



## Neonatal Graves' Disease: Atypical Course with Direct Hyperbilirubinemia and Persistent Hypothyroidism

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### Case Presentation

A 3-d-old girl born at 30 wk was evaluated because of tachycardia, elevated liver transaminases, and direct hyperbilirubinemia soon after birth. Her mother had a history of Graves' disease treated with radioactive iodine 5 yr before the pregnancy and replaced with L-T<sub>4</sub> 112 µg daily. Maternal thyroid function tests during pregnancy revealed a TSH of 7.92 µIU/ml and FT<sub>4</sub> of 1.14 ng/ml at 10 wk gestation, and a TSH of 3.39 µIU/ml and FT<sub>4</sub> of 0.92 ng/ml at 26 wk gestation. Besides progressive tachycardia in the neonate and liver function abnormalities, there were no other symptoms of hyperthyroidism such as diarrhea, tremors, or heart failure. The rest of the neonatal intensive care unit course was significant for parenteral nutrition, a negative sepsis evaluation, negative titers for TORCH (toxoplasmosis, rubella, cytomegalovirus, and herpes), and a normal hepatic ultrasound. Chest x-ray revealed cardiomegaly without effusion. There were no other family members with Graves' disease or other autoimmune disorders.

On physical exam, the newborn's birth weight of 1700 g, birth length of 41.5 cm, and head circumference of 29 cm were appropriate for gestational age. The neonate was tachycardic and tachypneic, with heart rate of 184 beats/min and respiratory rate of 76, respectively. She had a diffusely enlarged and palpable thyroid gland without bruits. There was no heart murmur,

hepatomegaly, increased neuromuscular tone, tremor, or clonus.

Newborn's thyroid function tests were done on d 2 and revealed a TSH of 0.02 µIU/ml and FT<sub>4</sub> of >12 ng/ml. Liver transaminases rose to alanine aminotransferase (AST) of 76 and 336 U/liter, respectively, and total bilirubin peaked at 12.5 mg/dl with direct bilirubin of 10.6 mg/dl on d 4 of life (see Table 1).

In light of the maternal Graves' disease, symptoms and signs of hyperthyroidism, and highly elevated FT<sub>4</sub> on laboratory evaluation, a diagnosis of neonatal thyrotoxicosis due to maternal Graves' disease was made. Treatment with propylthiouracil (PTU), Lugol's solution, and propranolol was started, as well as ursodiol and Vitamins A, D, E, and K (ADEK) supplementation (Table 1).

D.L. had an interesting treatment course, characterized initially by direct hyperbilirubinemia and persistent hyperthyroidism, and thereafter by prolonged hypothyroidism. Maternal thyroid-stimulating Ig (TSI) postpartum was 481% (normal < 129%). The newborn initially required Lugol's solution, in addition to PTU and propranolol, to control her thyrotoxicosis. She had a thyroid ultrasound that showed a normal-size gland in a normal location. By 4 wk of age, she required only L-T<sub>4</sub> supplementation of 8.8 µg/kg-d and PTU. By 12 wk of life, TSH receptor antibodies were negative, and PTU, ursodiol, and ADEK were discontin-

ued. However, our patient continued to be hypothyroid, requiring L-T<sub>4</sub> supplementation until the present age of 12 months, long after maternal antibodies have cleared.

### Discussion

Maternal Graves' disease is the most common cause of neonatal hyperthyroidism. It is a rare condition, occurring in only 1–2% of women with active and inactive Graves' disease, who in turn make up only about 0.2% of females; thus, the incidence is estimated to be only one in 25,000–50,000 neonates. However, it is a serious, sometimes life-threatening disorder and can compromise both metabolic status and neural development of the newborn (1).

The mechanism responsible for a newborn developing Graves' hyperthyroidism lies in the TSI, which is a stimulating TSH receptor antibody that crosses the placenta (2, 3). Even in women who have undergone a thyroidectomy or radioactive iodine treatments in the past, as is in the case of this infant's mother, the antibodies may still be present. Many endocrinologists have noted that one of the best predictors of neonatal Graves' disease is the level of TSI in the mother during the third trimester; a level above 250% requires close monitoring of the neonate, and that above 500% strongly correlates with neonatal thyrotoxicosis (1, 3–5). However, this finding has not been embraced by the American College of

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## LETTER FROM THE CHAIR

With this issue of *EndoTrends*, I am pleased to announce a major reorganization of the administrative structure of EFF. After 10 years of tireless, dedicated, and altogether successful service to EFF as Executive Director, Marilyn Fishman has retired. We will always remember Marilyn, not only for these qualities, but also for the great personal interest that she took in all of you. She will be a hard act to follow.

We are delighted to announce that Association Resources, Inc., a management company with headquarters in West Hartford, CT, and a branch in Washington, DC, has been selected to provide executive leadership to and management of EFF. I have known Sue and Peter Berry, co-presidents of AR, for many years in connection with their work with the International Society of Clinical Densitometry. They are a first-class organization that will carry on in the tradition of Marilyn. Anne Mercer of AR will become our Executive Director. On behalf of the leadership of EFF and all of you, I am pleased to welcome the AR team and Anne to our family. The EFF headquarters will be in Washington, DC. Anne can be reached at (877) 877-6515 extension 205, or by e-mail at [amercer@endocrinefellows.org](mailto:amercer@endocrinefellows.org). Our new mailing address is 1310 19th Street, NW, Washington, DC 20036.

Sincerely,  
John P. Bilezikian, M.D.  
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# EndoTrends

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## Neonatal Graves' Disease: Atypical Course with Direct Hyperbilirubinemia and Persistent Hypothyroidism

Obstetrics and Gynecologists (ACOG). According to the 2003 ACOG guidelines on thyroid disease in pregnancy, routine evaluation of maternal TSI levels is not recommended. However, maternal TSI as an important and useful marker of newborn outcome. Had the maternal TSI level of 481% been discovered prenatally, treatment with PTU would have been considered and, through transplacental transfer, would likely have prevented thyrotoxicosis in this newborn.

Clinical features of neonatal Graves' disease, both pre- and postnatal, are listed in Table 2; manifestations seen in our infant are shown in *bold*. The hyperbilirubinemia of neonatal Graves' disease is classically indirect. However, other reports have shown isolated conjugated hyperbilirubinemia, which was attributed solely to neonatal thyrotoxicosis (6). There are several theories behind the direct hyperbilirubinemia. One stems from congestive heart failure (CHF) that can accompany hyperthyroidism, usually in adults; the CHF then leads to liver dysfunction, cholestasis, and direct hyperbilirubinemia. Another hypothesis is that the hyperthyroid state leads to increased hepatic oxygen

consumption without sufficient hepatic circulation, in turn causing liver dysfunction and conjugated hyperbilirubinemia (6). The elevated AST in the case of this infant supports these theories of liver dysfunction.

In most studies of neonatal Graves' hyperthyroidism, infants become both clinically and biochemically euthyroid by 12 wk of life, when the maternal TSI is cleared from the newborn's circulation (1, 3). This was not the case with our infant, where hypothyroidism ensued and continued into the age of her eighth month. A mechanism proposed by Matsuura *et al.* (7) is that of transient hypothyroidism, where the fetal thyroid axis is suppressed *in utero* by the high  $T_4$  from the maternal circulation. In a Dutch study by Kempers *et al.* (8) pituitary dysfunction and hypothyroidism was detected in 17 out of 18 neonates born to mothers with Graves' disease. There, too, the prevailing hypothesis was that of hyperthyroid fetal environment, impairing the normal maturation of hypothalamic-pituitary-thyroid axis. Therefore, both hypothalamus and pituitary are hyporesponsive to falling levels of  $FT_4$ , as the

TSI and the accompanying hyperthyroidism resolve. This process was found to take up to a year, and it is unknown what subtle changes in the thyroid axis distinguish those neonates who exhibit this persistent central hypothyroidism. Kempers *et al.* (8) also suggested a TRH test to evaluate the maturity of the thyroid axis, where a normal TSH response could guide discontinuation of  $L-T_4$  supplementation. Higuchi *et al.* (9) presented three cases, 27–37 wk of gestation, where all three neonates had central hypothyroidism confirmed by a TRH test.

Prematurity is an important factor likely contributed to this infant's ongoing hypothyroidism after her hyperthyroidism has resolved. Because normal maturation of thyroid axis is not complete until approximately 32 wk gestation, it is not surprising that, initially, the infant's already immature axis would be further suppressed by high levels of maternal circulating  $T_4$ . In a study by Smith *et al.* (10), inhibitory TSH receptor antibodies were suspected to cause hypothyroidism. The authors found four out of

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**Table 1**  
**Thyroid and Liver Function Test Results and Respective Interventions**

Age	TSH (mIU/ml)	ft <sub>4</sub> (ng/dl)	tt <sub>4</sub> (µg/dl)	tt <sub>3</sub> (NG%)	Thyroid AB	ALT/AST (U/liter)	BILI T/D (mg/dl)	Intervention
DOL2	0.02		>12			39/218	10.1/7.7	PTU 7 mg/kg · d Propranolol 2 mg/kg · d Ursodiol 15 mg/kg · d ADEK 1 ml
DOL 4				518	TSI: 481	73/336	12.5/10.6	Lugol's solution 8 mg (ldr) daily
DOL 8	0.03	1.59	4.8	64		58/143	7.5/6.8	Stopped Lugol's
DOL 11						65/247	6.0/4.3	Stopped PTU, Propranolol
DOL 12	0.01		2.1	85				Synthroid 15 µg/kg · d
DOL 15	0.03		>30	689		131/554	9.8/7.7	Stopped Synthroid Restarted propranolol
DOL 18	0.04		29.8	584	TSH Rec. Ab: 390	130/385	12.4/11.6	Restarted PTU
DOL 22			4.7	88		93/194	9.5/8.5	Decreased PTU 3.5 mg/kg · d Stopped propranolol
DOL 24			3.3	80		67/133	7.9/7.0	Restarted Synthroid 15 µg/kg · d
DOL 29	0.01		6.8			54/113	6.5/5.6	
DOL 32	<0.01	1.8	5.8	102				
DOL 33					TSH Rec. Ab: 54.5 TBG: 11.5			
DOL 39	<0.01	1.39		87			5.4/4.4	Decreased Synthroid 10 µg/kg · d Decreased PTU
7 wk	0.02	1.16		94				
9 wk	0.03	1.31		93	TSH Rec. Ab: 14	41/56	1.0/0.5	Stopped PTU, Ursodiol, ADEK
12 wk	0.03	1.36	6.1	91	TSH Rec. Ab: 7			
16 wk	0.01	1.96	8.9	103				
20 wk	0.01	1.86	8.8	116				
26 wk	0.01	1.98	9.2	101				
30 wk	<0.01	1.34	6.6	102				
8 months	0.02	1.53	6.6	91				Synthroid 6 µg/kg · d
10 months	0.06	1.1	5.1	106				Synthroid 5 µg/kg · d
12 months	0.22	1.3		118				Synthroid 4 µg/kg · d

Ab, Antibody; ADEK, vitamins A, D, E and K; ALT, alanine aminotransferase (1–53 U/liter); AST, aspartate aminotransferase (1–150 U/liter); Bili T/D, bilirubin total direct; DOL, day of life; FT<sub>4</sub>: Free T<sub>4</sub> (0.89–1.76 ng/dl); PTU, Prophythiouracil; TSH, (0.35–5.0 µIU/ml); TSH Rec. Ab., TSH receptor antibody (<10 U/ml); TSI (0–129%); TT<sub>3</sub>, total T<sub>3</sub>, (79–149 ng%); TT<sub>4</sub>, total T<sub>4</sub>, (4.5–10.9 ng/dl).

seven premature neonates, gestational age between 25 and 36 wk, to have biochemical hypothyroidism, and one infant exhibited prolonged hypothyroidism (duration not specified). Because our laboratory evaluation did not specifically test for TSH-receptor blocking antibodies,

it is unknown whether these antibodies played a role.

This case of neonatal Graves' disease in a 30-wk premature neonate underscores the importance of screening and treatment of mothers with history of Graves'

disease, particularly by performing a TSI assay in addition to thyroid function tests. The atypical conjugated hyperbilirubinemia further confirms this feature as one of the manifestations of neonatal hyperthyroidism, supporting prior reports. More studies looking into the biochemical mechanisms responsible for this direct hyperbilirubinemia in neonates with maternal Graves' disease are needed. Finally, the prolonged hypothyroidism, likely central and caused by suppression of the thyroid axis by maternal hyperthyroidism, may have been further exacerbated by our infant's prematurity. Her current L-T<sub>4</sub> supplementation will optimize growth and neural development at this critical time of infancy. Modalities such as TRH testing and evaluating for blocking TSH-receptor antibodies would be important to consider in such cases of suspected central hypothyroidism associated with neonatal Grave's disease.

**Table 2**  
**Clinical Manifestations of Fetal and Neonatal Graves' Hyperthyroidism**

Fetal	Neonatal
Intrauterine growth restriction	Small for gestational age
Nonimmune fetal hydrops	<b>Premature birth</b>
Craniosynostosis	Microcephaly/frontal bossing/triangular facies
Goiter	Hyperkinesis/irritability/poor sleep
Tachycardia	Diarrhea
Cardiomegaly/cardiomyopathy	Vomiting
Fetal demise	Failure to thrive
	<b>Cardiomegaly</b> /cardiomyopathy/arrhythmia/cardiac failure
	Flushing/diaphoresis
	Goiter, small and diffuse
	Hypertension (pulmonary/systemic)
	Cholestasis/hepatosplenomegaly
	Ophthalmopathy/exophthalmos
	<b>Hyperbilirubinemia</b> (indirect/ <b>direct</b> )
	Thrombocytopenia
	Hyperviscosity

Items in *bold* represent manifestations found in the neonate presented in this case report.

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# Advanced Sexual Maturity Rating and Growth Failure in a 14-Year-Old Male

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## Introduction

Growth disorders are one of the most common referrals to a pediatric endocrinologist. In many respects, a child's growth may be viewed as a mirror into his/her general health status, and abnormal growth velocities are often the sequelae of both endocrine and nonendocrine disease manifestations.

In addition, apart from pathologic causes of short stature, there may be variations of normal growth. Constitutional delay of growth, a diagnosis of exclusion, is a normal variant and may display familial tendencies in its occurrence. Since growth and puberty are usually inextricably linked, disorders that affect one may simultaneously affect the other. Hence, by this tenet, a failure of growth progression should be associated with a delay of Tanner staging. When Tanner staging and growth are discordantly affected, we need to look at more uncommon presentations of common disorders.

We report a case of advanced Tanner staging in the presence of simultaneous growth failure in a 14-yr-old male. This seemingly paradoxical finding may be explained by a unifying diagnosis.

## Case Presentation

A 14-yr-old Caucasian male with no prior medical conditions was referred to the Endocrine Clinic for acquired severe short stature possibly due to a brain tumor. Historically the adolescent had not seen a primary care physician in over a 5-yr period. At a new patient visit, his mother expressed concern about the child's failure to grow over the last 3 yr. Over a 2- to 3-yr period, he had become the shortest child in his class. His mother also stated that he had a poor appetite when compared with other teenage relatives. He also had a history of cold intolerance but no change in skin texture or pigmentation. He had no history of fatigue, poor concentration, emesis, constipation, diarrhea, polyuria, or polydipsia. He had no complaints of headaches or visual changes. The patient had developed pubic hair a few years ago and had been using deodorant for the last year.

A single point on the growth curve supplied by his original primary care physician showed him near the 50th percentile for both weight and height several years ago. Bone age examination performed at his current primary care physician's office revealed discordance when compared with chronologic age. At a chronologic age of 14 yr and 1

month, the bone age was representative of an 8-yr-old male.

Past medical history revealed one hospitalization for a pneumonia and also a history of mild intermittent asthma. The latter was managed by albuterol use without the need of oral or inhaled steroid use. Developmental history and family history were unremarkable. Calculated mid parental height was 5 ft 10.5 in. (50th–75th percentile).

Physical examination revealed a male who looked younger than his stated age in no apparent distress. BP was 86/59 with a pulse of 61. Height was 133 cm (−4 sd below the mean for age), and weight was 33.8 kg (less than 5th percentile for age). He had no obvious dysmorphic features. He had no palpable thyroid gland. He was Tanner stage 5 for pubic hair and Tanner stage 5 for genitalia with a testicular volume of 25 cc. His patellar deep tendon reflexes were 3+ bilaterally. His skin was extremely dry and sallow in appearance. Remainder of the physical exam was unremarkable.

## Clinical Course

The patient was found to have significant primary hypothyroidism second-

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**Table 1**  
**Laboratory Data**

Test	Value	Ref. range
Basic metabolic panel	Within normal limits	
Complete blood count		
Hemoglobin	10.9 g/dl	14.5 g/dl
Hematocrit	32 l/l	43 l/l
White blood cell	4.9	4–11
Platelets	321	Greater than 150
ESR	7 mm/h	0–15 mm/h
Free T <sub>4</sub>	<0.1 ng/dl	0.8–2.0 ng/dl
Total T <sub>4</sub>	0.4 µg/dl	4.5–10 µg/dl
TSH	353 mIU/ml	0.5–4.5 mIU/ml
Anti-thyroglobulin antibody	885 IU/ml	0–40 IU/ml
Anti-thyroid peroxidase antibody	>1,000 IU/ml	0–35 IU/ml
Testosterone	135 ng/dl	7–490 ng/dl
FSH	1.7 IU/liter	Normal
LH (ultrasensitive)	0.8 IU/liter	Normal
Prolactin	26	2–14 ng/ml
IGFBP3	1.9 µg/ml	3.3–9.8 µg/ml
IGF-I	65 ng/ml	228–957 ng/ml
Cortisol (pm)	18.6 µg/dl	

have a weak intrinsic FSH activity and hence cause stimulation of the gonads. However, even when elevated, pituitary gonadotropins appear not to be the responsible bio-active moiety causing sexual precocity (3). In addition, high levels of TSH have been shown in *in vitro* models to cross-react with the human FSH receptor. Intrinsically, human TSH possesses very little FSH activity; however, relatively high concentrations are needed to elicit an FSH-like response (4). Decrease in testicular size can also occur after treatment with thyroid hormone replacement therapy and normalization of TSH level as illustrated in this patient.

Reports in the literature indicate that treatment of juvenile hypothyroidism may result in rapid bone age advancement. As a result, there may be permanent height loss if therapy is started shortly before or during puberty (5). With puberty beginning, concomitant sex steroid secretion often triggers rapid epiphyseal fusion, thus resulting in a compromised final adult height. As a result of the early pubertal gonadotropin levels in our patient as well as the increase in testosterone to 365 ng/dl, there was concern that height attenuation would occur due to rapid progression through puberty. This would ultimately prevent him from achieving his full targeted height potential as calculated based on his genetic potential.

There have been case reports evaluating the use of GH and GnRH agonist in addition to L-T<sub>4</sub> in the attainment of normal adult height in patients with Hashimoto's thyroiditis (6). This strategy has been utilized in various medical conditions in which there may be a compromised final height and has been found to improve one's chances of attaining a final height close to that predicted based on the child's genetic potential. The overall rationale of using GnRH analog in conditions like central precocious puberty, congenital adrenal hyperplasia, and idiopathic short stature is to prolong the period of growth while halting pubertal progression and bone age advancement. This also ultimately will delay epiphyseal fusion.

ary to Hashimoto's thyroiditis. The decreased IGF-I and IGFBP3 were due to GH deficiency secondary to a hypothyroid state. The elevated prolactin was thought to be secondary to the elevated TSH. Thyroid hormone replacement was initiated at 25 µg of L-T<sub>4</sub> for 4 d, 50 µg for 4 d, and then 75 µg orally daily with significant improvement in thyroid hormone function. Laboratory results obtained 2 wk after thyroid hormone replacement revealed a total T<sub>4</sub> of 10 mg/dl with a TSH of 90.2 [reference (ref.) range 0.34–5.6]; see Table 1. The patient subsequently returned to clinic 2 months later. His level of energy had significantly improved. In addition, he had an increase in appetite that was associated with weight loss. Physical exam: height 134.8 cm (height gain over 2 months was 1.8 cm for an annualized growth velocity of 10.8 cm/yr). Weight 31.9 kg (decreased by 1.9 kg). Both parameters were less than the 5th percentile for age. Genitourinary exam showed decrease in testicular volume to 20 ml bilaterally. Skin with normal complexion. Thyroid function tests normalized with TSH of 1.29 (ref. range 0.5–4.5 mIU/ml), free T<sub>4</sub> of 0.9 (ref. range 0.8–2.0 ng/dl), and total T<sub>4</sub> of 4.8 (4.5–10 µg/dl) after 2 months of therapy with L-T<sub>4</sub>. Total testosterone was increased to 365 ng/dl (ref. range 7–490) and LH of 1.3 IU/liter was pubertal with FSH of 1.6 IU/liter. Therapy with a GnRH analog, Peds Depot Lupron 11.25 mg, im every month was initiated in addition to daily L-T<sub>4</sub> as a consequence. This was initiated to prevent an anticipated rapid

progression of his bone age while receiving replacement thyroid hormone therapy.

## Discussion

Severe hypothyroidism may be associated with profound growth retardation and height attenuation secondary to incomplete catch-up growth after longstanding treatment for juvenile hypothyroidism (1). It is usually associated with delayed bone age and delay in sexual maturation. However, hypothyroidism rarely may be associated with iso-sexual precocity. In this instance, there is often no simultaneous advancement of bone age. This is in distinction to what occurs in other conditions associated with pubertal advancement such as congenital adrenal hyperplasia, precocious puberty, and hyperthyroidism where there is concordant advancement in bone age and increased rate of growth. Iso-sexual precocity in our patient was manifested by discordance between bone age and Tanner staging. Van Wyk and Grumbach originally postulated a syndrome of sexual precocity seen in juvenile hypothyroidism in 1960. This unusual syndrome of sexual precocity and juvenile hypothyroidism has also been called an "overlap" syndrome or Van Wyk-Grumbach syndrome (2). In this syndrome, there is a hormonal "overlap" and the negative feedback occurring as a result of thyroid hormone deficiency causes increase in TSH and prolactin levels. The TSH elevation has been postulated to

## Conclusion

This case is illustrative of the paradox that advanced sexual maturity may occur in the setting of growth failure. Profound hypothyroidism as shown above may rarely be associated with discordance between physical and sexual development. Also, while receiving thyroid hormone replacement therapy, there may be rapid pubertal advancement associated with epiphyseal fusion and resultant height attenuation. The use of GnRH agonist must be considered in a timely fashion

to avoid further compromise of the height lost during the existing period of profound hypothyroidism.

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# Adrenocorticotrophic Hormone-Secreting Pheochromocytoma Presenting as a Central Nervous System Vasculitis

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## Case Report

A 33 yr-old female presented to an outside hospital with new-onset headache and left-sided facial droop and upper and lower extremity weakness. Evaluation for infectious, cardiac, and hypercoagulable etiologies—including lumbar puncture, cardiac echocardiogram, and carotid Doppler ultrasound—was negative. Antinuclear antibody testing was positive at a ratio of 1:160, magnetic resonance imaging (MRI) of the brain revealed acute left basal ganglia infarct, and computed tomography (CT) angiogram of the cerebral vessels showed narrowing suggestive of vasculitis. Her neurologic deficits resolved within 24 h, she was given the diagnosis of central nervous system (CNS) vasculitis, and prednisone and cyclophosphamide therapies were initiated before discharge to home.

One month after her initial presentation, the patient again presented with neurologic deficits, this time manifesting right-sided weakness. She was transferred to a local tertiary care hospital where MRI showed acute left caudate and left frontal ischemic changes. Magnetic resonance spectroscopy showed no evidence of neoplasm. Angiograms showed small-

caliber cerebral vessels with alternating beaded stenosis involving the left anterior cerebral artery (ACA), middle cerebral artery (MCA), posterior inferior cerebellar artery, posterior cerebral artery (PCA), and right ACA, MCA, and PCA arteries with normal mesenteric and renal vasculature. More extensive infectious and rheumatologic work-up—including lumbar puncture, myeloproliferative antibody, neutrophil antibody, smith antibody, Epstein-Barr virus PCR, and herpes simplex virus PCR—were negative. She was treated with iv methylprednisolone with neurologic improvement and again discharged on prednisone and cyclophosphamide.

The following months were marked by progressive decline in memory, cognitive function, and muscular strength. Transient focal neurologic deficits continued to occur. A weight loss of 100 lbs and diabetes mellitus, attributed to chronic corticosteroid use, developed. Repeated admissions for new neurologic deficits were punctuated by tachycardia, hypertension, and radiologic studies showing increasing cerebral ischemia and progression of cerebral vasculitis despite escalations in cyclophosphamide and prednisone doses to a maximum of 175

mg and 80 mg daily, respectively. Brain biopsy showed no active vasculitis and no malignancy. CT of the chest captured a 2.6- × 3.1-cm left adrenal adenoma and 2.3- × 3.0-cm right adrenal mass, incompletely characterized. Imaging also showed bile duct obstruction and the patient underwent cholecystectomy 7 months after initial presentation. During each hospitalization, she was treated with iv methylprednisolone and discharged to home on prednisone and cyclophosphamide.

One year after her initial presentation, the patient developed acute confusion and visual hallucinations. She was found to have a gluteal decubitus with cultures of the wound growing *Staphylococcus aureus* and *Escherichia coli*. She was treated with multiple rounds of iv antibiotics with improvement in the size and appearance of the decubitus, but her weakness worsened, resulting in readmission to an outside hospital followed by transfer to our tertiary hospital.

Upon admission, multiple neurologic abnormalities including orientation only to person and place, loss of recent and remote memory, left lateral visual field

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cut, loss of light-touch sensation on the left, and marked lower extremity weakness resulting in inability to ambulate were noted. Other notable physical findings included obesity with an admission weight of 244.2 lbs (111 kg), rounded facies, thinning of scalp hair, hirsutism, ptosis with periorbital edema, linear areas of ecchymosis on her upper extremities, and blanchable erythematous macules on her lower extremities. A hematocrit of 31.4% and iron studies consistent with anemia of chronic disease were noted. White blood cell count, general chemistry, liver functions, coagulation studies, and thyroid hormone were normal.

It was initially felt her cushingoid appearance was related to the year-long course of prednisone. The cyclophosphamide was discontinued upon admission, but the prednisone continued at her current outpatient dose of 50 mg daily. Dermatology was consulted for the skin lesions and biopsies showed early thrombi consistent with vasculopathy. MRI of the brain showed marked progression of white matter gliosis, more prominent in the right hemisphere, diffuse atrophy, and diminished caliber of cerebral vessels consistent with progressive vasculitis. Electroencephalogram was abnormal with generalized slowing and absence of normal background activity, suggestive of encephalopathy. Repeat brain biopsy again showed no malignancy or active vasculitis, and cultures were negative for infection. Concurrent right deltoid muscle biopsy was also negative for active vasculitis.

Her hospital course was complicated by Varicella-zoster viral infection above her right eye requiring acyclovir therapy and *Pseudomonas aeruginosa* urinary tract infection treated with levofloxacin. Because of persistent hyperglycemia, hypertension, and tachycardia during the hospitalization, serum metanephrines were checked and found to be elevated at 0.54 nmol/liter, as were serum normetanephrines at 4.19 nmol/liter. Chromogranin A was less than 200 ng/ml, CRH was 141 pg/ml, ACTH was 146 pg/ml, and cortisol was 127 mg/dl. Twenty-four-hour urinary vanillylmandelic acid was 26.4 mg, epinephrine 48 µg, norepineph-

rine 1020 µg, metanephrines 118 µg, normetanephrines 3773 µg, and urinary free cortisol 5850 µg. An abdominal MRI showed a 4.0- × 3.6-cm left adrenal mass with loss of signal on out-of-phase images consistent with adenoma and a 3.8- × 3.3-cm right adrenal mass, slightly hyperintense on both T1- and T2-weighted images without evidence of signal loss on out-of-phase imaging. This was not consistent with adenoma and felt to represent either adrenal hemorrhage or neoplasm. After pretreatment with potassium iodide, meta-iodobenzylguanidine scintiscan (MIBG) using 0.5 µCi I-131 was performed. This showed no evidence for adrenal or extra-adrenal sites of increased MIBG activity.

Clinically, the patient's neurologic status continued to deteriorate, with worsening of orientation, new dysphagia and dysarthria, and increased somnolence. Because of this, the decision was made to pursue the right adrenal mass as the most likely etiology for the pheochromocytoma and hypercortisolism. The patient had been treated with labetalol throughout her hospital course, α-blockade with phenoxybenzamine was added pre-operatively. Laproscopic right adrenalectomy was performed. The patient tolerated the procedure well, with immediate improvement in hypertension and tachycardia. She was placed on 60 mg iv methylprednisolone three times daily in the immediate post-operative period, which was to be change to oral corticosteroids and titrated down slowly over the next several months. Pathology from the right adrenal gland showed positive immunohistochemical staining for synaptophysin and chromogranin consistent with pheochromocytoma. Immunohistochemical staining for ACTH was also positive. CRH staining could not be performed.

Postoperatively, serum ACTH fell to 3 pg/ml, metanephrines to <0.15 nmol/liter, and normetanephrines to 0.26 nmol/liter. Cortisol was not measured as the patient continued to require corticosteroid therapy. Clinically, resolution of tachycardia and hypertension were noted, as was improvement of the macular rash present at admission. One month after adrenalectomy the patient remained without new

neurologic deficits, was verbally interactive, ambulating with assistance, and participating in physical therapy.

## Discussion

In this case, the diagnosis of Cushing's syndrome was clearly delayed due to the administration of corticosteroids to treat suspected CNS vasculitis. Corticosteroid use is a common cause for ACTH-independent Cushing's syndrome, manifesting with typical cushingoid symptoms such as rounded facies, thinning skin, ecchymosis, and hyperglycemia. This patient demonstrated all such symptoms. However, the patient also experienced a 100-lb loss during her 12-month course, a sign more typically seen with ectopic Cushing's syndrome. Moreover, once checked, her CRH and ACTH levels were elevated in the presence of exogenous corticosteroid use, confirming an endogenous source for her hypercortisolism.

This patient's initial presentation was actually that of headaches and transient neurologic deficits. Investigation of these complaints revealed cortical infarct on MRI of the brain and cerebral vessel narrowing with intraluminal beading on CT angiogram consistent with cerebral vasculitis. These findings were repeated on multiple examinations. Despite this, treatment with a typical immunosuppressive regimen of cyclophosphamide and corticosteroids failed to induce remission and, in fact, the patient's condition continued to deteriorate despite aggressive therapy. No active vasculitis was ever found on repeated brain biopsies. Tissue ischemia in the setting of pheochromocytoma has been previously attributed to catecholamine-induced vessel narrowing. Angiographically, this narrowing resembles vasculitis, however histologically no evidence of a vasculitic process is seen (7, 8). It has been postulated the radiologic changes actually represent catecholamine-induced vasospasm rather than vasculitis; thus, the absence of histologic changes on biopsy. This clinical scenario is characterized by failure of the vasculitis-like symptoms and radiologic imaging to respond to typical therapies, but reversal of symptoms with resection of the pheochromocytoma and has been termed "pseudovasculitis" (7-9).

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The lack of cytologic evidence of vasculitis and the rapid neurologic improvement seen after resection of the pheochromocytoma, would suggest the neurologic deficits and radiologic findings in this case are consistent with a diagnosis of CNS pseudovasculitis due to pheochromocytoma.

The natural course of the angiographic changes and symptoms of CNS pseudovasculitis are unknown; however, CNS pseudovasculitis due to pheochromocytoma has been shown to result in cerebrovascular accidents and intracranial hemorrhage if left untreated. The appropriate treatment of these patients is unknown, but resolution of angiographic abnormalities and clinical improvement have been seen with resection of the pheochromocytoma, suggesting surgical therapy is the treatment of choice for pheochromocytoma-induced CNS pseudovasculitis (7, 10, 11).

To date, only one other case of pheochromocytoma associated with cerebral vasculitis and causing ectopic Cushing's syndrome has been reported (7). That case involved a woman diagnosed during pregnancy who ultimately succumbed to sepsis complicated by disseminated intravascular coagulation. Our case is unique in that the patient demonstrated not only elevated ACTH levels but also elevated CRH levels. Immunohistochemical staining confirmed ectopic production of ACTH by the pheochromocytoma. Unfortunately, we did not have the capability

to perform immunohistochemical staining for CRH on tissue from the pheochromocytoma. However, ACTH elevations and subsequent hypercortisolism due to hypothalamic-mediated CRH hypersecretion would not have resolved with resection of the pheochromocytoma. Our patient showed neither hypothalamic or pituitary abnormalities on cranial imaging and had resolution of her ACTH excess following adrenalectomy, suggesting that the pheochromocytoma was the source of the excess CRH. Immunohistochemical staining of the pheochromocytoma for CRH would confirm this. A review of the literature reveals a case report of co-secretion of CRH and ACTH from a malignant gastrinoma; however, if CRH immunohistochemical staining in this case proved positive, this would be the first reported case of a pheochromocytoma co-secreting both CRH and ACTH (12).

This case highlights a rare but important cause of hypertension and neurologic deficits in previously healthy individuals and underscores the importance of considering pheochromocytoma when pursuing an etiology for ectopic Cushing's syndrome. Additionally, it raises the possibility of a pheochromocytoma co-secreting both CRH and ACTH, an etiology of ectopic Cushing's syndrome not previously reported.

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## Anne L. Mercer Named New Executive Director of the Endocrine Fellows Foundation



The Board of Directors of the Endocrine Fellows Foundation recently selected the management company of Association Resources, Inc. as EFF's new headquarters.

Anne Mercer began her position as Executive Director on October 20, 2008, stepping into the position previously held by Marilyn Fishman for many years.

A Virginia native, Anne has concentrated her association management career in the Washington, DC, area, headquarters for many national and international associations. Her association experience includes trade, educational, sport, and, most recently, medical societies. Working her way up the management ladder

to the position of executive director, Anne had the opportunity to work in several association specialties, including membership, meetings, fundraising, publications, administration and finance. Anne brings this knowledge to EFF at a time when we are hoping to expand our outreach efforts and services to endocrine Fellows. Anne graduated from the University of South Carolina with a B.A. in Journalism and received an M.A. in American Studies from George Washington University in 2004.



# Hypercalcemia in a Patient with Nephrogenic Systemic Fibrosis

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## Introduction

Nephrogenic systemic fibrosis (NSF) has received increasing attention since it was first reported in 2001 as a scleromyxedema-like skin reaction in patients with renal failure (1). It has been linked to gadolinium contrast material used for magnetic resonance imaging and is associated with significant morbidity and, in some cases, death (2). One case of hypercalcemia and NSF has been documented in the past. Otherwise, little is known about how hypercalcemia may be associated with NSF. The following case report describes a patient with NSF who developed marked hypercalcemia. Potential etiologies are considered.

## Case Report

A 69-yr-old woman with recently diagnosed hepatitis A-induced fulminant hepatitis and acute renal failure presented with hypercalcemia of unknown etiology. Four weeks before the onset of hypercalcemia, she developed fulminant liver failure most likely attributed to recently acquired hepatitis A after a trip to South America. At the time of her hospitalization, she was encephalopathic and in renal failure. She was intubated for airway protection and dialyzed. Dialysis was discontinued after 5 wk when adequate renal function returned. The patient's liver disease was treated conservatively. Magnetic resonance imaging of the abdomen with gadolinium contrast showed periportal edema consistent with acute liver disease. Four weeks into her hospital course, she developed hypercalcemia. There was no history of total parental nutrition, calcium, or vitamin D administration either during the hospitalization or earlier. She had never received a thiazide diuretic. There

was no history of nephrolithiasis or fracture.

Her past medical history included a cerebrovascular accident without residual neurologic abnormalities, hypertension, hyperlipidemia, lumbar spine disc disease and a venous spinal infarction in connection with a lumbar interbody fusion 6 yr previously. The spinal infarct rendered her incontinent of urine as well as with residual sensory and proprioceptive loss in both feet and legs. Her medications in the hospital included Rifaximin, Ursodiol, Cholestyramine, Plavix, Thiamine, folic acid, Darbopoietin, and Bacitracin ointment. Linezolid and Fluconazole had been discontinued 10 d earlier. She denied any history of alcohol or tobacco use and had no family history of hypercalcemia.

On transfer to the rehabilitation service, she reported increasing activity, including walking with an assisted device. On physical exam, she was alert and oriented with good historical recall. She had icteric sclerae. The lungs, heart, and abdomen were normal. On neurologic exam, she had decreased motor strength below both knees with spastic reflexes bilaterally. Other than jaundice, there were no other skin findings.

Calcium levels were in the low- to mid-normal range until 4 wk into hospitalization when they rose to 11.2 to 13.6 mg/dl (corrected for albumin). PTH (17 pg/mol) and PTHrP (<0.2 pmol/liter) were normal but the 25-hydroxy- (22 ng/ml) and 1,25-dihydroxyvitamin D (4 pg/ml) levels were low. Other causes for hypercalcemia, including vitamin A toxicity, adrenal insufficiency, rhabdomyolysis, hyperthyroidism and multiple myeloma were ruled out (see Table 1).

Urinary calcium was 191 mg/24 h. Markers of bone turnover were elevated; bone-specific alkaline phosphatase activity was 32.0  $\mu$ g/liter and urinary N-Telopeptide excretion was 149 nM. A technetium bone scan demonstrated two foci of increased radiotracer uptake in the calvarium. Additionally, there was widespread soft tissue calcification in the left arm, and bilaterally in the buttocks and thighs. Given the bone scan findings, there was initial concern for calciphylaxis, but this possibility could not be pursued by skin biopsy because of a coagulopathy.

Five weeks into the hospital course, she developed bilateral cobble-stoning and dimpling of the skin on the upper and lower extremities, proximal and distal to the elbows (Fig. 1) and the buttocks. She reported pruritus over affected areas. On palpation, the skin was woody and indurated with fine scales. The skin findings suggested a diagnosis of nephrogenic systemic fibrosis. Intravenous fluids were administered for a short period but stopped when calcium levels returned to the high-normal range and stabilized. In a matter of weeks, the patient's strength and clinical status improved. The overall clinical profile was consistent with the diagnosis of NSF. Because of the coagulopathy, a skin biopsy to confirm this likely diagnosis could not be obtained.

Over the ensuing year, skin abnormalities continued to improve with increasing joint mobility. Calcium levels remained normal. Vitamin D supplementation was resumed without calcium. Bone mineral density 1 yr after discharge demonstrated osteopenia, unchanged from the year before.

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Figure 1. Left arm demonstrates a cobblestoned, dimpled appearance and induration on palpation.

### NSF—Review of the Literature

NSF was first observed in 1997 and later reported in 2000 as a scleromyxedema-like cutaneous disorder in patients with renal dysfunction (1). NSF manifests as a symmetrical thickening and hardening of the skin in the limbs and trunk. Lesions initiate as papules that coalesce to form erythematous and brawny plaques with a peau d'orange appearance (3). Unlike scleromyxedema, there is no evidence of paraproteinemia; NSF also spares the head and neck (2). Joint contractures, pruritus, and pain have been reported in the affected areas (3).

Immobility may develop rapidly and patients may become wheelchair dependent, which increases the risk for falls and fractures. NSF was initially termed nephrogenic fibrosing dermopathy but renamed in 2005 when systemic manifestations were reported, including infiltration of sc tissue, striated muscle, the diaphragm, pleurae, myocardium, and pericardium (4). One death due to diaphragm-related respiratory failure has been reported (5). Additionally, increases in thrombotic risk have been reported, including deep venous thrombosis, pulmonary embolus, atrial thrombus, and thrombosed arterio-venous

<b>Causes of Hypercalcemia</b>
Primary hyperparathyroidism
Malignancy
—Humoral hypercalcemia
—Direct bone involvement
Vitamin D intoxication
Familial hypocalciuric hypercalcemia
Granulomatous disease
Hyperthyroidism
Thiazide diuretics
Lithium
Vitamin A toxicity
Adrenal insufficiency
Immobilization
Milk-alkali syndrome
Tertiary hyperparathyroidism

access (2). Abnormalities in anticardiolipin and antiphospholipid antibodies as well as factor V leiden, protein C, protein S, and antithrombin III have been seen (2). At this time, there are no consistent, effective approaches to treat NSF. Extracorporeal photopheresis, plasmapheresis, UV light, sodium thio-sulfate, and physical therapy have been used with some benefit but no clinical trials have formally evaluated these approaches (2). Disease regression is more likely to occur with improvement in underlying renal dysfunction.

Recently, gadolinium exposure has been etiologically linked to NSF (6). In June 2006, the Food and Drug Administration issued a black box warning for the use of gadolinium contrast in magnetic resonance imaging in patients with renal failure (7). It is estimated that the risk of developing NSF after gadolinium exposure is approximately 2.4% in patients with acute and chronic renal failure (8).

Few reports have linked NSF with hypercalcemia. In our case, an exhaustive work-up revealed no specific cause to account for elevated calcium levels. Typical causes of hypercalcemia are listed (Table 2) and were ruled out in this case. Of note, one more case of NSF and hypercalcemia, not yet reported, is known (personal communication, Dr. Vivian Pao, University of California San Francisco, Division of Endocrinology).

It is not clear whether hypercalcemia and NSF share a common mechanism,

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<b>Test</b>	<b>Value</b>	<b>Normal range</b>
Calcium (uncorrected)	11.0 mg/dl	8.4–9.8
Creatinine	2.8 mg/dl	0.5–0.9
Albumin	3.0 g/dl	4.0–5.0
Magnesium	1.6 mg/dl	1.5–2.3
Phosphorus	2.4 mg/dl	2.5–4.3
PTH	17 pg/mol	8–51
25-Hydroxyvitamin D	22 ng/ml	20–57
1,25-Dihydroxyvitamin D	4 pg/ml	15–75
TSH	2.75 µU/ml	0.34–4.25
PTHrP	<0.2 pmol/L	<2.0
Vitamin A	0.33 mg/L	0.3–1.2
Cortisol	25.0 µg/dl	5–25
Urinary N-Telopeptide (Serum Cr 1.3 mg/dl)	149 nM	26–124
Bone-specific alkaline phosphatase (Serum Cr 1.5 mg/dl)	32.0 µg/liter	7.0–22.4
24-h urinary calcium (Serum Cr 2.3 mg/dl)	191 mg/24 h	150–300

but there are possible etiologic explanations that make for interesting discussion. Examination of affected skin in NSF demonstrates haphazardly arranged, thickened collagen bundles with mucin deposition (2). Fibroblasts found within the thickened tissue stain positive for CD34 and procollagen-1, which have origins in bone marrow. Skin biopsies in patients with NSF have demonstrated deposits of calcium, phosphate, and gadolinium (9). Although calcium-sensing receptors play a central role in calcium homeostasis (10), gadolinium is a strong calcium sensing receptor agonist and therefore would not be expected to increase calcium levels. It is therefore doubtful that gadolinium itself directly affects calcium homeostasis. In addition to calcium and phosphate deposition, TGF- $\beta$  (11) has been documented in NSF-affected skin. Although TGF- $\beta$  can increase PTHrP mRNA expression in osteoblast-like osteosarcoma cells (12), there was no evidence of elevated PTHrP levels in our patient.

Dermal calcium deposition is described in NSF, but it is uncommon (1, 13–20), estimated to occur in 2–5% of cases (18). Additionally, one report has identified two cases of NSF with tartrate-resistant acid phosphatase (TRAP)-positive osteoclast-like giant cells in the dermal skin layer (18). It was postulated that giant cells and calcifications in NSF may reflect a dysregulated matrix homeostasis. The two cases had elevated levels of ionized calcium (the only two cases of hypercalcemia found in the literature). Phosphorus levels were either normal or elevated, and in one case, 1,25-dihydroxyvitamin D levels were decreased. One case presented with diffuse dermal calcification and both were complicated by unresolved chronic renal failure. One patient died 7 months after the diagnosis of NSF and the other had resolving skin lesions. In this report, rapid tissue fibrosis was accompanied by mononuclear cell infiltrates, increased synthesis of TGF- $\beta$  and decreased activity of metalloproteinases (18). Although the pathogenesis of multinucleated giant cell formation is unknown, metalloproteinases can regu-

late activation of TGF- $\beta$  and enhance fibrosis and osteoclast recruitment and activation. This report of dystrophic calcification is quite interesting and provides clues into dysregulated calcium homeostasis. It suggests that calcium may leak from skeletal tissue into peripheral areas of dermal calcification. Temporary hypercalcemia may ensue similar to that seen in humoral hypercalcemia of malignancy.

In our patient with NSF and hypercalcemia, a skin biopsy was not performed and therefore it is impossible to determine whether TGF- $\beta$ , osteoclast-like giant cells or other factors were present. A bone scan was positive for diffuse uptake suggesting calcium deposition and dystrophic calcification. Markers of bone turnover were quite elevated suggesting increased skeletal calcium mobilization, which in turn could have led to transient hypercalcemia, whereas calcium was presumably mobilized from skeletal tissue en route to the dermis. Additionally, relatively low 24-h urinary calcium suggests a preferential uptake of intravascular calcium into the skin, rather than elimination through renal mechanisms. Interestingly, 1,25-OH dihydroxyvitamin D levels were low during hospitalization and have remained undetectable for 1 yr after resolution of hypercalcemia despite normalization of renal function and repletion of parent vitamin D. Phosphorus levels have fluctuated between low and normal. A factor regulating fibroblast skin deposition in NSF may also affect vitamin D metabolism and could be further evaluated. With the rarity of this condition, studies designed to elucidate the underlying mechanism(s) for the hypercalcemia will be a challenge.

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## Eating Disorders and Diabetes

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### Case

A 13-yr-old girl with type 1 diabetes mellitus (DM) of 3 yr duration presents to pediatric endocrine clinic for follow-up. She feels generally well. She reports mildly increased frequency of urination and increased thirst since her last visit. She has no known complications of diabetes. She is on a regimen of glargine insulin 18 U in the evening and aspart insulin 2 U for every 15 g of carbohydrate with a correction of 1 U for every 50 mg/dl glucose level over 150. She checks her blood sugars one to two times daily. She reports fasting morning blood sugars of about 180–220 on average and pre-dinner blood sugars around 150–210. These numbers are moderately higher than when she was seen 3 months prior, and she is checking her blood sugars a bit less frequently. She reports that classmates at school tease her for being overweight. When she is told during the office visit that she has lost 7 lbs, she seems elated. When told that her hemoglobin A1c has increased from 7.5 to 8.8%, she appears unconcerned. When asked whether or not she ever skips or under-doses her insulin, she denies such practices vehemently and becomes defensive. On further questioning regarding the possible connection between her weight loss and her worsening glycemic control, she becomes increasingly irritated and keeps asking her parents when she can leave. The following day, her mother calls to report that the patient's insulin vials seem more full than usual since she would normally be ready for refills.

### Discussion

The prevalence of eating disorders in people with type 1 diabetes has been found to be higher than that of the general population (1). This higher risk may be related to a high level of concern regarding food choices and detailed meal planning, precision in

portions, and constant monitoring. Patients with type 1 diabetes and an eating disorder may present with noncompliance with insulin, unstable metabolic control, hyperglycemia, recurrent diabetic ketoacidosis, and early onset of microvascular complications. They are more likely to be of normal weight or overweight than nondiabetic counterparts with eating disorders. Proposed predisposing factors include the developmental effects of a chronic medical condition on body image and self-concept and the higher body mass index associated with insulin use (2). Two recent studies, respectively, found that 18 (3) to 30% (4) of adolescents with type 1 diabetes admitted to avoiding insulin to control weight. A cross-sectional study of 9- to 14-yr-old girls with type 1 diabetes *vs.* controls found 8% of the patients currently engaging in two or more disturbed eating behaviors *vs.* 1% of controls (the two behaviors were typically intense exercise for weight loss plus dieting) and 3% reporting binge eating *vs.* 0.3% of controls (5). These findings are not exclusive to adolescents. Polonksy *et al.* (6) found that among female patients who were 13–60 yr of age, 31% reported intentional insulin omission for weight loss with 8.8% reporting frequent omission. Those who intentionally skipped insulin were found to have worse glycemic control, more diabetes-related hospitalizations, and higher rates of retinopathy and neuropathy.

Another study that examined 91 young women aged 12–18 yr assessed for eating disorders at baseline and 4 yr later (7). Reported rates of binge eating, insulin omission, self-induced vomiting, and laxative use all increased in prevalence over the course of the study. Retinopathy was present at 4 yr follow-up in 85% with highly disordered eating *vs.* 43% with moderately disordered eating *vs.* 24% with

nondisordered eating. Albuminuria was present at 4 yr follow-up in 43% with highly disordered eating *vs.* 20% with moderately disordered eating *vs.* 18% with nondisordered eating. Disordered eating status was statistically a stronger predictor of retinopathy than duration of disease or HgbA1c.

The most accepted treatment for eating disorders involves an interdisciplinary team including a medical provider, dietitian, and mental health professional. The medical provider must monitor for vital sign instability, electrolyte abnormalities, hydration status, and fluctuations in weight. Long-term sequelae, including bone loss, amenorrhea, and poor growth in younger patients—particularly in the presence of anorexia nervosa—need to be followed (8). Nutrition therapy for patients recovering from severe eating disorders should focus on slow nutrition repletion and rehabilitation. It is challenging to balance the goal of gradual weight changes with diabetes meal planning. Goals of “good” blood sugars as opposed to “optimal” blood sugars may be preferable while the body readjusts to normal eating patterns and the patient begins to benefit from psychotherapy (10). Some recommend food journals as part of treatment, but this may in fact exacerbate the problem. Lowering the amount of time spent on diabetes management may help to lessen stress associated with the diabetes, which may in turn help to alleviate disordered eating behaviors. Adjunctive family therapy may be beneficial (9).

One small uncontrolled study examined pharmacologic treatment of 10 women with type 1 diabetes and bulimia or binge eating disorder (BED) (10). All received naltrexone 200 mg twice daily

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for 1 yr. Three patients with BED experienced 42, 62, and 86% reduction in binge episodes at 2 months and 31, 52, and 86% reduction, respectively, at 1 yr. There was 4% weight loss at 2 months, 6% weight loss at 1 yr and their A1c values decreased from 11.3, 12.1, and 14.1% to 9.0, 8.7, and 9.8% at 1 yr. Of the seven patients with bulimia, there was a 50–86% reduction in purging by 2 months and a 52–100% reduction in purging by 1 yr. Their body weights remained stable and their A1c values decreased. All patients had improved self-esteem score on Eating Disorder Inventory 2 questionnaire. These provocative findings merit a controlled study.

The prevalence of eating disorders and disordered eating behavior may be difficult to determine. However, it is clear that they occur frequently enough to be encountered by most practicing endocrinologists and may be missed if the

index of suspicion is not sufficient. Adult endocrinologists must be just as aware of insulin omission as pediatric endocrinologists because the likelihood for the disorder persisting beyond childhood is high and because the consequences include earlier microvascular complications.

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## ENDOCRINE FELLOWS FOUNDATION ANNOUNCES ITS RESEARCH GRANT RECIPIENTS FOR THE FALL CYCLE OF 2008

Derek LeRoith, M.D., Ph.D., Director, Grants Program

The Endocrine Fellows Foundation received 32 grant applications for the fall cycle. Awardees receive \$7,500 to facilitate their research. Applications were received covering several subjects, including glucose, insulin, T-cells, and vitamin D. Among the 36 experts who were asked to review these applications, the EFF received 100% participation from across the country. 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 seven grants were approved for funding. The awardees are listed below:

**Edward Chao, D.O.—University of California, San Diego**  
“The Role of Fatty Acid Oxidation in the Insulin Resistance of the Metabolic Syndrome: The Effects of Pioglitazone Therapy”  
Program Director, Nai-Wen Chi, M.D., Ph.D.

**Kjersti Kirkeby, M.D.—Stanford University Medical Center**  
“Growth Hormone Deficiency and Cognitive Function”  
Program Director, Laurence Katznelson, M.D.

**Guido Lastra, M.D.—University of Missouri**  
“Renin Angiotensin Aldosterone-Induced Oxidative Stress Impairs Cardiovascular and Skeletal Muscle Sensitivity through RHO Kinase Activation”  
Program Director, David W. Gardner, M.D.

**Daniel Moore, M.D., Ph.D. — Vanderbilt Children’s Hospital**  
“Intracellular Targeting of Proinflammatory Pathways to Ameliorate Type 1 Diabetes”  
Program Director, William E. Russell, M.D.

**Utpal Pajvani, M.D., Ph.D.—Columbia University**  
“The Role of Notch 1 in Regulation of Hepatic Gluconeogenesis”  
Program Director, Shonni Silverberg, M.D.

**Christine Skadidas, M.D.—Brigham and Women’s Hospital**  
“Gene Expression in Cumulus Granulosa Cells”  
Program Director, Mark Hornstein, M.D.

**Raymond Soccio, M.D, Ph.D.—Hospital of the University of Pennsylvania**  
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Program Director, Susan Mandel, M.D.



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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.

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