoplasia Type 2: A Case Report

parathyroidectomy, and genetic screening for both him and his family members to identify a multiple endocrine neoplasia (MEN) syndrome.

### Discussion

MEN type 2 (MEN2) is an autosomal dominant syndrome with an incidence of 1 in 30,000 worldwide. It is subclassified into three distinct syndromes: MEN2A, MEN2B, and familial medullary thyroid cancer (FMTC). Over 75% of cases are of the MEN2A variant consisting of medullary thyroid cancer (MTC), unilateral or more commonly bilateral pheochromocytomas, and hyperparathyroidism due to parathyroid hyperplasia. MEN2A can also be associated with cutaneous lichen amyloidosis, a rare skin condition consisting of a pruritic, scaly, papular, pigmented rash usually located on the extensor surfaces of the extremities or in the intrascapular region.

Approximately 5% of cases are classified as MEN2B with medullary thyroid cancer and pheochromocytomas but no parathyroid involvement. MEN2B is associated with the most aggressive tumors, often presenting earlier in life

with increased morbidity and mortality. Moreover, it can also be associated with a distinctive phenotype such as a marfanoid habitus with decreased upper to lower body ratio, mucosal neuromas, various skeletal abnormalities, and intestinal ganglioneuromas resulting in disturbances of colonic function.

FMTC is the most limited variant of MEN2 with only medullary thyroid cancer as its clinical presentation. Because medullary thyroid cancers have a near 100% penetrance rate and are the first manifestation of MEN2 in 40% of cases, FMTC is defined only by the presence of more than 10 carriers in a family, with a large number of affected individuals over 50 yr of age. Because a misdiagnosis of FMTC can miss a potentially fatal pheochromocytoma, such rigorous criteria are indeed necessary to ensure diagnostic accuracy.

Over 98% of MEN2 patients have a c-RET proto-oncogene point mutation in chromosome 10, making DNA testing the gold standard for screening. Studies have shown that the exact site of this gain of function mutation predicts both the variant of the disease and the aggressiveness of the tu-

mors, thereby demonstrating a high genotype-phenotype correlation and having significant therapeutic implications. For example, individuals with a mutation located on codon 634 usually express pheochromocytomas by the age of 10, whereas those with a codon 768 mutation rarely develop them. Similarly, mutations found on 922 are associated with more aggressive MTC than their counterparts on codon 791, necessitating earlier thyroidectomies with more extensive nodal dissections.

Because MTC is a life-threatening disease that can be cured or prevented by early thyroidectomy, genetic screening of all appropriate patients and at-risk family members is absolutely essential. Anyone who presents at a young age with either medullary thyroid cancer or pheochromocytoma, as well as anyone who presents with involvement of two endocrine glands (MTC + pheochromocytoma or MTC + hyperparathyroidism) should be screened for MEN2. Once a RET mutation has been identified, all blood relatives, especially children, should undergo genetic counseling and testing. A list of U.S.-

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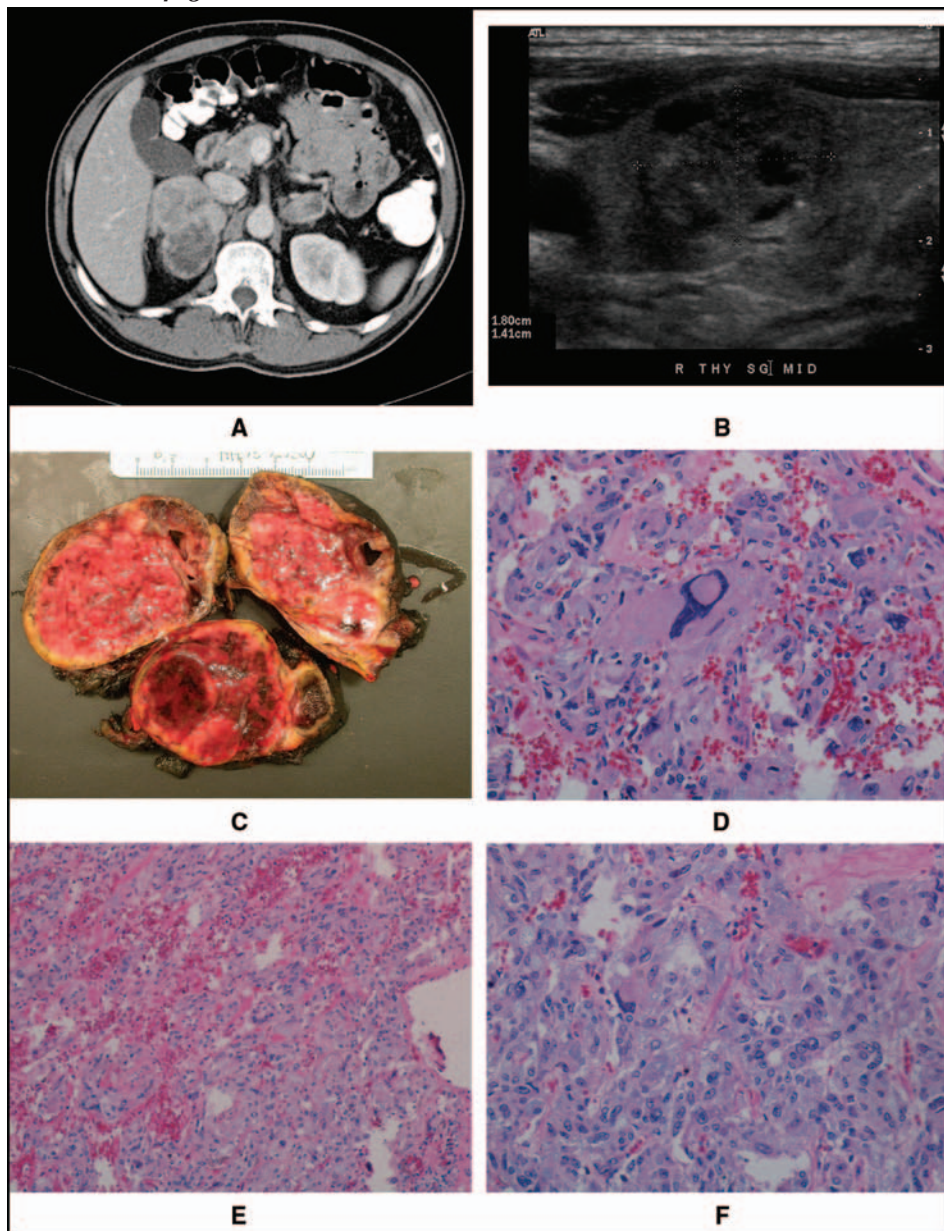


Figure 1. A, Abdominal/pelvic CT scan; B, thyroid ultrasound; C, the pathology; D, histology: large bizarre nuclear feature with inclusion; E, hemorrhagic background surrounding nests; F, basophilic granular cytoplasm.

based laboratories performing this RET gene analysis can be found at <http://www.genetests.org>.

The hallmark of MEN2 therapy is surgical resection of the tumors, and in the case of MTC, preferably before they even occur. If a pheochromocytoma is identified, it should be successively removed first and foremost to prevent death from a catecholamine crisis. If primary hyperparathyroidism is confirmed, subtotal parathyroidectomy should be pursued in cases of symptomatic hypercalcemia, nephrolithiasis,

or bone disease. All cases of MTC should undergo a total thyroidectomy, along with varying degrees of nodal dissection. Although there is no universal consensus as to the timing of prophylactic thyroidectomy in carrier children, the 2001 MEN consensus guidelines state that total thyroidectomy optimally should be performed in children between the ages of 4 and 6. Some experts in the field categorize RET mutations as high, intermediate, or low risk depending on the site of the mutation and argue that those children carrying the highest risk should undergo

total prophylactic thyroidectomies with central lymph node dissection within 6 months of age.

In conclusion, although MEN2 is a rare syndrome, it is a potentially lethal one, making early recognition and therapy essential. Commercially available DNA testing has helped to identify asymptomatic carriers of the disease, guide appropriate therapeutic interventions, and thus dramatically reduce morbidity and mortality in this day and age.

## References

- Brandi ML, Gagel RF, Angeli A, Bilezikian JP, Beck-Peccoz P, Bordi C, Conte-Devolx B, Falchetti A, Gheri RG, Libroia A, Lips CJ, Lombardi G, Mannelli M, Pacini F, Ponder BA, Raue F, Skogseid B, Tamburrano G, Thakker RV, Thompson NW, Tomassetti P, Tonelli F, Wells Jr SA, Marx SJ. Guidelines for diagnosis and therapy of MEN type 1 and type 2. *J Clin Endocrinol Metab.* 2001; 86: 5658–5671.
- Eng C, Clayton D, Schuffenecker I, Lenoir G, Cote G, Gagel RF, van Amstel HK, Lips CJ, Nishisho I, Takai SI, Marsh DJ, Robinson BG, Frank-Raue K, Raue F, Xue F, Noll WW, Romei C, Pacini F, Fink M, Niederle B, Zedenius J, Nordenskjold M, Kominoth P, Hendy GN, Mulligan LM. The relationship between specific RET proto-oncogene mutations and disease phenotype in multiple endocrine neoplasia type 2. International RET mutation consortium analysis. *JAMA.* 1996; 276:1575–579.
- Lips CJ, Hoppener JW, Van Nesselrooij BP, Van der Lijft RB. Counselling in multiple endocrine neoplasia syndromes: from individual experience to general guidelines. *J Intern Med.* 2005; 257:69.
- Machens A, Ukkat J, Brauckhoff M, Gimm O, Dralle H. Advances in the management of hereditary medullary thyroid cancer. *J Intern Med.* 2005; 257:50.
- Mulligan LM, Ponder BA. Genetic basis of endocrine disease: multiple endocrine neoplasia type 2. *J Clin Endocrinol Metab.* 1995; 80:1989.
- Raue F, Frank-Raue K, Grauer A. Multiple endocrine neoplasia type 2: clinical features and screening. *Endocrinol Metab Clin North Am.* 1994; 23:137.
- Van Heurn LW, Schaap C, Sie G, Haagen AA, Gerver WJ, Freling G, van Amstel HK, Heineman E. Predictive DNA testing for multiple endocrine neoplasia type 2: a therapeutic challenge of prophylactic thyroidectomy in very young children. *J Pediatr Surg.* 1999; 34:568–571.
- Wells Jr SA, Donis-Keller H. Current perspectives on the diagnosis and management of patients with MEN2 syndromes. *Endocrinol Metab Clin North Am.* 1994; 23:215.
- Yip L, Cote GJ, Shapiro SE, Ayers GD, Herzog CE, Sellin RV, Sherman SI, Gagel RF, Lee JE, Evans DB. Multiple endocrine neoplasia type 2: evaluation of the genotype-phenotype relationship. *Arch Surg.* 2003; 138:409–416.



## Case Report

# You CAN Judge a Book by Its Cover (A Case of Factitious Cushing's Syndrome)

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## Introduction

Clinical and biochemical presentation of endocrine disease is not always consistent. It is therefore the responsibility of the clinical endocrinologist to assess the congruence or disparity of this information to accurately diagnose and treat (or not treat) "endocrinopathies."

## Case Presentation

L.A. was a 45-yr-old woman who presented to a local hospital with a 1-month history of facial swelling, generalized weakness, fatigue, frequent falls, and "weight loss in her arms and legs." Six months before this admission she had been diagnosed with a seizure disorder after a witnessed tonic-clonic seizure while she was working at a hospital as a licensed vocational nurse (LVN). A head computed tomography (CT) scan and magnetic resonance imaging (MRI) were negative at that time. Two months before this admission she started noticing muscle weakness with an inability to "get out of a chair" or climb stairs. Her past medical history was remarkable for a seizure disorder, hypertension, carpal tunnel syndrome, major depression, and chronic low back pain. She had no history of diabetes mellitus, kidney stones, or peptic ulcer disease. Her social history was complex. She had a history of substance abuse with alcohol and marijuana, although she was currently not smoking or drinking. She denied iv drug use. She was an unemployed LVN who was previously married to a plastic surgeon. She was living with and taking care of her seriously ill current husband and autistic son. Her gynecologic history was remarkable for regular periods including during the 6 months before admission.

Her physical exam at the local hospital was remarkable for an obese female

WBC	18.3 (87% N, 4% L), H/H: 12/35
Chemistry panel	Normal glucose, LFT, calcium (albumin, 2.9 g/dl (3.5–4.8))
TSH	0.7 $\mu$ U/ml (0.47–6.2)
FT4	0.98 ng/dl (0.75–2)
FSH	1 mIU/ml (1–34)
LH	0.9 mIU/ml (0.8–40)
GH	0.17 ng/ml (0.03–10)
IGF-I	125 ng/ml (90–360)
Prolactin	11.8 ng/ml (3–19)
Cortrosyn stimulation test (250 $\mu$ g iv):	See Table 2

with "moon facies," buffalo hump, thin extremities with proximal muscle wasting, facial plethora, thin skin, and multiple bruises. She was hypertensive with a blood pressure of 134/101, weight: 210 lbs, height: 68", body mass index: 31 kg/m<sup>2</sup>. Because of her generalized fatigue and frequent falls, several studies were obtained. Head CT was unremarkable. MRI of the brain and pituitary showed a 3-mm pituitary microadenoma with no mass effect.

Table 1 shows laboratory results after the MRI findings.

The diagnosis at the outside hospital (made by an endocrinologist) based on the labs listed above was "secondary adrenal insufficiency secondary to a pituitary tumor." The patient was started on hydrocortisone 20 mg a.m., 10 mg p.m., and hormone replacement therapy. She was referred to another institution for neurosurgical resection of her 3-mm pituitary tumor.

Due to lack of insurance, the patient never saw a neurosurgeon. She came to the Ventura County Medical Center (VCMC) Emergency Department 2 wk after discharge from the outside hospital with the same symptoms as she originally presented with even on her new medications. She appeared overtly cushingoid (Fig. 1A), and therefore her hydrocortisone and hormone replace-

ment therapy were discontinued. An abdominal CT was unremarkable for adrenal pathology. The patient had never had headaches, blurry vision, nausea, vomiting, abdominal pain, anorexia, or a change in her skin color.

## Discussion

Figure 1A is a photograph of the patient 1-month after admission to VCMC. Her clinical exam and history were consistent with Cushing's syndrome (1), which completely contradicted the diagnosis from the outside hospital. Because of the incongruent clinical and biochemical findings, the patient was thought to have probable factitious Cushing's syndrome (FCS), and the 3-mm pituitary tumor was considered an incidental finding with otherwise normal pituitary function (2, 3).

The patient was thought to have FCS for many reasons. She had low ACTH and cortisol values (Table 2) with clinical signs of Cushing's syndrome. She had no evidence of adrenal insufficiency by symptoms or signs to otherwise explain the lab data. She had a pituitary tumor that was too small to cause a suppressed ACTH and secondary adrenal insufficiency by mass effect. She had no radiological evidence of primary causes of Cushing's syndrome (no macro/micronodular adrenal glands or

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Figure 1. Facial photographs of patient: A, 1 month after presentation; B, 1 yr after stopping injections; and C, 3.5 yr after presentation.

adenoma). Finally, she had characteristics of a patient with FCS (age 30–45, female, history of medical occupation or contacts, psychiatric history, current or previous drug abuse) (3).

Table 2 Cortrosyn Stimulation Test	
Time	Cortisol level
Baseline (0600)	0.4 µg/dl (a.m. >10) (ACTH: 4 pg/ml (6–58))
30 min	6.6 µg/dl
60 min	9.5 µg/dl (>20 µg/dl)

Table 3 Time Line of Normalization of Pituitary-Adrenal Function			
Date	Triamcinolone acetonide	ACTH (6–58)	a.m. cortisol
8-29-03	3.4 µg/dl (<0.03)	<5 g/ml Medic Alert Bracelet	<0.2 µg/dl
9-12-03	0.86		
1-13-04	0.29	<5 pg/ml	<0.2 µg/dl
2-23-04	0.20	29	9 µg/dl
8-19-04	Negative		

The patient was confronted with the possibility of exogenous steroid use, which she adamantly denied. Due to her delicate psychiatric status, I saw her almost weekly in the outpatient endocrine clinic. I repeatedly, yet gingerly, discussed exogenous steroid use and she told me 1 month after discharge, “Where are the steroids coming from? I’m not taking any. I swear!” During this month, her blood had been sent to Mayo Medical Labs (4) to look for the presence of nonanabolic synthetic steroids in a test that is now called Synthetic Glucocorticoid Screen in Serum (SGSS). Six weeks after discharge, the patient returned to the hospital Emergency Department with bilateral buttock abscesses requiring surgical debridement. The SGSS results came back positive for triamcinolone acetonide 3.4 µg/dl (< 0.3).

During this hospitalization the patient admitted to self-injections with triamcinolone acetonide in her buttocks for “an unknown period of time.” She had a supply of the drug left over from when her ex-husband used to give her injections occasionally for back pain. Table 3 gives a time line of the normalization of her pituitary-adrenal function after discontinuing triamcinolone acetonide injections. Triamcinolone acetonide has an “unknown half-life” according to Epocrates 2007 and the PDR 2003. The drug lasted for more than 6 months in this particular patient. Figure 1B shows the patient 1 yr after stopping injections. Figure 1C shows the patient 3.5

yr after presentation. Although there have been several cases of factitious Cushing’s syndrome in the literature (2, 3, 5–8), this appears to be the first case secondary to self-injections of triamcinolone acetonide.

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### References

1. Newell-Price J, Trainer P, Besser M, Grossman A. The diagnosis and differential diagnosis of Cushing’s syndrome and pseudo-Cushing’s states. *Endocr Rev.* 1998; 19:647–672.
2. Villanueva RB, Brett E, Gabrilove JL. A cluster of cases of factitious Cushing’s syndrome. *Endocr Pract.* 2000; 6:143–147.
3. Cizza G, Nieman LK, Doppman JL, Passaro MD, Czerwiec FS, Chrousos GP, Cutler Jr GB. Factitious Cushing syndrome. *J Clin Endocrinol Metab.* 1996; 81:3573–3577.
4. Mayo Medical Laboratories synthetic glucocorticoid screen in serum by liquid chromatography-tandem mass spectrometry (LC-MS/MS) stable isotope dilution analysis.
5. Quddusi S, Browne P, Toivola B, Hirsch IB. Cushing syndrome due to surreptitious glucocorticoid administration. *Arch Intern Med.* 1998; 158:294–296.
6. Cook DM, Meikle AW. Factitious Cushing’s syndrome. *J Clin Endocrinol Metab.* 1985; 61:385–387.
7. Anderson PW, Galamarini M, Vagnucci A, Horton R. Factitious Cushing’s disease. *West J Med.* 1993; 159:487–489.
8. Boscaro M, Barzon L, Sonino N. The diagnosis of Cushing’s syndrome: atypical presentations and laboratory shortcomings. *Arch Intern Med.* 2000; 160:3045–3053.



## The Second Annual Endocrine Fellows Research Forum in Metabolic Bone Diseases

The Endocrine Fellows Foundation, in cooperation with The Endocrine Society, presented its Second Annual Endocrine Fellows Research Forum in Sante Fe, NM, on August 1–2, 2007. This program was part of the Osteoporosis Update Program of The Endocrine Society. This program was designed for a selected group of endocrinology fellows who are focusing their training in metabolic bone diseases. The forum consisted of four

faculty giving plenary lectures: Dr. John Bilezikian (Columbia University), “Primary Hyperparathyroidism: New Concepts;” Dr. Deborah Sellmeyer (University of California, San Francisco) “Nutritional Aspects of Skeletal Health and Disease;” Michael McClung (Director, Oregon Osteoporosis Center) “The Design of Clinical Trials: Promises and Pitfalls;” and Dr. Steven Harris (University of California, San Francisco) “Paget’s Disease of Bone.”

The program is a unique one, in that all of the fellows presented their own research either in the format of an oral abstract presentation or a poster viewing. This was a highly successful experience for fellows, many of whom were given their first opportunity to present their research in a public forum. We are grateful to the following companies who provided unrestricted educational grants for this program: Amgen, Eli Lilly, Merck, Novartis, NPS, and Roche.



### ENDOCRINE FELLOWS FOUNDATION ANNOUNCES ITS RESEARCH GRANT RECIPIENTS FOR THE FALL CYCLE OF 2007 Derek LeRoith, M.D., Ph.D., Director, Grants Program

The Endocrine Fellows Foundations received 25 grant applications for the fall cycle. Awardees receive \$7,500 to facilitate their research. Applications were received covering projects on diabetes/obesity, bone, thyroid, lipids, pituitary, reproductive endocrinology, and pediatrics. The grants funded cover the fields of diabetes, bone, and pituitary.

Among the 36 experts who were asked to review these applications, the EFF received reviews from 98% of the participants. The average grant received three separate reviews. Using an NIH-based priority system, many grants were very favorably received. We are pleased to announce that four grants were approved for funding. The awardees are noted below:

**Bismruta Misra, M.D.—Columbia University, College of Physicians & Surgeons:**  
“Prevalence and Characterization of Normocalcemic Hyperparathyroidism”  
Program Director, John P. Bilezikian, M.D.

**Judy Shih, M.D.—Joslin Diabetes Center:**  
“Exploring the Presence of a Novel Circulating Pancreatic Islet Alpha-Cell Growth Factor”  
Program Director, William Hsu, M.D.

**John Ausiello, M.D.—Columbia University, College of Physicians & Surgeons:**  
“Differential Effects of rhGH vs. rhIGF-1 Therapy on Cardiovascular Risk Factors in Adult Patients with Growth Hormone Deficiency”  
Program Director, John P. Bilezikian, M.D.

**Alison Sawyer, M.D.—University of New Mexico Health Science Center:**  
“Postprandial Hyperglycemia and Oxidative Stress”  
Program Director, Katherine Colleran, M.D.



# Thyroid Transcription Factor 2 Expression Is Regulated by the Phosphoinositide 3-Kinase Signaling Pathway in Thyroid Cancer and Thyroid Cancer Cell Lines

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## Introduction

Local invasion and metastasis are more common in pediatric thyroid cancer than in similar tumors in adult patients. Therefore, there is a critical need to determine the key pathways utilized by thyroid cancer to invade and metastasize to devise effective therapies for these patients.

Recent data suggest that the molecular mechanisms controlling invasion during embryological development could be reactivated during cancer progression. We hypothesized that the mechanisms involved in regulation of thyroid gland migration during embryogenesis could be reactivated during thyroid cancer invasion.

The key molecular mechanisms controlling thyroid gland development and migration during embryogenesis involve the interaction of thyroid transcription factor (TTF)-2, in concert with TTF-1 and the paired box homeoprotein (1). TTF-2 knockout mice either develop thyroid remnants that remain in the pharynx or fail to develop a thyroid entirely (1). In the mouse, TTF-2 mRNA begins to fall on embryonic d E13.0, immediately before the rise in TTF-1, thyroglobulin, and sodium iodide symporter, suggesting that TTF-2 can suppress thyroid-specific gene expression during migration of the primitive thyroid (2).

TTF-2 expression is regulated by insulin, IGF-1, and TSH (3, 4). Genes downstream of TTF-2 have been evaluated in stable TTF-2-expressing cell lines. TTF-2 induces expression of genes belonging to the retinol binding family of proteins, TGF $\beta$  signaling pathway, apoptosis-related genes, and other genes with largely unknown functions (5).

The role for TTF-2 in thyroid cancers is potentially complex (6–9). TTF-2 expression is low in normal thyroid tissue, but increased in Graves' disease and goiter (10). TTF-2 is also detected in 55% of benign adenomas, 50% of papillary thyroid carcinomas (PTC) and follicular thyroid carcinomas, and is absent from anaplastic thyroid cancers (10). These studies did not indicate the particular mutation status of examined tumors so that further delineation of the relationships between TTF-2 and thyroid cancer remain unclear.

Based on the central role of TTF-2 for thyroid migration during embryogenesis, we believe that TTF-2 could be involved in the regulation of thyroid cancer cell invasion. We explored the relationship between TTF-2 and the phosphoinositide (PI3-kinase)-AKT pathway, previously shown to play an important role in thyroid cancer invasion (11–13).

## Materials and Methods

### Immunohistochemical Staining in Human Thyroid Tissue Samples

We examined thyroid tissue from 10 papillary thyroid carcinomas with corresponding normal tissues, 5 follicular adenomas, and one Graves' disease sample. Immunohistochemical staining on human thyroid tissue was performed with anti-phospho AKT antibody (Cell Signaling, Beverly, MA) and anti-TTF 2 antibodies (Abcam Inc., Cambridge, MA) using the universal vectastain kit (Vector, Burlingame, CA). Negative control was applied by omission of anti-serum.

### Thyroid Cancer Cell Lines

NPA (papillary), WRO (follicular), and ARO-81 (anaplastic) thyroid cancer cells

were grown in RPMI medium supplemented with 10% fetal calf serum (FCS). TTF-2 mRNA expression in these thyroid cancer cells was examined by RT-PCR using specific primer (Maxim Biotech, Rockville, MD). TTF-2 protein level was assessed in these cells by Western blot analysis with anti-TTF-2 antibodies (Abcam Inc.).

To examine the role of the PI3-kinase-AKT pathway on TTF-2 expression, cells were incubated with LY294002, a specific inhibitor of PI3-kinase. Using the Lipofectamin 2000 method, NPA cells were transiently transfected with constitutively active AKT construct (generous gift of Motoyasu Saji, Ohio State University, Columbus, OH). Empty vector was used as a control.

### Cells Migration Assays

A total of  $3 \times 10^4$  cells in 0.5% FCS RPMI medium were seeded in a Boyden chamber (8- $\mu$ m pore size). The bottom chamber contained 10% FCS RPMI medium. The gradient of FCS concentration between top and bottom chambers induced NPA cell migration. After 6, 12, and 24 h, cells on the membrane were fixed and subjected to Diff Quick staining or cells were collected for RNA extraction.

## Results

In all examined benign and malignant thyroid tumors, TTF-2 expression was found to be higher than in corresponding normal thyroid tissue (Fig. 1A). In thyroid follicular adenomas (Fig. 1B), nuclear TTF-2 expression was increased compared with the normal thyroid tissue. High levels of cytoplasmic TTF-2 expression was found in 4 of 10 examined PTC (Fig. 1C). PTCs with

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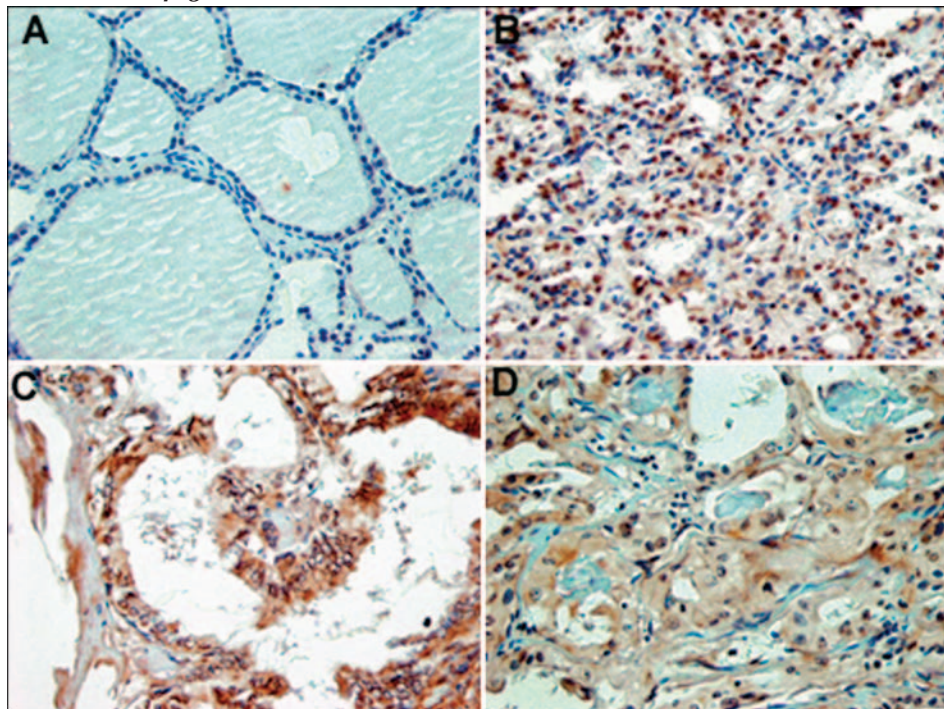


Figure 1. A, TTF-2 expression in normal thyroid tissue; B, thyroid follicular adenoma; C, thyroid papillary carcinoma without mutation; and D, thyroid papillary carcinoma with *RET/PTC 3* rearrangement.

BRAF mutations and with *RET/PTC3* rearrangement showed decreased level of TTF-2 staining compared with the tumors without mutation (Fig. 1, C and D). In the invasive front of thyroid cancer the level of TTF-2 expression was decreased in comparison to cells located in the central area of the tumor. An inverse relation was observed between the level of AKT activation in thyroid cancer detected by immunohistochemistry and the level of TTF-2 expression. Invasive thyroid cancer demonstrated high levels of AKT activation.

To explore the relationship between thyroid cancer cell invasion and TTF-2 expression we performed an *in vitro* invasion assay using NPA thyroid cancer cells. In 12 h, almost 50% of cells migrated through an 8- $\mu$ m pore membrane. We collected RNA from already migrated and not yet migrated NPA cells after 12 h of migration and established the level of TTF-2 expression by RT-PCR. Similar to data observed in human thyroid cancers, not-yet-migrated cancer cells showed high levels of TTF-2 expression whereas already migrated cells showed low levels of TTF-2 expression.

To explore the mechanism regulating TTF-2 expression, we analyzed the role of the PI3-kinase signaling pathway, previously reported to be primarily involved in thyroid cancer cell migration. In 0% FCS medium conditions, TTF-2 was expressed in NPA cells. Stimulation with 10% FCS medium resulted in downregulation of TTF-2 expression. Cell treatment with LY294002, a PI3-kinase inhibitor, prevented the FCS inducible downregulation of TTF-2 expression. Cell transfection with constitutively active AKT resulted in AKT activation and decreased TTF-2 expression (Fig. 2) confirming that the PI3-kinase-AKT signaling pathway negatively regulates TTF-2 expression in thyroid cancer cells.

## Discussion

We hypothesized that TTF-2, a key regulator involved in embryonic thyroid gland development and migration, may be involved in thyroid carcinoma invasion. Our study explored the relationship between the PI3-kinase-AKT signaling pathway, a pathway known to be involved in cancer invasion, and TTF-2 expression in thyroid cancer cells both *in vivo* and *in vitro*.

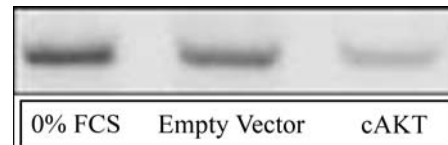


Figure 2. TTF-2 expression in NPA cells in 0% FCS, in NPA cells transfected with empty vector, and in NPA cells transfected with constitutively active AKT construct (cAKT).

In agreement with previously published data, we found high levels of TTF-2 expression in Graves' disease and in thyroid adenomas. These diseases are characterized by increased levels of proliferation, but not by invasion or the development of metastasis. In support of these findings where TTF-2 may not be critical for invasion, we demonstrated decreased levels of TTF-2 expression in the invasive front of the human thyroid tumors. Previous studies examining anaplastic thyroid cancer, characterized by extremely aggressive local invasion, also showed complete loss of TTF-2 expression.

Analysis of the signaling pathways known to be critical in thyroid cancer cell invasion showed that activation of the PI3-kinase-AKT pathway resulted in decreased levels of TTF-2 expression. This again supports our findings in human thyroid cancers that TTF-2 overexpression is not critical for thyroid cancer invasion. Finally, as confirmation, we evaluated nonmigrated and migrated thyroid cancer cells for pattern of TTF-2 expression and showed that TTF-2 expression is decreased in migrating cancer cells.

## Conclusion

Together, these data suggest the mechanism by which the thyroid gland changes position during embryogenesis and the mechanism involved in thyroid cancer cell invasion are different. The exact role of TTF-2 expression in thyroid cancer invasion remains to be elucidated.

## Acknowledgments

This research was sponsored by a generous grant from the Endocrine Fellows Foundation. The opinions or assertions contained herein are the private views of the authors and are not to be con-

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strued as official or to reflect the opinions of the Uniformed Services University of the Health Sciences, the U.S. Army, or the Department of Defense.

## References

1. Di Lauro R, Damante G, De Felice M, Arnone MI, Sato K, Lonigro R, Zannini M. Molecular events in the differentiation of the thyroid gland. *J Endocrinol Invest.* 1995; 18:117-119.
2. Zannini M, Avantiaggiato V, Biffali E, Arnone MI, Sato K, Pischetola M, Taylor BA, Phillips SJ, Simeone A, Di Lauro R. TTF-2, a new forkhead protein, shows a temporal expression in the developing thyroid which is consistent with a role in controlling the onset of differentiation. *EMBO J.* 1997; 16:3185-3197.
3. Ortiz L, Zannini M, Di Lauro R, Santisteban P. Transcriptional control of the forkhead thyroid transcription factor TTF-2 by thyrotropin, insulin, and insulin-like growth factor I. *J Biol Chem.* 1997; 272:23334-23339.
4. Santisteban P, Acebron A, Polycarpou-Schwarz M, Di Lauro R. Insulin and insulin-like growth factor I regulate a thyroid-specific nuclear protein that binds to the thyroglobulin promoter. *Mol Endocrinol.* 1992; 6:1310-1317.
5. Hishinuma A, Ohmika N, Namatame T, Ieiri T. TTF-2 stimulates expression of 17 genes, including one novel thyroid-specific gene which might be involved in thyroid development. *Mol Cell Endocrinol.* 2004; 221:33-46.
6. Fabbro D, Di Loreto C, Beltrami CA, Belfiore A, Di Lauro R, Damante G. Expression of thyroid-specific transcription factors TTF-1 and PAX-8 in human thyroid neoplasms. *Cancer Res.* 1994; 54:4744-4749.
7. Fabbro D, Pellizzari L, Mercuri F, Tell G, Damante G. Pax-8 protein levels regulate thyroglobulin gene expression. *J Mol Endocrinol.* 1998; 21:347-354.
8. Ros P, Rossi DL, Acebron A, Santisteban P. Thyroid-specific gene expression in the multi-step process of thyroid carcinogenesis. *Biochimie (Paris).* 1999; 81:389-396.
9. Shimura H, Suzuki H, Miyazaki A, Furuya F, Ohta K, Haraguchi K, Endo T, Onaya T. Transcriptional activation of the thyroglobulin promoter directing suicide gene expression by thyroid transcription factor-1 in thyroid cancer cells. *Cancer Res.* 2001; 61:3640-3646.
10. Sequeira MJ, Morgan JM, Fuhrer D, Wheeler MH, Jasani B, Ludgate M. Thyroid transcription factor-2 gene expression in benign and malignant thyroid lesions. *Thyroid.* 2001; 11:995-1001.
11. Chen PN, Hsieh YS, Chiou HL, Chu SC. Silibinin inhibits cell invasion through inactivation of both PI3K-Akt and MAPK signaling pathways. *Chem Biol Interact.* 2005; 156:141-150.
12. Mawrin C, Sasse T, Kirches E, Kropf S, Schneider T, Grimm C, Pambor C, Vorwerk CK, Firsching R, Lendeckel U, Dietzmann K. Different activation of mitogen-activated protein kinase and Akt signaling is associated with aggressive phenotype of human meningiomas. *Clin Cancer Res.* 2005; 11:4074-4082.
13. Miyagi E, Braga-Basaria M, Hardy E, Vasko V, Burman KD, Jhiang S, Saji M, Ringel MD. Chronic expression of RET/PTC 3 enhances basal and insulin-stimulated PI3 kinase/AKT signaling and increases IRS-2 expression in FRTL-5 thyroid cells. *Mol Carcinog.* 2004; 41:98-107.



## Preceptorial in Metabolic Bone Diseases, College of Physicians & Surgeons, Columbia University

The Endocrine Fellows Foundation was pleased to provide another successful Preceptorship in Metabolic Bone Diseases that was held May 14-25, 2007. With generous unrestricted grants from the Alliance for Better Bone Health and also Abbott Pharmaceuticals, EFF was able again this year to provide a comprehensive and detailed course that covered essentially all elements of metabolic bone diseases.

The topics covered included osteoporosis, hypercalcemia, hypocalcemia, Paget's disease, primary hyperparathyroidism, secondary hyperparathyroidism, parathyroid cancer, osteoporosis in men, metastatic bone disease, vitamin D, imaging of the skeleton with conventional and new high resolution imaging technologies, histomorphometric analysis of bone biopsies, clinical research, osteoporosis after transplantation and in Asian-Americans.

Over 30 faculty participated in this 2-week experience including guest faculty from Brazil and Washington University in St. Louis. The fellows who were



(Left to right) Chenyi Lin, M.D.; Chhavi Agarwal, M.D.; Ramon Martinez, M.D.; Amal Shibli-Rahhal, M.D.; Wanda Lakey-Cook, M.D.; John P. Bilezikian, M.D.; Karla Pou, M.D.; Lourdes Aguayo-Figuerora, M.D.; and Laura Knecht, M.D.

selected to participate in this preceptorial came from the University of Arizona in Phoenix, Winthrop University Hospital, University of Massachusetts, Beth

Israel Medical Center, Columbia University Medical Center, University of Iowa Hospital, State University of New York/Stony Brook, and Duke University.



## FALL PRECEPTORSHIP PROGRAM AWARDEES

The Endocrine Fellows Foundation is pleased to announce the awardees for the fall 2007 Preceptorship Program.

This program, which was instituted in 1999, has provided an opportunity for over 175 endocrine fellows to spend 2 weeks with a mentor (and his/her faculty) and to be exposed to an extensive experience in a specific area of endocrinology. During this time, fellows participate in specialty clinics and are introduced to research approaches and techniques that are particularly useful in the subspecialty area of endocrinology and metabolism.

### Childrens Hospital Los Angeles

Los Angeles, California

November 5–16, 2007

**Rebecca J. Brown, M.D.**  
National Institutes of Health  
Bethesda, MD

**Mimi Kim, M.D.**  
Brown University  
Providence, RI

**Anita M. Swamy, M.D.**  
University of Texas H.S.C.  
San Antonio, TX

**Bradley J. Van Sickle, M.D.**  
Vanderbilt Children's Hospital  
Nashville, TN

**Eric Sherman, M.D.**  
Uniformed Services University of  
The Health Science Center  
Bethesda, MD



## Contribute to *EndoTrends* . . .

Submit a patient case study, journal review, or research update to *EndoTrends*. It is an innovative, quarterly newsletter for endocrine fellows sponsored by the Endocrine Fellows Foundation (EFF). In each issue, we seek to provide practical clinical information on a variety of topics.

The Endocrine Fellows Foundation realizes that, as dedicated medical practitioners, our mentors and peers are our best resource for growth and education. Endocrine Fellows are encouraged to submit ideas and/or articles for publication and will receive a \$300 honorarium for accepted material.

Articles should range from 800–1000 words or two to four typewritten pages. Exceptions for longer or shorter articles may be made based on content. Submissions should include an original manuscript (including all applicable bibliographic references), a diskette containing the article (Word 6.0 preferred, ACSII format also accepted), plus any accompanying photographs, charts, or graphs (graphic accompaniment to submitted articles is highly encouraged).

Figures should be submitted as TIFF or EPS files. Photoshop files are also acceptable. Please submit artwork at the size it should be printed. See <http://cjs.cadmus.com/da> for additional information. Please provide a good quality hard copy for each figure submitted. Please send figures on CD or disk rather than e-mail.

Please note: EFF reserves the right to edit the material as necessary to accommodate the available space. **Your Mentor must review, approve, and sign off on your articles before you submit them to our office.**

If you have a topic that you think would be of interest to our readers, please forward your submission to Marilyn Fishman, Executive Director, The Endocrine Fellows Foundation, 5959 W. Century Boulevard, Suite 550, Los Angeles, CA 90045. For questions, please call (877) 877-6515.



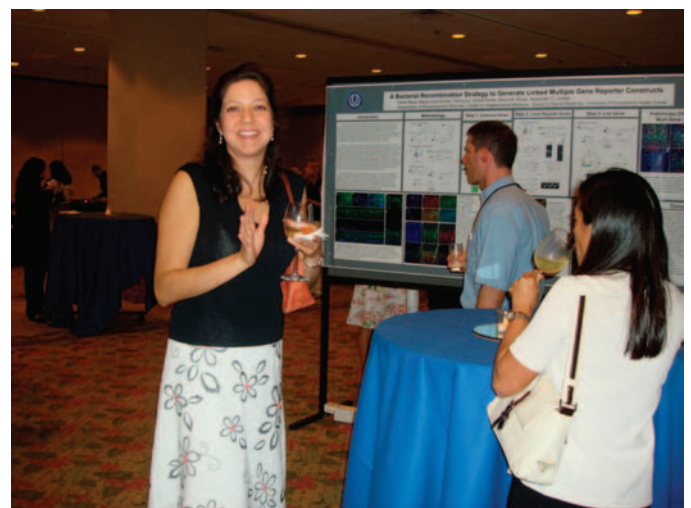
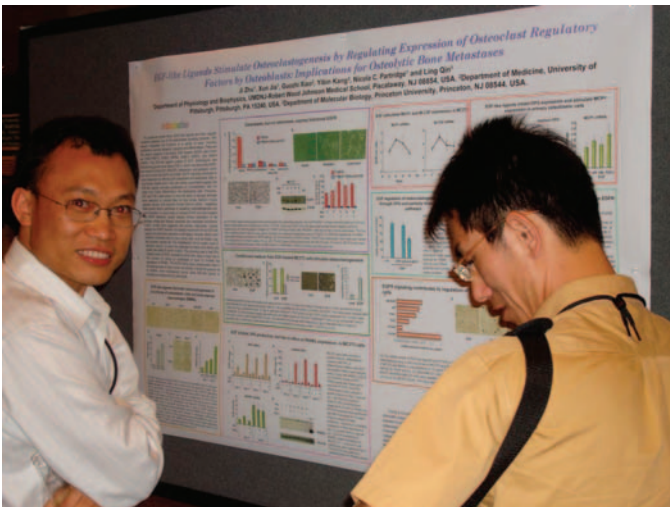
## Second Annual Forum in Metabolic Bone Diseases

The Endocrine Fellows Foundation, in co-sponsorship with the American Society for Bone and Mineral Research, conducted the Second Annual Fellows Forum in Metabolic Bone Diseases. This Forum was held at the time of the American Society for Bone and Mineral Research Annual Meeting in Honolulu, HI, on September 15, 2007. The idea of this Forum is to provide fellows who are training in endocrinology and other specialties focused on metabolic bone diseases the opportunity to hear and interact with some of the world's experts in metabolic bone diseases.

The program consisted of three plenary lectures by Professors Clifford Rosen (Genetics and Biology of Bone); Lawrence Raisz (New Therapeutic Concepts in Osteoporosis), and Ego Seeman (The Periosteum: Do Bone Size and Shape Matter?). There were eight breakout sessions; four focused on clinical aspects of metabolic bone diseases, and four focused on basic bone biology. The leaders of the basic bone biology breakout sessions were Drs. Mary Bouxsein (Assessment of Bone Quality: New Technologies); Jane Lian (Osteoblast Biology and An-

abolic Mechanisms); Lynda Bonewald (The Osteocyte); and Stavroula Kousteni (Biochemical Pathways of Bone Cells that Lead to Bone Build Up and Bone Breakdown). The clinical breakout sessions were led by Drs. Robert Heaney (Calcium and Vitamin D as Nutrients and Nutraceuticals); Stuart Silverman (Quantitative Risk Assessment: The Future of Therapeutic Decision-Making); Michael McClung (Clinical Trials: What Have We Learned from Them; How Will They be Conducted in the Future); and John

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Bilezikian (Primary Hyperparathyroidism: New Concepts and New Approaches for 2007). There were over 110 applicants from both the United States and abroad. Of the 67 applicants selected, 35 presented posters that completed the very successful day.

This Forum has made it possible for the fellows not only to learn from and interact with these world experts but also to attend the Annual Meeting of the American Society for Bone and Mineral Research, one of the most important meetings of the year for clinicians and

investigators in their field. This program was made possible by unrestricted educational grants from Amgen, Merck, the Alliance for Better Bone Health (Procter & Gamble/sanofi-aventis), Eli Lilly, GlaxoSmithKline, and Novartis.

## PHYSICAL THERAPY AND NUTRITION NEWS



### Benefits of Physical Activity for Overweight and Obese Individuals

Karen Kemmis, PT, DPT, MS, CDE

Physical Therapist/Exercise Physiologist/Certified Diabetes Educator, Joslin Diabetes Center & University Endocrinologists and Physical Medicine & Rehabilitation at SUNY Upstate Medical University, Syracuse, New York

#### Introduction

Exercise presents several benefits and challenges for the overweight or obese person. Many exercise with the primary goal of weight loss, and most are disappointed with the results. Physical activity (PA) is often very difficult for obese people, and healthcare professionals are frequently questioned about the benefits, which need to outweigh the costs to make it worthwhile for an individual. This article will review the cardiometabolic benefits, recommendations, and barriers of PA for overweight and obese individuals.

#### Prevention and Treatment of Type 2 Diabetes

PA is an effective component for the prevention and treatment of type 2 diabetes. In the Diabetes Prevention Program, the lifestyle intervention group was given a goal of completing at least 150 min/wk of moderately paced PA combined with a modest calorie-restricted diet to achieve a 7% weight loss. As a result of the lifestyle intervention, there was a reduction in onset of type 2 diabetes by 58% compared with the control group (1). In older, overweight women without diabetes, high-intensity (HI) exercise is more beneficial for glucose utilization than moderate- or low-intensity exercise. In men and women without diabetes, activity level is inversely associated with 2-h plasma glucose but not fasting glu-

cose (2), and overweight active people have similar insulin sensitivity and glucose levels to lean inactive people (3). The risk of developing diabetes is increased in those with a high body mass index (BMI), high waist circumference, and low activity levels (4). In those with diabetes, aerobic exercise and resistance training (RT) improve glycemic control, even with no change in body mass or body fat (5).

#### Aerobic Fitness

Cardiorespiratory fitness is improved with exercise in those with type 2 diabetes. A meta-analysis of randomized, controlled trials (RCTs) of aerobic exercise in those with diabetes shows an increase in maximal oxygen uptake ( $VO_{2max}$ ) with 3.4 sessions/wk, 50 min/session, at 50–75%  $VO_{2max}$ . HI exercise produces greater improvements in  $VO_{2max}$  and glycemic control than higher volumes of exercise (6).

#### Dyslipidemia

In general, exercise has not been shown to produce substantial changes in cholesterol (7, 8). However, when comparing combinations of high to low amounts of exercise and high- to low-intensity exercise, there is evidence that high-amount (HA)/HI exercise can increase high-density lipoproteins, decrease some subfractions of low-density lipoproteins, and decrease triglyceride levels. The HA/HI exercise is equivalent

to jogging 20 miles/wk at 65–80%  $VO_{2max}$  (9).

#### Hypertension

High blood pressure (BP) can be improved with aerobic exercise. A meta-analysis of RCTs determined that systolic and diastolic BP was lowered in normotensive and hypertensive, and in normal and overweight individuals, even without change in body weight. Blood pressure changes with exercise were modest, with a decrease of 3–5 mm Hg for systolic blood pressure (SBP) and 2–3 mm Hg for diastolic blood pressure (DBP) (10). In a systematic review, SBP was reduced more with diet than exercise, and the addition of exercise to diet did not produce significant improvements in SBP. Exercise reduced DBP modestly (2 mm Hg). When comparing diet to exercise, there was a clinically significant decrease in DBP with no difference between interventions (8).

#### Morbidity and Mortality

Cardiovascular morbidity and mortality are positively affected by increased PA. In the Nurses' Health Study, the risk of cardiovascular disease (CVD) decreased as levels of moderate and vigorous activity increased. The women who were active more than 2 h/wk had twice the risk of CVD compared with those who were active more than 4 h/wk (11).

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**Table 1**  
**Barriers to Exercise and Possible Solutions**

Pain	Choose the best activity ( <i>i.e.</i> for low back and lower extremity pain, choose an activity with less weight bearing such as stationary bicycle, elliptical trainer, glider, recumbent stepper, water exercise and swimming, and/or resistance training).
Lack of time	Prioritize activities to include exercise. Put it into the daily/weekly schedule. Do shorter bouts of exercise through the day (10–15 min, 2–3 times/d). Add steps throughout the day and track with a pedometer. Look for opportunities to take extra steps ( <i>i.e.</i> stairs rather than elevators, park further away).
Lack of motivation	Provide the patient with a specific exercise prescription and an explanation of the importance. Provide community resources, an exercise log, choose a suitable activity. Have the person find an exercise partner and/or support person. Encourage exercise early in the day when possible. Set specific goals.
Discomfort (skin chafing and irritation, muscle soreness, discomfort around others, etc.)	Choose an appropriate exercise (see above). Suggest proper clothing and skin lubricant to decrease skin irritation, and prescription deodorant if needed. Suggest joining a program with similar people ( <i>i.e.</i> size, age, fitness abilities, and gender).
Boredom	Use music, audio books, television. Exercise with others. Encourage variation in types of exercise to break up the routine.

Mortality in men with type 2 diabetes is increased in those who are inactive. In the Aerobics Center Longitudinal Study (ACLS), those who were classified as low fit and physically inactive were twice as likely to die compared with more fit and active individuals (12). The men who were in the low-fit category had a higher BMI. Once adjusted for fitness, there was no significant trend for mortality across BMI categories, with risk of mortality related to fitness in normal, overweight, and obese individuals. The authors suggested encouraging increased activity to improve fitness and decrease mortality even without the expectation of weight loss (13).

## Weight Loss

Losing weight is often the primary reason for an overweight person to begin an exercise program, and many are disappointed when they have put time and effort into exercise, with little change in weight. Shaw *et al.* (8) performed a systematic review of RCTs of exercise for overweight and obese individuals. When comparing diet and exercise to diet alone, there was a reduction in weight with the combination of 1.1 kg over diet alone. BMI changes are improved with the addition of exercise to diet but the benefit is small (0.4 kg/m<sup>2</sup>). HI exercise was more beneficial for weight loss compared with lower intensity exercise. Cardiometabolic benefits of exercise were present without changes in weight. When an individual has lost a substantial amount of weight, exercise has been shown to be an important component for maintenance. The most successful maintenance is

seen in those who combine diet with exercise and are highly active (14). The amount of activity needed to sustain weight loss is 80 min/d of moderate or 35 min/d of vigorous activity added to a previously sedentary lifestyle (15). To prevent the transition from overweight to obese, activity for 45–60 min/d is necessary (16).

## Resistance Training

Historically, aerobic exercise has been the primary form of exercise studied and promoted, especially for obese individuals. More recently, RT has been shown to provide positive cardiometabolic changes. Many overweight have difficulty performing aerobic exercise because of painful conditions and other challenges, but RT provides an alternative. Two RCTs of RT in older, overweight, sedentary people with type 2 diabetes have shown benefits including improved A1c, decreased diabetes medication, increased strength and lean body mass (LBM), decreased trunk and fat mass, and BP, without improved lipids (17, 18). Comparing diet with RT to diet alone, weight loss is equal. The addition of RT allowed preservation of LBM during weight loss, which allows maintenance of weight loss (18).

## Fit and Fat or Fit vs. Fat

Exercise and PA improve many cardiometabolic parameters in overweight, without weight loss. Though modest, the improvements in BP, lipids, and glycemic control combine to benefit the overweight person. This has led to support of the notion of “fat and fit” and the suggestion that weight loss

may not be important if a person is cardiometabolically fit. However, there are other considerations regarding the importance of weight loss in the obese. First, many cardiometabolic benefits occur through weight loss, supporting a calorie-restricted diet combined with an increase in PA to promote the greatest benefit. Secondly, the incidence of osteoarthritis (OA) is increased in overweight and obese individuals. When comparing the incidence of OA across BMI categories, those with a higher BMI are 6 times more likely to have unilateral, and 18 times more likely to have bilateral knee OA than those with a lower BMI (19). Obesity is a risk for the progression from unilateral to bilateral OA of the knee (20). People who are overweight in their younger years increase the risk of OA later in life (21). The symptoms of OA, which can severely restrict exercise and PA, decrease by over 50% with even small decreases in BMI ( $\geq 2$  kg/m<sup>2</sup>) (22). Therefore, even though cardiovascular benefits occur through exercise without weight loss, the prevention of painful, activity-limiting OA can allow increased activity throughout a person’s lifetime. Weight loss should be encouraged at the earliest age possible.

## Current Recommendations for PA (23)

- For diabetes prevention,  $\geq 150$  min/wk PA with diet-induced weight loss of 5–7% body weight.
- For glycemic control, weight maintenance and reduced risk of CVD for those with type 2 diabetes,  $\geq 150$  min/wk moderate-intensity and/or  $\geq 90$

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min/wk vigorous aerobic PA, at least 3 d/wk with no more than a consecutive 2 d without PA.

- For type 2 diabetes, in the absence of contraindications, resistance training, 3 times/wk, all major muscle groups, three sets of 8–10 repetitions, with a weight that cannot be moved greater than 8–10 times.

- For weight loss maintenance, 7 h/wk moderate or vigorous aerobic PA.

## Barriers to Exercise for Overweight and Obese Individuals

There are many barriers to exercise for all and even more for those who are overweight. Some barriers and possible solutions are provided in Table 1.

PA and exercise provide many cardio-metabolic benefits for the obese individual. However, weight loss through exercise alone is minimal. Prescribing the best exercise combined with diet, and explaining the likely results, may improve long-term success.

## References

1. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, Nathan DM. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med.* 2002; 346:393–403.
2. Healy GN, Dunstan DW, Shaw JE, Zimmet PZ, Owen N. Beneficial associations of physical activity with 2-h but not fasting blood glucose in Australian adults: the AusDiab study. *Diabetes Care.* 2006; 29:2598–2604.
3. Kavouras SA, Panagiotakos DB, Pitsavos C, Chrysoshoou C, Anastasiou CA, Lentzas Y, Stefanadis C. Physical activity, obesity status, and glycemic control: the ATTICA study. *Med Sci Sports Exerc.* 2007; 39:606–611.
4. Rana JS, Li TY, Manson JE, Hu FB. Adiposity compared with physical inactivity and risk of type 2 diabetes in women. *Diabetes Care.* 2007; 30: 53–58.
5. Boule NG, Haddad E, Kenny GP, Wells GA, Sigal RJ. Effects of exercise on glycemic control and body mass in type 2 diabetes mellitus: a meta-analysis of controlled clinical trials. [See comment]. *JAMA.* 2001; 286:1218–1227.
6. Boule NG, Kenny GP, Haddad E, Wells GA, Sigal RJ. Meta-analysis of the effect of structured exercise training on cardiorespiratory fitness in type 2 diabetes mellitus. *Diabetologia.* 2003; 46:1071–1081.
7. Thomas DE, Elliott EJ, Naughton GA. Exercise for type 2 diabetes mellitus. *Cochrane Database Syst Rev.* 2006; 3:002968.
8. Shaw K, Gennat H, O'Rourke P, Del Mar C. Exercise for overweight or obesity. *Cochrane Database Syst Rev.* 2006; 003817.
9. Kraus WE, Houmard JA, Duscha BD, Knetzger KJ, Wharton MB, McCartney JS, Bales CW, Henes S, Samsa GP, Otvos JD, Kulkarni KR, Slentz CA. Effects of the amount and intensity of exercise on plasma lipoproteins. *N Engl J Med.* 2002; 347: 1483–1492.
10. Whelton SP, Chin A, Xin X, He J. Effect of aerobic exercise on blood pressure: a meta-analysis of randomized, controlled trials. *Ann Intern Med.* 2002; 136:493–503.
11. Hu FB, Sigal RJ, Rich-Edwards JW, Colditz GA, Solomon CG, Willett WC, Speizer FE, Manson JE. Walking compared with vigorous physical activity and risk of type 2 diabetes in women: a prospective study. *JAMA.* 1999; 282:1433–1439.
12. Wei M, Gibbons LW, Kampert JB, Nichaman MZ, Blair SN. Low cardiorespiratory fitness and physical inactivity as predictors of mortality in men with type 2 diabetes. *Ann Intern Med.* 2000; 132: 605–611.
13. Church TS, Cheng YJ, Earnest CP, Barlow CE, Gibbons LW, Priest EL, Blair SN. Exercise capacity and body composition as predictors of mortality among men with diabetes. *Diabetes Care.* 2004; 27:83–88.
14. Klem ML, Wing RR, McGuire MT, Seagle HM, Hill JO. A descriptive study of individuals successful at long-term maintenance of substantial weight loss. *Am J Clin Nutr.* 1997; 66:239–246.
15. Schoeller DA, Shay K, Kushner RF. How much physical activity is needed to minimize weight gain in previously obese women? *Am J Clin Nutr.* 1997; 66:551–556.
16. Saris WH, Blair SN, van Baak MA, Eaton SB, Davies PS, Di Pietro L, Fogelholm M, Rissanen A, Schoeller D, Swinburn B, Tremblay A, Westerterp KR, Wyatt H. How much physical activity is enough to prevent unhealthy weight gain? Outcome of the IASO 1st stock conference and consensus statement. *Obes Rev.* 2003; 4:101–114.
17. Castaneda C, Layne JE, Munoz-Orians L, Gordon PL, Walsmith J, Foldvari M, Roubenoff R, Tucker KL, Nelson ME. A randomized controlled trial of resistance exercise training to improve glycemic control in older adults with type 2 diabetes. *Diabetes Care.* 2002; 25:2335–2341.
18. Dunstan DW, Daly RM, Owen N, Jolley D, de Courten M, Shaw J, Zimmet P. High-intensity resistance training improves glycemic control in older patients with type 2 diabetes. *Diabetes Care.* 2002; 25:1729–1736.
19. Hart DJ, Spector TD. The relationship of obesity, fat distribution and osteoarthritis in women in the general population: the Chingford Study. *J Rheumatol.* 1993; 20:331–335.
20. Spector TD, Hart DJ, Doyle DV. Incidence and progression of osteoarthritis in women with unilateral knee disease in the general population: the effect of obesity. *Ann Rheum Dis.* 1994; 53:565–568.
21. Felson DT. Epidemiology of hip and knee osteoarthritis. *Epidemiol Rev.* 1988; 10:1–28.
22. Felson DT, Zhang Y, Anthony JM, Naimark A, Anderson JJ. Weight loss reduces the risk for symptomatic knee osteoarthritis in women. The Framingham Study. *Ann Intern Med.* 1992; 116: 535–539.
23. Sigal RJ, Kenny GP, Wasserman DH, Castaneda-Sceppa C, White RD. Physical activity/exercise and type 2 diabetes: a consensus statement from the American Diabetes Association. *Diabetes Care.* 2006; 29:1433–1438.

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