ABSTRACTS

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ABSTRACTS

ADRENAL DISORDERS

Abstract #710

Three-in-One Adrenocortical Adenoma: Elevated Levels of Aldosterone, Metanephrines, and Cortisol From a Solitary Adenoma

Maria Patricia Deanna Delfin Maningat, MD, Antonette L. Picorro, MD, and Cecile A. Jimeno, MD

Objective: To present a rare case of a single adrenal adenoma in a patient with high levels of 3 hormones—aldosterone, metanephrines, and cortisol—and to discuss the work-up and perioperative management of a patient with multiple hormone elevations.

Case Presentation: A 57-year-old man had a 5-year history of hypertension. He had been admitted twice previously for a mild cerebrovascular accident and for hypertensive encephalopathy. He was maintained on multiple antihypertensive drugs. Seven months before the current consultation, he had recurrent lower extremity weakness. He had no palpitations, pallor, or diarrhea and no cushingoid facies. Initial laboratory studies showed hypokalemia. Findings on physical examination were unremarkable except for high blood pressure. He had no moon facies, buffalo hump, or striae. Results of cardiac and neurologic examinations were normal. Ophthalmoscopy showed hypertensive retinopathy. Levels of serum potassium and serum sodium were 1.9 mEq/L and 144 mEq/L, respectively. Urine potassium was normal, as were initial plasma renin activity and aldosterone. Repeated determinations showed aldosterone elevation at 50 ng/dL and plasma renin activity at <0.02 ng/mL per hour, with a ratio of 2,500. A computed tomographic scan of the abdomen showed a well-defined hypodense nodule (1.0 by 1.6 by 1.8 cm) in the right adrenal gland. In a 24-hour urine specimen, free cortisol was 192 µg/24 h (normal, 20 to 90); urine vanillylmandelic acid was elevated on 3 determinations, and urine metanephrines were 1.6 mg/24 h (normal, up to 0.9). The patient was prepared for operation by (1) adequate potassium replacement, (2) adequate hydration, (3) α-blockade, (4) perioperative corticosteroid coverage, (5) ensuring availability of blood, and (6) provision of nicardipine and esmolol for use in the operating room. The patient underwent an uneventful right adrenalectomy. His blood pressure was maintained at 80 to 130 mm Hg systolic and 60 to 90 mm Hg diastolic throughout the operation. Postoperative blood chemistry studies yielded normal results. Histopathologic examination showed an adrenocortical adenoma (2 by 2 by 1.5 cm), grossly continuous with the tissue of the adrenal medulla. At the time of dismissal from the hospital, the patient was receiving nifedipine, 30 mg once a day. His blood pressure had been well controlled and electrolytes were normal at last follow-up.

Discussion: Cases of combined hormonal elevations are rare. Most published cases have been attributable to 2 separate tumors either in one or in both adrenal glands. To our knowledge, this is the first report of elevated levels of 3 hormones from a single adrenal tumor. Proposed explanations for such occurrences include (1) coincidence, (2) unrecognized genetic predisposition to endocrine neoplasms, or (3) an interaction between medullary and cortical tissue, especially after the normal architecture has been distorted by an enlarging tumor.

In recent years, the conventional view that the adrenal cortex and adrenal medulla are distinct functional units has been challenged as a simplistic explanation of complex intra-adrenal interactions. The distribution of cells actually may not be clearly demarcated and may contribute to differences in hormonal expressions.

Several diagnostic assays have been developed to screen patients for excess hormonal production. Adrenal tumors are usually treated surgically, and appropriate preoperative preparation of patients, addressing primarily hypertension and electrolyte disturbances, is essential for prevention of complications.

Conclusion: Although rare, endocrine-related causes of hypertension are potentially curable. Accurate diagnosis and management of these disorders are necessary to offer patients the appropriate treatment. Future research should investigate the intra-adrenal interactions between the cells of the cortex and the medulla. Clinicians should be aware of the possibility of combined hormonal elevations from even a solitary adrenal tumor and should evaluate for the presence of this condition, in order to provide appropriate management during operative treatment.

Abstract #712

Metyrosine in the Treatment of Pheochromocytoma

Mathew Jason Levine, MD, and James David McCallum, MD, FACE

Background: Pheochromocytoma is rare and can be associated with a high degree of morbidity and mortality if unrecognized. In this disorder of the sympathochromaffin system, a tumor develops in the adrenal medulla or, less commonly, in sympathetic ganglionic neurons. The adrenal medullary cells, an important component of the
autonomic nervous system, are vital for synthesis and release of catecholamines. The overall prevalence of these tumors is approximately 0.1%, many of which are detected at autopsy. This same frequency has also been noted among patients with diastolic hypertension; however, the prevalence can be as high as 6% in patients with hypertension who also have symptoms and paroxysms suggestive of catecholamine excess. The prevalence is equal among male and female patients, and adrenal lesions are most often seen in the fourth through sixth decades of life (although any age-group can be affected). Pheochromocytomas can manifest with several nonspecific symptoms but are most commonly associated with a triad of symptoms—headaches, palpitations, and diaphoresis—that occur in paroxysms. The absence of all 3 components of this triad usually excludes the diagnosis. Of these adrenal lesions, 10% are malignant and 10% are bilateral.

Pheochromocytomas can arise sporadically or as part of a familial syndrome of endocrine or neuroendocrine tumors. Even 2.5% of sporadic cases emerge from an underlying genetic abnormality (which may remain undiscovered). Cases that are part of a familial syndrome are more likely to be bilateral, extra-adrenal, and heralded by symptoms typical of the genetic disorder as opposed to those typical of a pheochromocytoma. Pheochromocytoma is a component of several familial syndromes, including the multiple endocrine neoplasias (30 to 50% incidence), von Hippel-Lindau disease (25% incidence), neurofibromatosis type 1, and familial pheochromocytoma.

Traditionally, medical therapy in preparation for surgical removal of pheochromocytomas has consisted of α-blockade with or without β-blockade. The following patient, despite excellent preoperative heart rate and blood pressure control with these agents, required a little-used compound, metyrosine, in order to undergo a successful adrenalectomy.

**Case Presentation:** A 21-year-old woman had had intermittent “spells” for 2 years that had become worse after the birth of her second child 7 months previously. These episodes involved blood pressure elevations (documented), diaphoresis, palpitations, and dizziness. She also had increased levels of blood glucose, and type 2 diabetes mellitus was diagnosed after her delivery. One month before her referral to our service, a 24-hour urine study showed the following (normal ranges in parentheses): epinephrine, 772 µg (2 to 24); norepinephrine, 1,459 µg (15 to 100); normetanephrine, 13,622 µg (52 to 310); and metanephrine, 12,638 µg (19 to 140). Magnetic resonance imaging disclosed a right adrenal mass (7.2 by 5.8 by 7.5 cm), dimensions that were subsequently confirmed on a computed tomographic scan. The patient’s symptoms were controlled with doxazosin (4 mg daily) and propranolol (40 mg daily). She was referred for a right adrenalectomy.

In the operating room, severe hypertension (280/180 mm Hg) and a corresponding tachycardia (150 beats/min) developed. Her labile condition dictated that the operation be aborted, and she was moved to the intensive care unit, where her condition became even more tenuous. Her systolic blood pressure fluctuated from 60 to 230 mm Hg, pulmonary edema developed as a result of the hypertension, and hypoxemia, an anion-gap metabolic acidosis, and hyperglycemia were noted. She was already intubated from the operating room. Treatment was initiated with sodium nitroprusside, esmolol, and phentolamine to reduce her blood pressure, wide-open fluid resuscitation for periodic hypotension, and an insulin drip to correct the hyperglycemia. Her situation gradually improved and stabilized; extubation was possible 2 days after the initial surgical attempt.

After extubation of the patient, therapy was begun with metyrosine (1 g/day orally). This tyrosine hydroxylase inhibitor blocks catecholamine production in the adrenal gland. The goal was to attempt adrenalectomy again in approximately 2 weeks. Treatment with both α- and β-blockade was continued. She remained in the hospital while awaiting another surgical attempt and tolerated the metyrosine well, although thrombocytosis developed (platelet level of more than 1 million). The Hematology Division suggested that this finding was most likely a reactive thrombocytosis. The patient was also receiving antibiotics for pneumonia. The platelet count normalized during the next week, and the catecholamine depletion also appeared to be effective. After 8 days of therapy with metyrosine, urinalysis of a 24-hour specimen showed an epinephrine level of 24 µg, a norepinephrine level of 143 µg, a metanephrine level of 490 µg, and a normetanephrine level of 2,070 µg (all decreased from initial values). Furthermore, a serum metanephrine level was 0.44 nmol/L (normal, <0.50), and a serum normetanephrine level was 3.33 nmol/L (normal, <0.90) (initial values of 23.3 and 53.8 nmol/L, respectively).

Seventeen days after the initial surgical attempt (after 10 days of metyrosine therapy), the patient underwent an uncomplicated right adrenalectomy, and her blood pressure remained stable. Surgical pathology indicated a benign tumor. Two months later, with use of no further medications, 24-hour urine study showed a norepinephrine level of 56 µg, an epinephrine level of 4 µg, a normetanephrine level of 226 µg, and a metanephrine level of 30 µg—all within normal ranges. She is currently well and active, has had no further hypertensive episodes, and is taking no further medications.

**Discussion:** Although the circumstances surrounding this case were unsettling, intraoperative hypertension is a common complication of surgical treatment of pheochromocytoma, especially when the tumor is manipulated. The most widely used intraoperative antihypertensive agents are intravenously administered phentolamine and sodium nitroprusside. After tumor removal, hypotension can also occur and may necessitate volume replacement or even pressors for correction. We used doxazosin to treat the hypertension; prazosin is also often used for α-blockade. These 2 agents have a shorter duration of action (and per-
haps result in less hypotension postoperatively) as well as a more competitive and reversible blockade of postsynaptic α<sub>1</sub>-adrenergic receptors than does phenoxybenzamine.

As our case shows, despite preoperative preparation with α- and β-blockade, intraoperative hemodynamic instability and arrhythmias may still occur. Metyrosine can reduce the incidence of such complications. The normal risk of morbidity from removal of a pheochromocytoma can be as high as 40%, and the mortality risk is 2 to 4%. Steinsapir et al (1), in a 1997 retrospective analysis of patients undergoing adrenalectomy for pheochromocytoma, demonstrated that patients treated with metyrosine and α-adrenergic blocking agents required antihypertensive drugs and pressors less frequently than did those treated with α-blockers alone. Specifically, metyrosine plus prazosin (or phenoxybenzamine) caused a significant reduction in intraoperative hypertensive episodes necessitating use of phentolamine. Although specific mortality reduction was not demonstrated, absence of or insufficient preoperative pharmacologic treatment can lead to higher intraoperative mortality. Investigators have postulated that the blood pressure stability noted after treatment with metyrosine is caused by the long period of changes in catecholamine levels that result.

The study reported by Steinsapir et al (1) estimated a 19% incidence of side effects (usually fatigue) with metyrosine treatment, and those that did occur were transient. Our patient had no side effects with use of a 1-g daily dose. It is unclear but doubtful that the thrombocytosis in our patient was related to the use of metyrosine. The ideal result with metyrosine therapy is a 75% reduction in 24-hour urine metanephrine levels, an outcome achieved in our patient.

**Conclusion:** Whether preoperative use of metyrosine should become standard in patients scheduled for surgical removal of a pheochromocytoma is unclear; the associated cost may be prohibitive. In our subsequent experience, however, 2 other cases of pheochromocytoma were successfully managed intraoperatively and postoperatively after preoperative treatment with metyrosine and α-blockade (plus β-blockade if needed).

Reference


**Abstract #761**

**Pheochromocytoma Manifesting as “Idiopathic” Cardiomyopathy**

Ali Reza Moattari, MD, FACP, FACE, and Daniela Ciltea, MD

**Objective:** To present a case of pheochromocytoma manifesting as idiopathic cardiomyopathy of several years’ duration.

**Case Presentation:** A 52-year-old man was referred for evaluation of an adrenal tumor found incidentally during an ultrasound examination and subsequently confirmed by abdominal computed tomography. He had a history of irregular heartbeat and occasional chest pain. A stress test showed normal findings, and echocardiography revealed an ejection fraction of 20%. Cardiac catheterization demonstrated no evidence of coronary artery disease, and the patient was diagnosed as having cardiomyopathy. Subsequent electrophysiologic studies were unable to localize and correct the irregular heartbeat with use of different antiarrhythmic agents. The patient did not have documented hypertension. On direct questioning, he reported chest discomfort along with palpitations, occasional throbbing headaches, night sweats, and a chilling sensation over the entire body. His medications were amiodarone, pantoprazole, carvedilol, digoxin, and aspirin. A 24-hour urine study revealed a metanephrine value of 23,990 µg (normal, less than 230) and a normetanephrine level of 13,197 µg (normal, less than 540). The patient underwent a right adrenalectomy, which disclosed a multicystic mass measuring 13 by 11 by 7 cm and weighing 583 g. At 6-month follow-up, he was asymptomatic with no arrhythmia. At 2-year follow-up, repeated 2-dimensional echocardiography showed an ejection fraction of 50%; the plasma metanephrine level was normal.

**Discussion:** The unique features of this case include the presence of cardiomyopathy, manifesting as cardiac arrhythmia, chest pain, and congestive heart failure, without hypertension or other classic features of pheochromocytoma.

**Conclusion:** This is a case of pheochromocytoma in a normotensive patient who presented with cardiomyopathy and unexplained arrhythmia. Although this condition is very rare, because of its reversible nature we recommend measurement of plasma metanephrine in patients with “idiopathic” cardiomyopathy, if clinically warranted.

**Abstract #785**

**Estimation of Adrenocortical Function in Different Types of Obesity**

Richard Allen Dickey, MD, FACP, FACE, Ludmila I. Velikanova, MD, PhD, Natalia V. Vorokhobina, MD, PhD, Elena A. Volkova, MD, PhD, Nikita V. Ivanov, MD, and Tatiana A. Zelenina, MD

**Objective:** To determine the differences in steroidogenesis in 167 obese patients (body mass index, 30 to 35 kg/m²) with subclinical Cushing’s syndrome (CS), “hypothalamic” obesity (obesity with pink striae), or polycystic ovary syndrome with the use of reverse-phase high-performance liquid chromatography.

**Methods:** In the 167 obese study subjects, serum cortisol (F), cortisone (E), corticosterone, 11-deoxycorticos-
terone, and 11-deoxycortisol, as well as urine free cortisol (UFF) and urine free cortisone (UFE), were analyzed.

Results: In patients with subclinical CS, high concentrations of intermediate products of steroidogenesis, elevated UFF/UFE and F/E levels in blood, and high UFF and UFE levels were found in comparison with the obese patients in the other 2 study groups. Among the patients with hypothalamic obesity, 28.6% showed decreased UFF and FF/FE levels and an increased 11-deoxycortisol level in blood, the result of a steroidogenesis enzyme defect. In patients with polycystic ovary syndrome, the UFE level was increased and FF/FE was decreased in comparison with the findings in patients with subclinical CS, also related to a steroidogenesis enzyme defect (perhaps 11β-hydroxysteroid dehydrogenase-1).

Conclusion: The role of disturbances in steroidogenesis in the pathogenesis of different types of obesity has previously been unclear. Results of our study suggest that reverse-phase high-performance liquid chromatography of corticosteroids might add valuable information to the clinical features of obesity and could help to distinguish subclinical CS from other types of obesity accompanied by functional hyperadrenocorticism.

Abstract #801

Bilateral Adrenal Hemorrhage Causing Adrenal Insufficiency

Michalis K. Picolos, MD, Anuradha Gathikonda, MD, Anu Bhalla Davis, MD, and Philip R. Orlander, MD

Objective: To describe a case of adrenal insufficiency due to bilateral adrenal hemorrhage.

Case Presentation: A 68-year-old man with congestive heart failure, hypertension, and chronic atrial fibrillation who was receiving warfarin presented twice within a month for emergency care. His main complaints were weakness, dizziness, shortness of breath, and low back pain. During the first visit, hypotension was attributed to his antihypertensive regimen, which was discontinued. Treatment included fluids administered intravenously. Recurrent hypotension on a second visit was refractory to hydration, and dopamine infusion was initiated. The INR (international normalized ratio) was 4.71, electrolytes were normal, and serum cortisol was 5.9 µg/dL. Computed tomography revealed bilateral adrenal masses and a lung infiltrate. The patient received antibiotics, methylprednisolone intravenously and was transferred to our hospital where he failed a cosyntropin stimulation test while receiving dexamethasone. The corticosteroid regimen was reduced to a maintenance dose of hydrocortisone, the lung infiltrate resolved, and work-up for a malignant lesion was negative. Findings on magnetic resonance imaging of the adrenal glands were consistent with bilateral adrenal hemorrhage.

Discussion: Blunt abdominal trauma, antiphospholipid syndrome, thermal injuries, sepsis, anticoagulation, or idiopathic factors can lead to bilateral adrenal hemorrhage, a rare cause of adrenal insufficiency. Anticoagulation was the most likely cause in the current patient, in whom the subacute initial presentation, atypical features, and low index of suspicion contributed to the delay in diagnosis.

Conclusion: Physicians should maintain a high index of suspicion for subtle signs of adrenal insufficiency, even in the absence of refractory hypotension, in patients receiving anticoagulation. Computed tomography and magnetic resonance imaging are valuable for confirming the diagnosis.

Abstract #805

Male Infertility in Congenital Adrenal Hyperplasia Due to 21-Hydroxylase Deficiency

Shanjian Zhu, MD, Harris C. Taylor, MD, FACE, Baha Arafah, MD, and Thomas A. Murphy, MD, FACP, FACE

Objective: To confirm the existence of infertility and the lack of benefit of glucocorticoid therapy in some patients with congenital adrenal hyperplasia (CAH) attributable to 21-hydroxylase deficiency, documented by 3 cases.

Case Presentation: The first case was a 36-year-old man, who presented with infertility and CAH in 1995. He had fathered two children before sustaining a testicular injury in 1988. After he had been without therapy for years, oligospermia and the following laboratory results (normal ranges shown parenthetically) were noted: follicle-stimulating hormone (FSH) <0.3 IU/L (0.9 to 15.0), luteinizing hormone (LH) 0.2 IU/L (2.4 to 9.4), testosterone 14.97 nmol/L (12.85 to 37.15), and 17-hydroxyprogesterone (17-OHP) 182.4 nmol/L (1.5 to 7.6). Institution of hydrocortisone therapy, 20 mg every morning and 10 mg every evening for 3 months, resulted in minimal change in sperm count, after which this patient was lost to follow-up.

The second case was a 41-year-old man, who had been diagnosed as having CAH at age 4 months with a 17-ketosteroid value of 6.4 mg/24 h. A testicular biopsy when he was 11 years old showed adrenal rest tumors. Azoospermia was noted at age 25 years. While he was receiving prednisone (4 mg every bedtime) and hydrocortisone (10 mg every noon), the 17-OHP level was 10 nmol/L (<5.45). He had not fathered any children after 8 years of marriage.

The third case was a 38-year-old man, who presented with infertility and CAH. He had not taken glucocorticoids since the age of 15 years, except for 1 year in 1994. Azoospermia and the following laboratory results were
noted: FSH 4.4 IU/L (2 to 10), LH 2.6 IU/L (1 to 9), testosterone 6.42 nmol/L (10.42 to 34.7), androstenedione 38.91 nmol/L (1.78 to 9.27), aldosterone 800 pmol/L (26.7 to 826.7), plasma renin activity 5.28 ng/L/s (0.141 to 0.931), and 17-OHP 607.5 nmol/L (1.2 to 9.9). Testicular ultrasonography showed bilateral adrenal rest tumors. Treatment with dexamethasone, 0.5 mg daily for 10 months, resulted in decreases in androstenedione to 1.22 nmol/L and 17-OHP to 11.46 nmol/L as well as increases in FSH to 39.2 IU/L and LH to 27.2 IU/L, but no change was noted in the azoospermia. Human chorionic gonadotropin and clomiphene citrate therapy was instituted. Subsequent sperm analysis showed a concentration of 9.5 × 10⁹/mL, with 41% motility but 0% normal forms.

Discussion: The pathogenesis and indeed existence of infertility in male patients with CAH due to 21-hydroxylase deficiency and the recommendations to restore fertility with glucocorticoids have been controversial. In a report published in 1978 (1), 18 of 20 such patients were found to be fertile on the basis of a history of paternity or a sperm count (or both). Of 27 evaluable patients described in 2001, however, 10 had azoospermia and 6 had oligospermia (2,3). Our current cases involved 3 additional patients with infertility and CAH in whom glucocorticoid treatment failed to achieve fertility.

Conclusion: CAH-associated infertility does exist, and glucocorticoid therapy is often ineffective in restoring fertility. Human chorionic gonadotropin and clomiphene citrate therapy may be helpful, despite evidence of primary hypogonadism and adrenal rest tumors. In all 3 current cases, long-standing poor compliance with treatment may have been contributory.

References

Abstract #863

Hyperinsulinemia in Late-Onset Congenital Adrenal Hyperplasia

Jean Dy Uy, MD, and Maria Honolina Sero Gomez, MD, FPCP, FPSEM, FACE

Objective: To describe a rare case of late-onset congenital adrenal hyperplasia compounded by hyperinsulinemia in an 11-year-old Filipino girl.

Case Presentation: An 11-year-old girl had been born to a 26-year-old gravida 5, para 4 (1 abortion) mother after a term pregnancy, delivered by a traditional birth and with no standard prenatal care. Her father was diagnosed as having type 2 diabetes mellitus at the age of 38 years. The patient was asymptomatic as a neonate and had no symptoms of failure to thrive. Throughout her childhood, she had no major illnesses necessitating hospitalization. One of her siblings has autism but has had no genetic work-up. At 6 years of age, the patient noted enlargement of her clitoris, which was ignored by her mother. At that time, the patient was the tallest among her peers. Two years later, the patient noted appearance of pubic hair followed by appearance of axillary hair. No consultation was sought at that time. One year later, when the patient had deepening of her voice and appearance of a mustache at the outer margins of her upper lip, a medical consultation was scheduled.

On physical examination, the patient was obese (body mass index of 31.6 kg/m²). Her height for age was >95th percentile, and her weight for age was >95th percentile. Her weight for height was 170.54%. She had normal blood pressure (120/80 mm Hg). Her development was Tanner stage 4, with a Ferriman-Gallwey score of 11. Acanthosis nigricans was present on the nape and in the axillary areas.

Laboratory studies showed normal results of thyroid function tests (normal ranges in parentheses): thyroid-stimulating hormone (thyrotropin) (by immunoradiometric assay) 0.34 mIU/L (0.3 to 3.0) and thyroxine (by radioimmunoassay) 120 nmol/L (60 to 160). The follicle-stimulating hormone level was normal at 5.0 IU/L (2.0 to 6.0), and the luteinizing hormone level was slightly elevated at 6.2 IU/L (1.6 to 5.7). The serum testosterone was likewise slightly increased at 4.6 nmol/L (0.2 to 3.0). The 17-hydroxyprogesterone (17-OHP) level was 4.4 nmol/L (or 151.8 ng/dL) (normal values for age, 7 to 69), and after adrenocorticotropic hormone (ACTH) stimulation, 17-OHP increased to 12.0 nmol/L (or 396.0 ng/dL). The fasting glucose level was 62 mg/dL, and insulin was 68 µU/mL (0 to 30); thus, the ratio was 0.91. Two hours after oral intake of 75 g of glucose, the plasma glucose level was 100 mg/dL and serum insulin concentration was 420 µU/L, with a ratio of 0.238—both consistent with hyperinsulinemia. Chromosome analysis showed XX karyotype, consistent with a female. Treatment was begun with metformin (500 mg twice a day), and dexamethasone (0.5 mg once a day) was subsequently added. At follow-up 2 months later, a decrease in facial hair and lightening of the acanthosis nigricans were noted; however, clitoromegaly was still present. Menarche occurred 3 months after initiation of treatment.

Discussion: Premature adrenarche with appearance of pubic hair, advanced bone age, and rapid somatic growth in conjunction with a moderately elevated 17-OHP level is the most common presentation of untreated nonclassic congenital adrenal hyperplasia in young children. The heterozygous state for 21-hydroxylase deficiency has been detected with increased frequency in children with premature adrenarche. Heterozygotes or carriers of a single mutant CYP21 allele have slightly increased (range, 200 to 1,000 ng/dL) 17-OHP levels after ACTH stimulation.
This range overlaps with that in the general population to some extent. It is possible that a heterozygotic defect is subclinical in most cases but becomes apparent when it is associated with other defects in the patient’s genetic and constitutional backgrounds. This 11-year-old girl may have been a heterozygote with only a mildly increased 17-OHP level on ACTH stimulation. Her heterozygous state for congenital adrenal hyperplasia compounded by a genetically and constitutionally determined mild insulin resistance predisposed her to the polycystic ovary syndrome. Insulin resistance may potentiate the effects of the heterozygosity on the adrenal glands, ovary, or both and may lead to overt adrenal or ovarian hyperandrogenism manifested as premature adrenarche or the polycystic ovary syndrome.

**Conclusion:** This case illustrates the coexistence of hyperinsulinemia and hyperandrogenism in late-onset congenital adrenal hyperplasia, and it emphasizes the importance of prompt administration of metformin or another insulin sensitizer plus glucocorticoid to reverse hirsutism and avoid progression to overt polycystic ovary syndrome.

**Abstract #905**

**Virilizing Form of Congenital Adrenal Hyperplasia and a Giant Myelolipoma in a Mexican Woman**

*Fanny Rodriguez Vallejo, MD, Andrés Duarte Rojo, MD, Cesar Lara Torres, MD, Bernardo Pérez Enriquez, MD, Francisco J. Gómez Pérez, MD, and Juan A. Rull Rodrigo, MD*

**Objective:** To describe a 30-year-old Mexican woman with a virilizing variant of congenital adrenal hyperplasia and a giant myelolipoma.

**Case Presentation:** A 30-year-old Mexican woman had a family history of diabetes mellitus and a younger sister with congenital adrenal hyperplasia. Her personal medical history included ambiguous genitalia at birth that necessitated two surgical corrections at the age of 2 years. She had received prednisone therapy from 2 to 14 years of age. She had had one menstrual period at the age of 12 years. At 14 years of age, she decided to discontinue all her medications. At 21 and 28 years old, she had two episodes of seizures, the cause of which was unknown. At 30 years old, she noted the onset of dull pain in the upper right quadrant of the abdomen, which was associated with intake of food. Symptoms of dyspepsia were also present. Weight loss was denied. An abdominal ultrasound study disclosed a heterogeneous solid mass (23 by 9 cm) that occupied the entire left abdominal cavity and hypoplastic internal genitalia. A posterior abdominal computed tomographic scan confirmed these findings.

On physical examination, the patient had a body mass index of 36 kg/m². Her blood pressure was 120/70 mm Hg (both supine and upright). Acanthosis nigricans and hirsutism were noticed. A solid and fixed mass of the left hemiabdomen was palpable; it was slightly painful at the depth palpation. Vaginal examination revealed normal findings.

Results of laboratory studies were as follows: total cholesterol 132 mg/dL, triglycerides 503 mg/dL, high-density lipoprotein cholesterol 17 mg/dL, adrenocorticotropic hormone (corticotropin) 450 pg/mL, cortisol 120 µg/dL, prolactin 20.5 ng/mL, 17-hydroxyprogesterone >12.5 ng/dL, aldosterone 79 ng/dL, plasma renin activity (PRA) 27.4 ng/mL/h, aldosterone:PRA ratio 2.9, dehydroepiandrosterone sulfate 124 µg/dL, testosterone 4.31 ng/dL, follicle-stimulating hormone 4.3 mIU/mL, luteinizing hormone 2.9 mIU/mL, estrogen 117.85 pg/mL, progesterone 64.4 ng/mL, and growth hormone 5.5 ng/mL.

An oral glucose tolerance test showed the following results: glucose values (in mg/dL)—176 at baseline, 322 at 30 minutes, 404 at 60 minutes, 395 at 90 minutes, 325 at 120 minutes, 233 at 180 minutes, 143 at 240 minutes, and 108 at 300 minutes; the corresponding insulin values (in µU/mL)—14.72 at baseline, 62.78 at 30 minutes, 207 at 60 minutes, 231.08 at 90 minutes, 154 at 120 minutes, 65.71 at 180 minutes, 31.29 at 240 minutes, and 16.28 at 300 minutes.

In October 2004, a laparotomy was performed, and a 7.5-kg abdominal mass, compatible with liposarcoma, was resected. The histopathology report indicated that the tumor was a myelolipoma. Others studies with normal findings included electroencephalography, magnetic resonance imaging, and bone densitometry. Pelvic ultrasonography showed uterine atrophy; the ovaries were not observed.

**Conclusion:** The first description of myelolipoma was in 1905. It is a common tumor composed of fat occurring in the adrenal gland. It is usually asymptomatic and measures less than 4 cm in diameter. In a few cases, it has been associated with adrenal hyperplasia. This is the first report of a Mexican woman with a giant myelolipoma and the virilizing form of congenital adrenal hyperplasia.
DIABETES MELLITUS

Abstract #715

Effect of Pioglitazone on Glycemic Control, Lipids, and Weight in Patients With Type 2 Diabetes Treated With a Combination of Glyburide and Metformin in a Municipal Hospital

Issac Sachmechi, MD, FACP, FACE, Grishma Parikh, MD, David Reich, MD, FACE, Shirly Sebastian, NP, Richard Arena, PhD, Hildegarde Payne, RN, CDE, and Paul Kim, MD

Objective: To evaluate the effects of pioglitazone as an adjuvant therapy on fasting blood glucose (FBG), hemoglobin A1c (HbA1c), lipid levels, weight, and body mass index (BMI) in patients with type 2 diabetes treated with a combination of glyburide and metformin in a municipal hospital.

Methods: We conducted a retrospective study in which we reviewed medical records of 200 patients with type 2 diabetes mellitus in whom pioglitazone (30 to 45 mg) was added to their diabetic medications. We selected 50 patients (13 female and 37 male), with a mean age of 57.2 ± 11.1 years, who were treated with a combination of glyburide and metformin. We recorded their FBG, HbA1c, lipid profiles—total cholesterol (TC), triglyceride (TG), high-density lipoprotein (HDL), and low-density lipoprotein (LDL) levels—weight, and BMI initially and at 6 months after the addition of pioglitazone to their therapy.

Results: Six months after the addition of pioglitazone, statistically significant reductions were noted in FBG, HbA1c, TC, and TG. Although HDL and LDL levels had decreased, the changes were not statistically significant. In addition, in this study group the body weight and BMI had increased significantly after 6 months of therapy with pioglitazone.

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<tr>
<td>Patients (no.)</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>FBG (mg/dL)</td>
<td>178 ± 56</td>
<td>132 ± 57*</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>8.5 ± 1.22</td>
<td>7.7 ± 1.36*</td>
</tr>
<tr>
<td>TC (mg/dL)</td>
<td>185.0 ± 32.6</td>
<td>169.3 ± 34.2*</td>
</tr>
<tr>
<td>TG (mg/dL)</td>
<td>156.8 ± 73.1</td>
<td>132.1 ± 64.3†</td>
</tr>
<tr>
<td>HDL (mg/dL)</td>
<td>44.0 ± 12.1</td>
<td>43.7 ± 11.9</td>
</tr>
<tr>
<td>LDL (mg/dL)</td>
<td>105.5 ± 27.9</td>
<td>102.7 ± 25.4</td>
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<tr>
<td>Weight (lb)</td>
<td>174.9 ± 43.3</td>
<td>180.3 ± 45.0*</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>30.7 ± 6.6</td>
<td>31.4 ± 7.0†</td>
</tr>
</tbody>
</table>

Data are shown as means ± SD.
*Significantly different (P<0.01).
†Significantly different (P<0.05).

Discussion: The striking improvement in glycemic control (mean HbA1c decreased by 9.4%) and the reduction of TG level (decreased by 15.75%) in response to pioglitazone therapy confirm the peroxisome proliferator-activated receptor (PPAR)-gamma and PPAR-alpha effects of pioglitazone.

The unexpected decrease in TC (by 8.5%) and the lack of a significant change in HDL and LDL level suggest a reduction in non-HDL cholesterol. The main side effect of weight gain (mean increase 3.08%) is consistent with findings in other studies.

Conclusion: In patients with type 2 diabetes treated at a municipal hospital, the addition of pioglitazone to a combination of a sulfonylurea and metformin significantly improved FBG, HbA1c, TC, and TG levels, without significantly changing LDL and HDL levels. The addition of pioglitazone therapy was associated with a significant increase in weight and BMI.

Abstract #718

Type 2 Diabetes Mellitus in Glutamic Acid Decarboxylase Antibody-Positive 10- and 15-Year-Old White Children

Olusola Osundeko, MD, MRCPath, FACP, FACE

Objective: To present the cases of two white children with type 2 diabetes and positive glutamic acid decarboxylase (GAD) antibodies and a review of the related literature.

Case Presentation: Case 1: A 10-year-old white girl had a random blood glucose determination of 200 mg/dL during hospitalization for mental illness. Reassessment 4 months later showed a blood glucose level of 303 mg/dL, but the hyperglycemia was causing no symptoms. Her body mass index (BMI) was 27 kg/m² (>97th percentile for her age), the anion gap was normal at 14 mEq/L, and the serum bicarbonate level was 24 mEq/L. She had a C-peptide level of 8.9 ng/mL (normal, 0.8 to 3.1), GAD65 antibody was >30 U/mL (normal, 1 or less), and the islet cell antibody titer was 20 JDF (Juvenile Diabetes Federation) units (normal, <1.25). She was treated with NPH insulin and insulin aspart for 5 months before treatment was changed to metformin (1,000 mg twice a day) and pioglitazone (30 mg daily). Her hemoglobin A1c (HbA1c) improved from an initial value of 8.4% to 7.1% with use of insulin and to 6.1% with orally administered agents.

Case 2: A 15-year-old girl had a urinary tract infection, and urinalysis showed 4+ glucose. Her BMI was 38 kg/m² (>97th percentile for her age); the anion gap and serum bicarbonate levels were normal. GAD65 antibody was >30 U/mL, and the C-peptide level was 2.5 ng/mL. Her blood glucose concentration was 220 mg/dL. Metformin...
therapy was initiated, in conjunction with regular insulin coverage for blood glucose levels greater than 200 mg/dL. A dietary regimen was instituted. She lost 7.3 kg in weight, and her HbA1c improved from an initial value of 9.2% to 5.0% during a 7-month period. She had used no insulin for 18 months.

Discussion: Before 1990, type 2 diabetes mellitus accounted for 3% of new cases of diabetes in children 10 to 19 years of age. In the 21st century, this percentage has increased to 40% in some studies. This rise corresponded to the increased frequency of obesity. In 1980, 5% of children between 12 and 19 years old had a BMI that exceeded the 95th percentile. Twenty years later, this percentage had increased to 16%.

The screening variables that are often used to identify children at risk for type 2 diabetes are BMI >85th percentile at onset of puberty or >10 years of age, at-risk ethnic groups such as Hispanics, African Americans, and Native Americans, and negative results of antibody tests. The two patients presented in this report are unique for the following reasons. Both children were white patients, an ethnic group not thought to be at high risk for type 2 diabetes in children. Both patients had GAD antibodies with measurable C-peptide levels and had a clinical course typical of type 2 diabetes. The absence of autoimmune markers may not be a prerequisite for diagnosis of type 2 diabetes in children.

Conclusion: Type 2 diabetes is becoming more common in children, and white children may also be at risk if they are obese. The presence of GAD antibodies does not rule out type 2 diabetes in children.

Abstract #721

A Pilot Study of Chromium Supplementation Influences on Insulin Resistance and Glycemic Control in Type 2 Diabetes Mellitus

Daniel Evan Rosenberg, MD, Joel S. Edman, DSc, Barry J. Goldstein, MD, PhD, FACE, and Bonnie Falkner, MD

Objective: To determine whether chromium supplementation improves measures of glycemic control in patients who have stable type 2 diabetes mellitus (T2DM).

Methods: A double-blind, placebo-controlled pilot study was conducted and included 11 patients (7 women and 4 men) who had stable T2DM and were not receiving insulin therapy. The study subjects were randomly assigned to take 600 µg per day of chromium picolinate (200 µg with each meal) or a placebo for 4 weeks. Studies at baseline and 4-week visits included the following: assessment of weight; vital signs; fasting lipid profile; a 2-hour glucose tolerance test and insulin tolerance test in which blood samples were obtained at time 0, 30, and 120 minutes; and a 3-hour urinary sample collection for assessment of chromium content.

Results: The 11 study subjects ranged in age from 44 to 67 years (mean age, 58.4). The mean duration of T2DM was 5.9 years (range, 1 to 17). The initial hemoglobin A1c ranged from 6.2 to 7.6%, and the mean number of oral antidiabetic medications was 1.7 (range, 0 to 3).

Results showed a significant decrease in the area under the glucose tolerance curve between the baseline and the 4-week glucose tolerance test for the chromium-treated subjects in comparison with those who received placebo (P = 0.04). In addition, there was a decrease in the area under the insulin tolerance curve between the baseline and the 4-week insulin tolerance test for the chromium-treated study subjects compared with those who received placebo. Although this difference was not statistically significant, it may be clinically significant, and it may have been statistically significant with use of a larger sample size. We also found a statistically significant increase in the urinary chromium level in the chromium-supplemented study subjects in comparison with those taking placebo (P = 0.003). No statistically significant differences were observed between the two study groups for weight, lipid profiles, or insulin sensitivity (QUICKI [quantitative insulin sensitivity check index] model).

Discussion: These results show that the trace mineral chromium improved some surrogate measures of glycemic control in patients with stable type 2 diabetes. Although chromium picolinate has been shown in this study and in other studies to improve glycemic control in patients with T2DM, insufficient data are available to establish a clinical protocol regarding who should be treated, the specific dose required, and the duration of therapy. The small sample size and the short duration of chromium supplementation in the current study make it difficult to establish generalized guidelines. Additionally, although low chromium values have been associated with T2DM in prior studies, no clear evidence has verified that low chromium levels cause T2DM. One major obstacle to this research is that there is no reliable measure of chromium nutritional status. Although urinary chromium excretion was shown to increase significantly with chromium supplementation, future research could evaluate any correlation between glycemic control and level of chromium excretion to determine whether it is a useful marker of chromium nutritional status.

Conclusion: Our data suggest that administration of chromium picolinate may improve glycemic variables in patients with stable T2DM. Nonetheless, further research in larger populations of patients who undergo follow-up for longer periods is needed to establish more definitively the role of chromium picolinate in the treatment of T2DM.
Abstract #725

Type 2 Diabetes Mellitus in Remission in a Patient With Human Immunodeficiency Virus Infection Receiving Highly Active Antiretroviral Therapy

Deepak Thomas, MD, Roshan J. Lewis, MD, Faith X. Zhao, MD, Maria F. Renedo, MD, and Zewge S. Deribe, MD

Objective: To report the remission of type 2 diabetes a few months after initiation of antiretroviral therapy.

Case Presentation: A 66-year-old man had a history of hypertension, chronic renal insufficiency, and hepatitis B infection. In 1997, he was admitted to our hospital with a blood glucose level of 783 mg/dL and was diagnosed as having new-onset type 2 diabetes mellitus. His body mass index (BMI) was 29 kg/m², and tests for islet cell antibodies were negative. He was dismissed from the hospital with an insulin regimen, and his blood glucose levels were well controlled at the time of follow-up visits. In early 1999, he was diagnosed as having human immunodeficiency virus (HIV) infection and had a CD4 count of 358 cells/mm³. Treatment was initiated with nelfinavir, lamivudine, stavudine, and nevirapine. Later that year, he was found to be euglycemic and was tapered off insulin therapy but advised to continue use of a diabetic diet. At that time, he had a BMI of 27.3 kg/m².

For the next 5 years, the patient had regular follow-up visits at our clinic. During this period, he maintained euglycemia, with hemoglobin A1c levels ranging from 5.0 to 5.4% without use of insulin or orally administered antidiabetic agents. He has been physically active and walks regularly. During his last visit to the diabetes clinic, his fasting blood glucose level was 90 mg/dL. He continues to receive antiretroviral drugs and had a CD4 count of 347 cells/mm³, with an undetectable viral load.

Discussion: HIV infection and antiretroviral drugs such as protease inhibitors and nucleoside reverse transcriptase inhibitors often increase insulin resistance. Remission of new-onset diabetes mellitus in patients with HIV after the initiation of antiretroviral therapy has been reported (1). The remission in our patient could be attributable to relief of glucotoxicity and lipotoxicity by intensive treatment and lifestyle changes, resulting in a decrease in body weight of about 5%. HIV infection and subsequent use of antiretroviral medications did not worsen his diabetes but rather were associated with a clinical remission. How either of these factors can affect glucose homeostasis is yet to be described.

Conclusion: Remission of type 2 diabetes mellitus in a patient with HIV infection in whom antiretroviral therapy was initiated is an unusual observation. The effect of HIV infection and the use of antiretroviral drugs should be a worsening of the diabetes. Apart from the lifestyle changes, the remission of diabetes in our patient necessitates further inquiry into the actions of HIV infection and antiretroviral drugs on glucose metabolism.

Reference


Abstract #732

Correlates of Foot Ulceration in Nigerian Patients With Diabetes Mellitus

Anthonia Okeoghene Ogbera, MBBS, FMCP

Objective: To determine the risk factors and correlates of diabetes mellitus-related foot ulceration in Nigerian patients.

Methods: This study was performed in 47 patients with diabetes who had past or present foot ulceration. The study subjects were recruited from the Diabetes Clinic and from the surgical and medical wards of the Lagos University Teaching Hospital in Lagos, Nigeria. The 47 control subjects were selected from the rest of the pool of patients with diabetes who did not meet the foregoing criterion. Probability sampling methods were used to select the control subjects. Data were analyzed with use of a statistical software program for social sciences (SPSS) and Epi-Info version 6.4. The test statistics used included the unpaired Student t test, the chi-squared test, and correlation and logistic regression analysis. The level of significance was set at P<0.05.

Results: More than half of the patients with foot ulceration were elderly (>61 years) and overweight or obese. Hypertension, occurring in 32% of these subjects, was detected only in patients with type 2 diabetes. The commonest initial manifestation of diabetes mellitus foot syndrome was that of Wagner’s grade 3 lesions (deep ulcer with bony involvement). The development of diabetes mellitus-related foot ulceration is strongly associated with male sex, being elderly, the presence of neuropathy, nephropathy, retinopathy, peripheral vascular disease, cataract formation, poor glycemic control, the presence of tinea pedis, foot deformity, and a previous history of amputation or ulceration. Neuropathy was the most common risk factor in patients in this study. The proportion with neuropathy, neuroischemic lesions, and ischemic lesions was 87%, 31%, and 36.4%, respectively.

Discussion: The correlates of foot ulceration found in this study were mainly those that have been previously documented. Among a host of other factors, the most common risk factors for foot ulceration identified in this study were neuropathy, poor glycemic control, structural foot
Diabetic Neuropathy, the Great Masquerader: Truncal Neuropathy Manifesting as Abdominal Pseudohernia

Harvey Kenn Chiu, MD, and Dace Lilliana Trencé, MD

**Abstract #733**

**Background and Objective:** Diabetic neuropathy can masquerade in numerous forms and presentations. Truncal diabetic neuropathy, in particular, may be confused with conditions that necessitate extensive evaluation. A focused diagnostic evaluation is proposed, which would decrease the need for extensive and prolonged testing.

**Case Presentation:** A 55-year-old white man, with a known history of diabetes mellitus for 13 years, presented with left-sided flank pain and a left-sided lower abdominal visible mass. Initial vague discomfort was noted abruptly, without an inciting event, and then evolved during a 2-week period into a left-sided abdominal burning sensation, rated 7 of 10 on a pain scale. Because the pain was uncontrolled with over-the-counter analgesics naproxen and acetaminophen, the patient sought medical assistance when he began to note a visible bulge developing in the left lower quadrant. Prolonged sitting worsened the pain and increased the bulge effect of the abdominal mass. He denied having nausea or a change in bowel habit frequency. Although his medical history included significant alcoholism, he denied consumption of alcohol for the previous 6 months. His glucose control had been steadily improving, although the most recent hemoglobin A1c was still 7.2%. His weight had essentially remained unchanged throughout the past year. He had had no surgical procedures or hospitalizations, other than for alcoholism treatment during the past year. His history was further negative for diabetes-related complications of retinopathy, vasculopathy, or nephropathy.

Current medications were limited to insulin glargine (45 U subcutaneously each evening at bedtime), prandial insulin lispro (10 U at meals), pravastatin (80 mg daily), and ezetimibe (10 mg daily).

Physical examination revealed an uncomfortable-appearing man, who was not in distress. His blood pressure was 148/88 mm Hg and pulse was 92 beats/min, in sinus rhythm. Findings on cardiovascular and pulmonary examinations were unremarkable. Abdominal examination revealed an easily visible bulge in the left lower quadrant. No clear mass was detectable on palpation; however, examination was difficult because of tenderness to palpation in the left lower quadrant. No hepatomegaly, splenomegaly, or appreciable inguinal adenopathy was present. Bowel sounds were normal to auscultation, and the patient had no peripheral edema.

Laboratory evaluation demonstrated normal serum amylase and normal results of liver function tests (normal aspartate aminotransferase and alanine aminotransferase levels). Urinalysis was positive for trace proteinuria. The leukocyte count was elevated at 14.2 × 10^9/µL, with a shift to the left.

Computed tomography (CT) of the abdomen was performed because of concern about the possible presence of an intra-abdominal mass. It showed no mass effect but revealed a weakening of abdominal musculature, suggestive of a pseudohernia in the area of the clinically visible fullness. A subsequent electromyogram showed evidence of polyradicular neuropathy on the left throughout the thoracic and lumbar regions (T10-L2), as well as absent late responses to the bilateral tibial nerves (H waves) and sural sensory nerves, suggestive of diabetic neuropathy.

Treatment was initiated with gabapentin, titrated to 1,200 mg orally three times a day for control of pain. Eleven months after the initial assessment, the patient tolerated a decrease in dosage to 600 mg orally three times a day. Tylenol with codeine was used in the acute titration period but was discontinued after 2 to 3 months. At the patient’s most recent examination, 1 year after the initial presentation, the left abdominal bulge was no longer appreciable.

**Discussion:** Diabetic truncal neuropathy is a rarely recognized and likely underdiagnosed entity in patients with diabetes. Typically, the initial manifestation may involve an acute palsy of the abdominal musculature in conjunction with a subsequent focal prominence of the abdominal wall, even to the point of including intra-abdominal contents (1). Pain is exacerbated in the upright position and ameliorated with lying supine. A unilateral superficial burning sensation concurrent with hyperesthesia of the overlying dermatomes, especially nocturnally, is usually the predominant manifestation, with motor involvement less prevalent. No correlative relationship has been noted with nephropathy, retinopathy, dyslipidemia, or hypertension (2).

A misdiagnosis of abdominal hernia, herpes zoster, cholecystitis, appendicitis, myocardial ischemia, pleurisy, costochondritis, or abdominal vasculopathy may distract from a focused pertinent assessment and may prompt unnecessary surgical intervention or radiologic assessments. The acute onset of palsy suggests a transient ischemic cause, as seen in analogous acute mononeuropathy multiplex (3) and acute oculomotor palsy (4), which pathologically have been correlated with infarction of peripheral nerves and oculomotor nerves, respectively. An electromyogram of both the paraspinal and the abdominal musculature is the diagnostic study of choice; however, because initial evaluation, as in the presented case, will typically entail radiographic examination (either CT or...
magnetic resonance imaging), directing the focus on the abdominal wall could aid in narrowing the diagnosis to pseudohermia. A clinically apparent motor palsy of the abdominal musculature is difficult to appreciate, but an abnormal abdominal wall appearance on CT as described, coupled with confirmatory electromyographic findings, can minimize the need for additional tests for conditions frequently masquerading as diabetic abdominal pseudohernia.

Usual symptomatic treatments for diabetic neuropathic pain such as gabapentin, tricyclic medications (in particular, imipramine, amitriptyline, and desipramine), mexiletine (5), anticonvulsants (such as carbamazepine and phenytoin) (6), clonidine (7), or duloxetine (8) may alleviate the discomfort. Characteristically, the prognosis is good because the pain and palsy of diabetic truncal neuropathy typically resolve in 3 to 18 months, without specific intervention or recurrence (9).

**Conclusion:** Truncal diabetic neuropathy can masquerade as various entities, being an unrecognized complication of diabetes mellitus. Clinical suspicion with appropriate radiologic testing can more rapidly suggest the need for corroborative electromyography, in turn leading to initiation of treatment.

**References**


**Abstract #736**

**Factors Associated With Remission in Type 1 Diabetes Mellitus**

*Michael Scott Irwig, MD, and Dace Lilliana Trence, MD*

**Objective:** To profile the factors associated with prolonged remission, with possible spontaneous cure, of an autoimmune insult leading to type 1 diabetes mellitus (T1DM).

**Case Presentation:** An 11-year-old boy was enrolled in the Diabetes Prevention Trial in 1998 because he was at increased risk for developing T1DM. His family history was positive for T1DM in his only sibling, a sister. Baseline antibody status was negative for glutamic acid decarboxylase (GAD65) antibodies and insulin autoantibodies but positive for islet cell autoantibodies. At 34 months into the study, the subject had his first signs and symptoms of T1DM: polydipsia, polyuria, nocturia, and a fasting blood glucose level of 142 mg/dL. Two months later, he was admitted to a children’s hospital for a fasting blood glucose level of 212 mg/dL. At that time, he was formally diagnosed with T1DM and had a hemoglobin A1c (HbA1c) value of 8.6%. At the time of presentation, the patient had lost approximately 7.7 kg from his baseline weight of 104.3 kg. His BMI was 27.5 kg/m². Mild acanthosis nigricans on the neck and axillae was noted on his admission physical examination. He was not in ketoacidosis and spent 2 days in the hospital for the initiation of insulin therapy and diabetes education. He was dismissed from the hospital with a daily insulin regimen of 0.56 U/kg of body weight.

Four months later, the HbA1c was 6.5% while the patient’s insulin dose was 0.45 U/kg daily. At 21 months after his dismissal from the hospital, his HbA1c was 5.1% during insulin therapy with 0.30 U/kg daily—a level defined as being in remission. He reported frequent hypoglycemic values of 60 mg/dL or less on blood glucose self-monitoring; therefore, he had independently decreased his insulin dose. Subsequent to this visit, at which a further decrease in insulin dose was recommended, he discontinued the use of insulin entirely because of persistent hypoglycemia and has remained without exogenous insulin. At 19 months after the beginning of his remission, the patient’s HbA1c was 4.6% without insulin therapy or dietary restrictions. His current BMI is 22 kg/m², and he no longer has evidence of acanthosis nigricans on physical examination.

**Discussion:** Prolonged remission of diabetes mellitus, with possible spontaneous cure, has rarely been reported in patients with T1DM. Multiple factors have been identified as possible contributors to remission in T1DM. In the
Diabetes Autoimmunity Study in the Young (DAISY) (1), researchers found that, in comparison with community control subjects, genetically at-risk children under close follow-up for the development of T1DM had a less severe onset and a milder clinical course of T1DM during the first year after diagnosis. The stage of puberty has also been studied in relationship to remission in T1DM. In a prospective follow-up of 157 adolescents with T1DM for remission, Bonfanti et al (2) found that partial remission was more prevalent among postpubertal than among pre-pubertal and pubertal adolescents. Another key factor related to remission and age at diagnosis of T1DM is BMI. In a prospective trial of 362 patients with type 1 diabetes in Sweden, Scholin et al (3) used multiple regression analysis to show that the only factor that predicted remission was BMI. In comparison with those patients who had a BMI of less than 20 kg/m^2, the odds ratios for remission were 2.6 for patients with a BMI of 20 to 24.9 kg/m^2 and 3.5 for those with a BMI of 25 kg/m^2 or more. In addition to predicting remission, certain factors are correlated with the duration of remission in T1DM. In the study reported by Scholin et al (3), 43% of the study subjects experienced a remission, and the median duration of remission was 8 months. Of those patients with a remission, 16% had a duration of remission that exceeded 12 months. This study also found that the duration of remission was longer in patients with a low number of positive islet cell antibodies.

**Conclusion:** Our patient had an unusual prolonged remission of T1DM. Studies have suggested that an increased BMI is associated with an increased likelihood of remission, as is a younger age at diagnosis of diabetes. Puberty and insulin resistance also may have a role, with postpubertal patients experiencing a higher rate of partial remissions. Finally, duration of remission is inversely correlated with the number of islet cell autoantibodies, a finding that supports the role of close surveillance of individuals at risk. What defines risk, however, remains unclear at this time.

**References**


**Evaluation of the Antidiabetic Property of Tapinanthus butungii Leaves in Rats With Alloxan-Induced Diabetes**

*Abraham Adewale Osinubi, MBBS, MSc, Glory O. Ajayi, BSc, and Elijah A. Adesuyan, BSc*

**Background and Objective:** Diabetes mellitus is a major health problem worldwide. An estimated 2.1% of the world’s population has diabetes mellitus. It is the most important disease involving the endocrine pancreas. Approaches to the control and prevention of hyperglycemia are central to the management of diabetes mellitus. Despite considerable achievements in treatment modalities and preventive measures, the prevalence of diabetes has increased exponentially during the past decade. Because of these limitations, a continued need exists for new and more effective therapies for diabetes. An increasing number of people are using dietary and herbal supplements, even though there is a general lack of evidence for their effectiveness. This experimental study was designed to evaluate the hypoglycemic, antihyperglycemic, and antidiabetic effects of aqueous extract of fresh green leaves of *Tapinanthus butungii* in the rat.

**Methods:** Young adult, male Sprague-Dawley rats, weighing 180 to 200 g, were used in this experiment; food and water were allowed ad libitum. Diabetes mellitus was induced in the group of diabetic test rats by intraperitoneal injections of alloxan (150 mg/kg). The hyperglycemic state was induced by administration of subcutaneous injections of 50% dextrose in water (4 g/kg). Single doses of aqueous extract of leaves of *Tapinanthus butungii* (400 mg/kg orally) were administered to normal, hyperglycemic, and diabetic rats. The hypoglycemic, antihyperglycemic, and antidiabetic effects of this single dose were compared with those of glibenclamide (5 mg/kg), chlorpropamide (250 mg/kg), Lente insulin (1.0 IU/kg), and distilled water (2 mL/kg). Blood glucose levels of all the rats were measured before treatment, at 0 hour, and at 1, 2, 4, 8, 10, and 12 hours after administration of the extract.

**Results:** Aqueous extract of leaves of *Tapinanthus butungii* produced significant reductions (*P*<0.05 to 0.001) in the blood glucose concentrations of normal, hyperglycemic, and diabetic rats comparable to glibenclamide, chlorpropamide, and Lente insulin. Of interest, the plant extract was more effective in reducing the blood glucose concentrations of diabetic rats than in reducing the blood glucose concentrations of normoglycemic rats.

**Discussion:** This experimental animal study demonstrated that the tested aqueous leaf extract of *Tapinanthus*
butungii induced significant reductions in the blood glucose concentrations of normoglycemic, hyperglycemic, and alloxan-induced diabetic rats. Therefore, the findings of this investigation may suggest that this plant extract could, at least in part, stimulate insulin production and glucose utilization, to produce its hypoglycemic effects in the mammalian experimental model used. Although the current findings suggest the presence of a hypoglycemic compound (or compounds) in leaf extract of Tapinanthus butungii, the precise mechanism of its hypoglycemic actions is still speculative and necessitates further studies for appropriate elucidation.

**Conclusion:** These results suggest that the leaves of Tapinanthus butungii have strong and remarkable hypoglycemic, antihyperglycemic, and antidiabetic activities. The results of this study also suggest that further research on the characterization of the constituents of the extract of leaves of Tapinanthus butungii might help elucidate the mechanism of this plant’s glucose-lowering activity.

**Abstract #759**

Concomitant Hypertension and Type 2 Diabetes Mellitus in Nigerians: Prevalence of Obesity Indices in Comparison With Their Frequency in Normotensive Patients With Diabetes

Olufemi Adetula Fasanmade, MD

**Objective:** To determine the frequency of obesity in persons with coexistent type 2 diabetes mellitus (DM) and hypertension in a cohort of adult Nigerians.

**Methods:** The study population consisted of patients at the Diabetes Outpatient Clinic of the Lagos University Teaching Hospital in Lagos, Nigeria. This was a 3-month prospective study during which a registry of consecutive-ly attending patients with type 2 DM was initiated. After basic biologic data had been recorded, anthropometric indices were also recorded. The presence of hypertension was based on the World Health Organization-International Society of Hypertension 1999 criteria of a blood pressure measurement of 140/90 mm Hg (or higher) or treatment with antihypertensive medication. Data were analyzed with use of Epi-Info 2002, and appropriate statistical tests were applied.

**Results:** For this study, 258 adults with type 2 DM were recruited. Concomitant hypertension was present in 108 patients (41.9%), who were significantly older than the normotensive study patients. Obesity was found in 26 of the 108 hypertensive patients with diabetes (24.1%) compared with 22 of the 150 normotensive patients with diabetes (14.7%) (no significant difference; odds ratio, 1.84; 95% confidence interval, 0.98 to 3.47). The frequency of hypertension showed a trend to increase as body mass index (BMI) increased, and the mean BMI was significantly higher in the hypertensive patients with diabetes (27.9 ± 6.0 kg/m²) than in the normotensive patients with diabetes (26.3 ± 6.1 kg/m²) (P<0.05). The frequency of an increased waist-to-hip ratio was also significantly higher in the hypertensive patients with diabetes (86 of 108 or 79.6%) than in the normotensive patients with diabetes (98 of 150 or 65.3%) (P<0.05).

**Discussion:** This was a modest-sized cohort of Nigerian patients attending a tertiary referral center. The study subjects were predominantly middle-aged patients with fairly long-standing type 2 DM (about 7 years’ duration). Concomitant hypertension and DM was fairly common (41.9%), with a higher frequency in females (45.9% versus 37.4%) (P>0.05). The hypertensive patients were significantly older than the normotensive patients, despite having DM of similar duration. Hypertensive patients with diabetes constitute a subgroup of diabetic patients with an increased risk of end-organ damage. Other investigators in Nigeria have reported similar findings, but also with no sex bias—as opposed to many European and American studies that have reported older age and a female sex bias (especially in African American patients) among hypertensive patients with diabetes.

**Conclusion:** Obesity measured by several indices is strongly associated with hypertension in Nigerian patients with diabetes. This finding has both therapeutic and preventive implications on cardiovascular-related morbidity and mortality and should be emphasized in patient care.

**Abstract #763**

Histologic and Immunohistochemical Changes in Diabetic Microangiopathy

Milko Ksente Bogoev, MD, and Biljana Gligor Bogoeva, PhD

**Objective:** To analyze the potential etiologic factors involved in diabetic microangiopathy, a serious complication of diabetes.

**Methods:** Skin biopsy specimens from 50 patients (16 to 35 years old) with type 1 diabetes and from 50 patients (48 to 72 years old) with type 2 diabetes were obtained by drill technique from the upper side of the foot. All specimens were analyzed on histologic stains (hematoxylin-eosin and periodic acid-Schiff) and on immunologic and immunohistologic stains (direct immunofluorescence for detection of antihuman IgG and IgM, streptavidin absorption-immunoperoxidase, and monoclonal antibodies for CD4+ and CD8+).

**Results:** We found different morphologic changes in all patients with both types of diabetes. The most prominent changes were found in patients with a duration of diabetes longer than 5 years. In 26 patients with type 1 diabetes, we found deposits of IgG in the capillary wall. In only 5 patients of this group, we found deposits of IgM in the capillaries. In 10 patients, we found deposits of IgG at the dermoepidermal junction.
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Deposit of immunoglobulins (IgG) in the capillary wall were found in only 5 patients with type 2 diabetes. All 5 patients had had diabetes longer than 10 years.

All specimens were analyzed for the presence of CD4+ and CD8+. We found a correlation between the deposits of IgG and CD4+ in 43%.

Discussion: The deposits of immunoglobulins (IgG) in the capillary wall of patients with type 1 diabetes may suggest a possible etiologic role for immunologic factors in diabetic microangiopathy. The deposits of IgG are correlated with the histologic changes in the capillaries. They also are correlated with the presence of diabetic retinopathy. The role of the IgM deposits is still unclear; they are not specific for diabetic microangiopathy.

Conclusion: Diabetic microangiopathy is a complex process. The etiopathogenesis of this complication of diabetes may be attributable to not only metabolic but also immunologic factors, which have thus far not been sufficiently studied.

Abstract #764

Summary of Changes in Patient-Rated Pain Severity in Two Placebo-Controlled Trials of Duloxetine for the Treatment of Diabetic Peripheral Neuropathic Pain

Thomas Andrew Hardy, MD, PhD,
Michael Robinson, MD, Apu Prakash, BS,
Shuyu Shen, PhD, Yili Lu Pritchett, PhD, and
Amy Chappell, MD

Objective: Diabetic peripheral neuropathy (DPN) is one of the most common complications of diabetes mellitus, affecting 30 to 60% of patients with diabetes. Although not all patients with DPN have painful symptoms, the presence of pain negatively affects the quality of life, such as the ability to sleep. These painful symptoms are often difficult to treat effectively. Duloxetine is a selective serotonin and norepinephrine reuptake inhibitor that has recently been approved for the management of pain associated with DPN. Its pain-inhibitory action is thought to be related to the potentiation of serotonin and norepinephrine activity in the central nervous system. We present a summary of efficacy results for duloxetine in the treatment of pain related to DPN using patient-rated pain assessments from placebo-controlled clinical trials.

Methods: Patients with symptoms of DPN-attributed pain (without depression) were studied in two large, placebo-controlled clinical trials that used fixed dosages of duloxetine (20 mg daily [in one study], 60 mg daily, and 120 mg daily). The primary efficacy measure was the weekly mean score of the 24-hour average pain severity, as measured by a patient-rated 11-point Likert scale. Standard safety analyses were used. All analyses were done on an intent-to-treat basis.

Results: Patients treated with duloxetine at dosages of 60 or 120 mg daily reported significantly greater improvement in the weekly mean score of the 24-hour average pain severity compared with those given placebo. Significant separation from placebo occurred as early as week 1, was sustained at each time point throughout the 12 weeks, and was replicated between studies. In both studies, patients treated with duloxetine at dosages of 60 or 120 mg daily experienced a mean improvement from baseline in 24-hour average pain severity of 30% or greater after 2 weeks of treatment.

Discussion: By 12 weeks of treatment, the mean improvement with use of duloxetine at 60 or 120 mg daily approached or exceeded 50%. Duloxetine treatment produced significantly greater improvement than did placebo on all patient-rated pain assessments, including pain at night and “worst pain.” Similar benefit was observed in patients with moderate or moderate-to-severe pain at baseline. Adverse events most commonly reported in duloxetine-treated patients were nausea, somnolence, dizziness, constipation, dry mouth, hyperhidrosis, decreased appetite, and asthenia. Most of these side effects were reported as mild or moderate in severity and were more common at higher doses of duloxetine.

Conclusion: Duloxetine at a dosage of 60 or 120 mg daily provides rapid and effective relief of neuropathic pain associated with DPN.

Abstract #768

Comparison of the Prevalence of Weight Gain in Male Versus Female Patients With Diabetes Treated With Thiazolidinediones

Xiangbing Wang, MD, PhD, FACE, and
Amy M. Toscano-Zukor, MD

Objective: To determine whether a difference exists in the prevalence of weight gain in male versus female patients with diabetes mellitus (DM) treated with thiazolidinediones (TZDs).

Methods: We randomly reviewed the medical records of 31 men and 30 women in an outpatient endocrinology practice who had received or are currently receiving pioglitazone or rosiglitazone (TZDs) as either monotherapy or part of a multidrug regimen for treatment of DM. Weights recorded during office visits were analyzed for any subsequent changes since the initiation or discontinuation of TZDs. Records were also analyzed for any patient-reported weight changes during TZD treatment before presentation to our practice. Significant weight gain was defined as (1) >3% weight increase from baseline weight before the initiation of TZD therapy; (2) >3% weight loss after TZD therapy was discontinued; or (3) >10% patient-reported weight increase since initiation of TZD therapy. Patients with liver disease (alanine amino-
transferase or aspartate aminotransferase values >2 times the upper normal limit), end-stage renal disease and receiving hemodialysis, or stage 3 or 4 congestive heart failure and patients taking orlistat (Xenical) were excluded from the study. Student t and chi-square tests were used for statistical analysis. P values less than 0.05 were considered statistically significant.

**Results:** We found no statistically significant differences in age, body weight, body mass index (BMI), duration of DM, hemoglobin A1c (HbA1c), and combination therapy with insulin, metformin, or sulfonylureas between male and female patients (P>0.05). A higher percentage of female patients (60%) had significant weight gain than did male patients (26%) (P<0.01). Among the patients who gained weight, female patients gained a higher percentage of weight (9.3%) than did male patients (5.1%) (P<0.01).

<table>
<thead>
<tr>
<th>Factor</th>
<th>Men (N = 31)</th>
<th>Women (N = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>55.1 ± 12.8</td>
<td>57.1 ± 9.5</td>
</tr>
<tr>
<td>Weight (lb)</td>
<td>211 ± 47</td>
<td>188 ± 48</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>30.2 ± 6.1</td>
<td>33.8 ± 8.3</td>
</tr>
<tr>
<td>DM duration (yr)</td>
<td>12.7 ± 7.9</td>
<td>10.0 ± 7.5</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>7.4 ± 1.9</td>
<td>7.8 ± 1.3</td>
</tr>
<tr>
<td>Insulin use</td>
<td>11 (35%)</td>
<td>10 (33%)</td>
</tr>
<tr>
<td>Metformin use</td>
<td>23 (74%)</td>
<td>23 (77%)</td>
</tr>
<tr>
<td>Sulfonylurea use</td>
<td>15 (48%)</td>
<td>14 (47%)</td>
</tr>
<tr>
<td>Gained weight</td>
<td>8 (26%)</td>
<td>18 (60%)*</td>
</tr>
<tr>
<td>Percent weight gain†</td>
<td>5.1 ± 3.6</td>
<td>9.3 ± 4.4*</td>
</tr>
</tbody>
</table>

Data are shown as mean ± SD or number (%).

*Significantly higher (P<0.01) than in the male patients.
†Calculated as (gained weight/basal weight) × 100%.

**Discussion:** Weight gain is a potential side effect in patients with diabetes treated with TZDs. Proposed mechanisms include fluid retention and an increase in subcutaneous fat accompanied by a decrease in visceral fat. Currently, no data are available about the prevalence of weight gain in male versus female patients with diabetes treated with TZDs. Our preliminary data indicate that the prevalence of weight gain in female patients with diabetes is higher than that in male patients treated with TZDs in an outpatient endocrinology practice.

**Conclusion:** On the basis of our preliminary data, the prevalence of weight gain is higher in female patients than in male patients with diabetes treated with TZDs in an outpatient endocrinology practice. Female patients have significantly higher ratios between subcutaneous and visceral fat in comparison with male patients. Perhaps the proposed fat redistribution that occurs with TZD use is more pronounced in women because of their preexisting larger ratio of subcutaneous to visceral fat.

**Abstract #775**

**Rosiglitazone Does Not Prevent Insulin Resistance Caused by an Acute Load of Free Fatty Acids**

*Nishanth Sanalkumar, MBBS, Sandeep S. Dhindsa, MBBS, Devjit Tripathy, MD, PhD, Shreyas Ravishankar, MSc, Husam Ghanim, PhD, Ahmad Alfada, PhD, and Paresh Dandona, MBBS, DPhil, FACE*

**Objective:** To study the effect of a 6-week course of rosiglitazone, 8 mg/day, on insulin resistance induced by triglyceride (TG)-heparin infusion in obese human subjects.

**Methods:** Nine obese subjects (5 male and 4 female) with normal glucose tolerance volunteered for this study. Insulin sensitivity was measured by hyperinsulinemic euglycemic clamps performed at the beginning (0 to 2 hours) and end (4 to 6 hours) of TG-heparin infusion, at 0 and 6 weeks. All study subjects received rosiglitazone, 8 mg/day for 6 weeks. At 0 and 6 weeks, blood specimens were obtained for measuring free fatty acids (FFA), lipid profile, hemoglobin, C-reactive protein (CRP), serum amyloid A (SAA), macrophage migratory inhibitory factor, tumor necrosis factor-α, soluble intercellular adhesion molecule 1, and interleukin-6.

**Results:** We noted a 40% increase in insulin sensitivity (glucose infusion rates 4.49 ± 0.95 mg/kg per min at 0 week and 6.29 ± 0.81 mg/kg per min at 6 weeks; P = 0.03) after administration of rosiglitazone for 6 weeks. This result was accompanied by a small and statistically insignificant decrease in fasting FFA concentration (489 ± 63 µmol/L versus 397 ± 58 µmol/L; P = 0.16) but significant decreases in CRP (4.26 ± 0.95 µg/mL versus 2.03 ± 0.45 µg/mL; P = 0.007) and SAA (17.36 ± 4.63 µg/mL versus 8.77 ± 1.63 µg/mL; P = 0.033). TG-heparin infusion resulted in a 28.9% decrease in insulin sensitivity (based on glucose infusion rate) from baseline at 0 week and a 26.4% decrease at 6 weeks. The decrease from baseline in glucose infusion rate induced by TG-heparin infusion was similar at 0 week and after 6 weeks of rosiglitazone administration (1.47 ± 0.5 mg/kg per min versus 1.77 ± 0.36 mg/kg per min; P = 0.51).

**Discussion:** Elevated FFA concentrations are thought to contribute significantly to the pathogenesis of insulin resistance. Thiazolidinediones are believed to decrease insulin resistance predominantly through long-term lowering of FFA concentrations. The effect of thiazolidinediones on the insulin-resistant state induced by an acute load of FFA, however, is unknown. Our data suggest that (1) at least a part of the insulin-sensitizing action of rosiglitazone is independent of a reduction in circulating FFA, (2) the site of action of rosiglitazone on insulin signaling might be either proximal to or different from that of FFA and FFA metabolites, and (3) the insulin-sensitizing action of rosiglitazone can be overwhelmed by an acute FFA load.
Conclusion: We conclude that administration of rosiglitazone, 8 mg/day for 6 weeks, results in a 40% increase in insulin sensitivity in obese subjects. This result is accompanied by a significant decline in inflammatory markers such as CRP and SAA, but without a significant change in fasting FFA levels. Acute increase in FFA concentration results in a decrease in insulin sensitivity to a similar magnitude, even after administration of rosiglitazone for 6 weeks.

Acknowledgment
The study was supported in part by a grant from the Endocrine Fellows Foundation to Dr. Nishanth Sanalkumar.

Abstract #786
Changes of Microcirculation in Perimenopausal and Postmenopausal Women With Diabetes

Richard Allen Dickey, MD, FACP, FACE, Tatiana A. Zelenina, MD, Natalia V. Vorokhobina, MD, PhD, and Elena A. Volkova, MD, PhD

Objective: To study the endothelium-related and unrelated microcirculation and vessel reactivity in perimenopausal and postmenopausal women with type 1 and type 2 diabetes mellitus in an attempt to reveal clinical, hormonal, and biochemical factors associated with disturbances in the microcirculation.

Methods: The study group consisted of 31 women with diabetes mellitus (11 with type 1 and 20 with type 2). Investigation was done with the use of a dopplerograph (Minimax, Russia), testing standard points near the fingernail in a basal state and after warm and cold applications. Hemostasis values and serum lipids, gonadotropins, estradiol, progesterone, and testosterone levels were determined.

Results: In patients with type 1 diabetes, the basal microcirculation speed and cold test results depend primarily on the link of hemostasis and aggregation capacity of thrombocytes. In patients with type 2 diabetes, a paradoxical reaction of a decrease in capillary blood flow in response to a warm test was noted.

Conclusion: Our study found that an incongruous response of capillary blood flow may be related to estradiol level, type of obesity, resistance to insulin, and lipid abnormalities.

Abstract #789
Type 2 Diabetes-Related Intermediate Phenotypic Traits in North Indian Patients With Diabetes

Sandeep Kumar Mathur, MBBS, MD, DM, Piyush Chandra, Sandhya Mishra, MBBS, MD, Piyush Ajmera, PhD, and Praveen Sharma, PhD

Background and Objective: The genetic predisposition for development of type 2 diabetes mellitus (T2DM) among North Indians has not been studied systematically. Because assessment of disease-related intermediate phenotypic traits is an important step toward systematic genomic study, the diabetes-related intermediate phenotypic traits of insulin secretion and insulin resistance were studied in a North Indian population with T2DM.

Methods: This study was performed on 156 patients with T2DM (102 men and 54 women, ranging in age from 45 to 80 years), and 84 persons without diabetes and with no family history of diabetes (ranging in age from 45 to 75 years) served as control subjects. All study subjects were assessed for phenotypic traits of insulin resistance by determination of body mass index (BMI), waist-to-hip (W:H) ratio, and fasting free fatty acid (FFA) level. Insulin resistance and secretion were studied by using homeostasis model assessment (HOMA-IR and HOMA-beta, respectively).

Results: The patients with diabetes were found to have significantly higher W:H ratios ($P<0.001$), FFA levels ($P<0.001$), and HOMA-IR ($P<0.001$) in comparison with the control subjects. No significant difference could be observed, however, in BMI. In patients with diabetes, a positive correlation was noted between FFA level and HOMA-IR. Furthermore, patients with diabetes in a steady-state condition had higher HOMA-beta than did control subjects ($P<0.001$).

Discussion: Findings suggest that FFA-mediated insulin resistance associated with abdominal obesity may be an important causative factor for the increased prevalence of diabetes in North Indians. Moreover, increased HOMA-beta in patients with diabetes reflects compensatory insulin hypersecretion in these subjects.

Conclusion: A need exists for determining the relative contributions of factors such as central obesity and free fatty acidemia and the precise nature of genetic factors in the tendency to develop insulin resistance and diabetes. There is also a need to explore less expensive and more sensitive markers of dysfunction of insulin secretion for epidemiologic studies, inasmuch as parameters of basal insulin secretion such as HOMA-beta only suggest compensatory insulin hypersecretion.
Abstract #791

Repaglinide Stimulation of C-Peptide Test to Assess Endogenous Insulin Production

Stanley Andrew Tan, MD, PhD, FACE, Marilyn Kay Wilson, RN, FNP-C, MS, CDE, John Stephan Pasztor, RD, MPH, CDE, and Linda Giles Tan, MD, FACC

**Objective:** To introduce a C-peptide stimulation test as a method to assess endogenous insulin production and to determine the proper therapeutic management of diabetes mellitus (DM).

**Methods:** After a basal fasting C-peptide blood specimen is obtained, repaglinide (2 mg) is given before breakfast. A second stimulated C-peptide blood sample is obtained 2 hours after taking the repaglinide.

**Results:** The diagnostic interpretation of the C-peptide stimulation test and the recommended treatment are as follows:

<table>
<thead>
<tr>
<th>C peptide (ng/mL)</th>
<th>Diagnosis</th>
<th>Recommended treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal 2 h</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;4 &gt;5</td>
<td>Metabolic syndrome</td>
<td>Metformin + thiazolidinedione</td>
</tr>
<tr>
<td>1-4 &gt;1 rise</td>
<td>Type 2 diabetes mellitus</td>
<td>Add secretagogue</td>
</tr>
<tr>
<td>&lt;1 &gt;1</td>
<td>Diabetes mellitus, loss of reserve</td>
<td>Add bedtime insulin glargine</td>
</tr>
<tr>
<td>&lt;1 &lt;1</td>
<td>Insulin-requiring type 2 diabetes mellitus*</td>
<td>Add bolus insulin analogue, drop secretagogue, continue metformin + thiazolidinedione</td>
</tr>
</tbody>
</table>

*Loss of endogenous insulin production.

**Discussion:** Insulin resistance induces hyperinsulinemia in metabolic syndrome. Prolonged overwork of pancreatic beta cells leads to type 2 DM when 50% of the beta cells become nonfunctional. Total beta-cell dysfunction necessitates use of insulin. The clinical challenge in the management of DM is to determine when insulin therapy should be initiated. A practical objective diagnostic test is needed to assess endogenous insulin production, so the clinician does not need to rely on the conventional trial-and-error method of trying insulin after maximal oral hypoglycemic therapy fails to control blood glucose levels. Homeostasis model assessment is a complicated and clinically impractical method. Using serum C peptide as a marker of endogenous insulin, we have performed this test to determine precisely when to begin use of basal or bolus insulin (or both). We have stopped the unnecessary insulin use and resumed oral administration of antidiabetic agents if endogenous insulin production is still present. Thiazolidinedione and metformin use must be continued at all stages because insulin resistance persists, unless uncontrolled congestive heart failure or renal impairment occurs. This test also can rule out type 1 DM when endogenous insulin production is proved.

**Conclusion:** This C-peptide stimulation test is a simple and practical diagnostic method to determine the presence of endogenous insulin production, and it eliminates guesswork about when insulin therapy should be initiated in patients with type 2 DM.

Abstract #800

Effects of Atorvastatin and Candesartan on Inflammatory Cytokines Interferon-γ, Tumor Necrosis Factor-α, Interleukin-6, and C-Reactive Protein in Diabetic Patients With Hypertension, Hyperlipidemia, and Cardiac Hypertrophy

Stanley Andrew Tan, MD, PhD, FACE, and Linda Giles Tan, MD, FACC

**Objective:** To evaluate the effects of atorvastatin, candesartan, and the combination of atorvastatin + candesartan on interferon-γ (IFN-γ), tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and C-reactive protein (CRP) levels in diabetic patients with hypertension, hyperlipidemia, and left ventricular hypertrophy (LVH).

**Methods:** Sixteen diabetic patients with hyperlipidemia and LVH were divided into group A (receiving atorvastatin, 80 mg/day) and group C (receiving candesartan, 32 mg/day). At 6 months, candesartan was added to the regimen for group A, and atorvastatin was added to the regimen for group C. The lipid profile and cytokine levels were measured, and echocardiography was performed at baseline and bimonthly. Left ventricular mass indices were calculated from the echocardiograms.

**Results:** Cytokine levels were above normal in all patients before treatment was initiated with atorvastatin or candesartan. In group A, atorvastatin decreased low-density lipoprotein (LDL) cholesterol at 2 months and increased high-density lipoprotein (HDL) cholesterol at 4 months; it also decreased IFN-γ, TNF-α, and IL-6 at 4 months and CRP at 6 months. In group C, candesartan regressed LVH at 4 months; it also decreased IFN-γ, TNF-α, and IL-6 at 2 months and CRP at 4 months. When candesartan was added to the group A regimen and atorvastatin was added to the group C regimen, additive decreases in cytokine levels occurred. Atorvastatin lowered LDL cholesterol and increased HDL cholesterol when added to group C. Candesartan regressed LVH when added to group A.

**Discussion:** IFN-γ, TNF-α, and CRP aggravate atherosclerosis and myocardial hypertrophy. IL-6 increases CRP. Patients with diabetes have increased cytokine levels and are at increased risk for coronary artery disease, hypertension, and LVH. Atorvastatin decreases hyperlipidemia and CRP, and candesartan decreases hypertension.
Abstract #809

Effects of Exenatide on First- and Second-Phase Insulin Secretion in Response to Intravenous Administration of Glucose in Patients With Type 2 Diabetes

David G. Maggs, MD, MRCP, Frauke Fehse, MD
Michael Trautmann, MD, Jens Holst, MD
Amy Halseth, PhD, Mark Fineman,
Dennis Kim, MD, and Michael Nauck, MD

Background and Objective: The incretin mimetic, exenatide, increases insulin secretion (IS) during hyperglycemia. The current study examined whether intravenously administered exenatide enhances first- and second-phase IS in response to an intravenous glucose bolus in patients with type 2 diabetes mellitus (T2DM).

Methods: Thirteen patients (11 men and 2 women) with T2DM (age 56 ± 7 years; body mass index 31.7 ± 2.4 kg/m²; and hemoglobin A1c 6.6 ± 0.7%; all data mean ± SD), treated with diet and exercise, metformin, or acarbose, were compared with 12 healthy subjects (9 men and 3 women; age 57 ± 9 years; body mass index 32.0 ± 2.9 kg/m²) who did not receive exenatide.

Results: In patients with T2DM, insulin was infused to reduce blood glucose levels to 80 to 100 mg/dL within ~3 hours, at which time exenatide or placebo infusion commenced. After 180 minutes of infusion of exenatide or placebo, and 30 minutes after discontinuation of insulin, an intravenous glucose bolus was given. Before intravenous administration of the glucose bolus, exenatide had no stimulatory effect on IS. In patients with T2DM, exenatide increased insulin (P<0.005) and C-peptide area under the curve (P<0.005) integrated incremental responses during the first (0 to 10 minutes) and second (10 to 120 minutes) phases of IS by 2- to 3-fold.

Discussion: The rapid response of IS in healthy subjects was mimicked in exenatide-treated patients with T2DM. The maximal IS rate occurred 4 minutes after intravenous administration of glucose in both groups.

Conclusion: Exenatide restored first- and second-phase IS in patients with T2DM. This result is consistent with the ability of exenatide to improve beta-cell function rapidly.

Abstract #819

Use of Octreotide for Refractory Hypoglycemia Caused by Sulfonylurea Treatment of Diabetes Mellitus

Rita Rosemary González, MD, Susan B. Zweig, MD,
Romy J. Block, MD, and Loren W. Greene, MD, FACP, FACE

Objective: To describe a case of a man with renal insufficiency from diabetes who was treated with glyburide and who presented with prolonged hypoglycemia unresponsive to large intravenous doses of glucose, treated successfully with subcutaneously administered octreotide.

Methods: A 60-year-old man with type 2 diabetes who was treated with glyburide (7.5 mg orally twice a day) and who had chronic renal insufficiency presented to the emergency department because of persistently low blood glucose levels accompanied by symptoms of fevers, sweats, and nightmares. Laboratory tests revealed a blood glucose level of 33 mg/dL and a serum creatinine concentration of 6.2 mg/dL. The patient was treated with 5% dextrose and, subsequently, 10% dextrose infusions, without any improvement (mean glucose level of 35 mg/dL). Despite the additional administration of 4 ampules of 50% dextrose, the blood glucose value remained low. Sixteen hours after his presentation, he was given 50 µg of octreotide subcutaneously every 6 hours for 24 hours.

Results: Two hours after the subcutaneous administration of octreotide, his blood glucose level stabilized. His glucose values normalized in a range between 84 and 138 mg/dL during a 24-hour period after he received octreotide subcutaneously.

Discussion: Standard emergency treatment for hypoglycemia, regardless of the cause, begins with administration of ampules of 50% dextrose. If the hypoglycemia is persistent, glucose is administered intravenously. Glucose itself stimulates release of insulin in proportion to the blood glucose concentration. In the presence of sulfonylureas, this response is exaggerated.

Another mainstay treatment of hypoglycemia is the use of glucagon. Glucagon stimulates glycogenolysis in the liver, allowing for increased glucose in the bloodstream. In addition, glucagon directly stimulates the beta cells of the pancreas and thereby leads to increased insulin release. Consequently, glucagon should probably be contraindicated in the treatment of refractory hypoglycemia caused by sulfonylureas because it may exacerbate the same mechanism.

Several case reports support the use of diazoxide in sulfonylurea overdose. Unlike glucose and glucagon, the antihypertensive agent diazoxide does not increase insulin secretion. Unfortunately, the use of diazoxide is limited because of side effects, including hypotension, reflex...
tachycardia, and sodium retention. Therefore, diazoxide is not an ideal treatment option in patients with renal failure.

**Conclusion:** Octreotide is an effective and safe treatment for patients with refractory hypoglycemia attributable to sulfonylureas.

**Abstract #822**

**Latent Autoimmune Diabetes of Adulthood in a 39-Year-Old Woman With Congenital Rubella Syndrome**

*Eric Hoffman Orth, DO*

**Objective:** To discuss diabetes mellitus and latent autoimmune diabetes of adulthood (LADA) associated with congenital rubella syndrome (CRS).

**Case Presentation:** A 39-year-old woman with a remote medical history of CRS resulting in congenital deafness and heart disease was self-referred to the University of Missouri Diabetes Center for management of diabetes mellitus. Diabetes had been diagnosed 1 year earlier and managed with Ultralente insulin, 10 U twice daily, which the patient had discontinued using 3 months previously because of recurrent adrenergic hypoglycemic symptoms. Body mass index was 18.5 kg/m². Laboratory evaluation revealed the following: hemoglobin A₁c, 7.0% (normal range, 4 to 6%); glutamic acid decarboxylase antibodies, positive at 8.92 U/mL (normal range, 0 to 1.45); thyroid peroxidase antibodies, positive at >70 IU/mL (normal range, 0 to 2.0); C peptide, 0.508 pmol/mL (normal, 0.22 to 1.20); and fasting serum glucose, 116 mg/dL. The patient accepted and tolerated small-dose basal insulin therapy with insulin glargine, 6 U daily (each morning).

**Discussion:** LADA is a relatively new term used to explain the indolent onset of islet cell antibody-positive diabetes, after age 35 years. In contrast to patients with type 1 diabetes mellitus (T1DM), those with LADA are older, have fewer hyperglycemic symptoms, and have fewer metabolic crises.

Chronic thyroiditis, T1DM, and other autoimmune disorders have long been recognized as disproportionately common in patients with CRS, an underlying genetic predisposition plus an infectious or environmental trigger being the most evidence-supported explanation. As in patients with T1DM without CRS, an increased prevalence of HLA-DR3 and a reduced prevalence of HLA-DR2 haplotypes have been recognized in patients with CRS in whom “classic” T1DM develops. Pancreatic islet cell cytotoxic surface antibodies have also been identified in 20% of patients with CRS.

**Conclusion:** This case demonstrates that LADA as well as “classic” T1DM may occur as a late autoimmune consequence of CRS.

**Abstract #823**

**Long-Term Postoperative Outcome in Patients With Diabetes After Forefoot Amputation for Underlying Osteomyelitis**

*Nirali Amarish Patel, MBBS, Stefan Bughi, MD, Jennifer Sumcad, BS, Richard Chambers, MD, Maureen O’Hara, PA-C, Alice To, PharmD, and Sylvia J. Shaw, MD, FACE*

**Background and Objective:** The optimal duration of postoperative antibiotics after diabetes-related foot amputation has not been well defined. With the availability of new and potent orally administered antibiotics and the changes in medical practice, the duration of hospitalization has decreased. The aim of this study was to compare the outcome after a foot surgical procedure in patients with diabetes who had long-term (14 day) versus short-term (7 day) hospitalization.

**Methods:** In this retrospective study, we compared the postsurgical outcome in 42 patients with type 2 diabetes (T2DM) who underwent forefoot amputation (toe, transmetatarsal, or ray resections) at a tertiary referral center for diabetic foot and then participated in follow-up at the orthopedic foot and shoe clinic. All patients received a total of 2 weeks of postoperative antibiotic therapy, which was based on the intraoperative culture results. The patient group in year 2002 (N = 22) had 2 weeks of hospitalization and parenterally administered antibiotics, whereas the patient group in 2003 (N = 20) had 1 week of hospitalization during which antibiotics were given parenterally, followed by 1 week of orally administered antibiotics as an outpatient. At the time of dismissal from the hospital, none of the study patients had evidence of residual infection at the surgical site.

**Results:** There were no significant differences between the two groups (2002 versus 2003) in regard to age (51 ± 11 years versus 51 ± 11 years), duration of T2DM (11 ± 11 years versus 10 ± 8 years), fasting blood glucose (158 ± 74 mg/dL versus 144 ± 44 mg/dL), leukocyte count (9.4 ± 12 × 10⁹/µL versus 8.5 ± 3 × 10⁹/µL), and serum albumin (3.1 ± 0.5 g/dL versus 2.9 ± 0.5 g/dL). The numbers of patients seen for follow-up were 28 of 42 (67%) at 3 months and 24 of 42 (57%) at 6 months. Postsurgical complications—such as cellulitis, recurrent ulcer, drainage at the surgical site, or repeated proximal
foot amputation—at the 3-month and 6-month follow-up visits were as follows:

<table>
<thead>
<tr>
<th>Year</th>
<th>Complications at follow-up</th>
<th>Repeated proximal amputation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3 mo</td>
<td>6 mo</td>
</tr>
<tr>
<td>2002*</td>
<td>2/13</td>
<td>0/11</td>
</tr>
<tr>
<td></td>
<td>(15%)</td>
<td>(0%)</td>
</tr>
<tr>
<td>2003†</td>
<td>7/15</td>
<td>2/13</td>
</tr>
<tr>
<td></td>
<td>(47%)</td>
<td>(15%)</td>
</tr>
<tr>
<td>*</td>
<td>Hospitalization for 2 weeks.  †</td>
<td>Hospitalization for 1 week.</td>
</tr>
</tbody>
</table>

**Discussion:** Our data show a trend toward more complications at 3 months in the group of patients with shorter hospitalization. This finding suggests early use of the residual limb, noncompliance (that is, with medications, use of anteroposterior splints, or weight bearing on the heel), or a combination of these factors.

**Conclusion:** Our preliminary data show no statistically significant difference in postoperative complications between the two groups of patients studied. Further studies enlisting larger numbers of patients are needed to assess the significance of the duration of hospitalization on the long-term outcome of patients with diabetes who undergo foot amputation.

**Abstract #825**

**Correlation of C-Reactive Protein Levels With Insulin Resistance in a Healthy North Indian Population**

Ritesh Panwar, MD, and Sachin Kumar Jain, MBBS, MD, DM, FACE

**Objective:** To study the correlation of circulating levels of C-reactive protein (CRP) with insulin resistance in a healthy population.

**Methods:** We enrolled 100 healthy adults (50 men and 50 women), who ranged in age from 20 to 55 years, in this study. CRP levels were measured by a quantitative immunoturbidimetric method. Blood glucose and serum insulin levels were measured in the fasting state and at 2 hours after a 75-g oral glucose load in all subjects. Insulin resistance was estimated by homeostasis model assessment (HOMA-IR) (1).

**Results:** The mean CRP level was 5.57 mg/L (SD + 3.00; range, 0.8 to 15.4). CRP levels showed a positive correlation with fasting blood glucose ($r = 0.241; P<0.05$), postprandial blood glucose ($r = 0.237; P<0.05$), fasting serum insulin ($r = 0.348; P<0.0001$), postprandial serum insulin ($r = 0.429; P<0.0001$), and also HOMA-IR ($r = 0.343; P<0.0001$). Moreover, we observed a gradual increase in values of fasting blood glucose, postprandial blood glucose, fasting serum insulin, postprandial serum insulin, and HOMA-IR across the quartiles into which the study population was stratified on the basis of CRP levels.

<table>
<thead>
<tr>
<th>CRP</th>
<th>FBG</th>
<th>PPBG</th>
<th>FSI</th>
<th>PPSI</th>
<th>HOMA</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.8-3.5</td>
<td>85.46</td>
<td>105.9</td>
<td>13.1</td>
<td>66.5</td>
<td>2.6</td>
</tr>
<tr>
<td>3.6-4.8</td>
<td>89.46</td>
<td>106.2</td>
<td>19.2</td>
<td>89.4</td>
<td>4.3</td>
</tr>
<tr>
<td>4.9-6.3</td>
<td>90.40</td>
<td>111.9</td>
<td>25.57</td>
<td>90.4</td>
<td>6.2</td>
</tr>
<tr>
<td>6.4-15.4</td>
<td>92.54</td>
<td>111.1</td>
<td>36.7</td>
<td>92.5</td>
<td>8.4</td>
</tr>
</tbody>
</table>

**Discussion:** Increased insulin resistance has been associated with increased levels of various cytokines in normal healthy populations. In this study, we found that CRP levels were positively correlated with various measures of insulin resistance in our study population and that progressively higher CRP quartiles were associated with increases in measures of insulin resistance.

**Conclusion:** CRP is a measure of subclinical and clinical inflammation. CRP levels are strongly correlated with insulin resistance (as measured by HOMA-IR), even in healthy adults. Accordingly, increased CRP levels may predispose to accelerated or premature atherosclerotic disease.

**Reference**


**Abstract #826**

**Insulin Autoimmune Hypoglycemia—An Unusual Presentation in a White Woman**

Andrea Tom, MD, and Ananda Basu, MD, MRCP

**Background and Objective:** Autoimmune hypoglycemia is rare; the prevalence is increased in the Asian population in comparison with the white population. We describe a white patient with this disorder.

**Case Presentation:** A 72-year-old woman without diabetes presented with hypoglycemia after a recent hospitalization. She was in her usual state of health until April 2004, when she was treated for cellulitis and septic arthritis with 6 weeks of vancomycin, clindamycin, and
piperacillin-tazobactam. She recovered fully until June 2004, when she began to experience night sweats. She was admitted to the hospital, where her plasma glucose level was 30 mg/dL and she had symptoms of shaking, clamminess, and hunger relieved by glucose intake. During the subsequent week, both fasting and postprandial episodes of repeated symptoms occurred and were relieved by glucose intake. No neuroglycopenic symptoms were reported. During an episode of hypoglycemic symptoms, her plasma glucose concentration was 43 mg/dL, serum insulin level was 2,154 μU/mL, and serum C-peptide value was 8.5 ng/mL. Magnetic resonance imaging of the abdomen and endoscopic ultrasonography revealed no evidence of an insulinoma. The patient was dismissed from the hospital and told to eat frequent meals. She had minimal hypoglycemic symptoms thereafter.

Subsequently, an outpatient fast was completed during which the patient was never hypoglycemic or symptomatic, but she had the following values at the end of an 18-hour fast: insulin 347 μU/mL, C peptide 1.9 ng/mL, β-hydroxybutyrate 0.9 mmol/L, and hemoglobin A1c 5.2%. A sulfonlurea screen (done by triple quadrupole tandem mass spectrometry) was negative. Insulin antibodies showed 61% binding to human insulin by the 125I-labeled method (normal, <3%).

Discussion: In a review of the literature, we found 31 cases of insulin autoimmune hypoglycemia in white patients (6 cases reported by the Mayo Clinic). Insulin autoimmune syndrome, also known as Hirata’s syndrome, has been well studied in Japanese and Korean populations. Although the Asian population has demonstrated an equal occurrence of this disorder in male and female patients, the white population has shown a female preponderance. There is a bimodal peak age at onset in the Asian population (in the 2nd and 6th decades of life), in comparison with a peak occurrence in the 4th decade of life in white subjects. The Asian population predominantly shows a polyclonal pattern of IgG insulin antibodies, whereas the white population shows a monoclonal pattern. In both, however, an HLA-DR4 association has been noted. There is no consistent pattern of symptom onset relative to being postprandial or fasting episodes. On the basis of our experience, white patients usually have a more protracted course, although our current patient was an exception. A clue to the diagnosis of the disorder is the presence of very high total insulin concentrations in non-diabetic patients with hypoglycemia. Insulin antibodies should be measured in all patients with hypoglycemia who have evidence of excessive endogenous pancreatic peptides.

Conclusion: Clinicians should consider the diagnosis of autoimmune hypoglycemia in patients with extremely high serum insulin levels. The features of autoimmune hypoglycemia differ in Asian patients in comparison with those in white patients.

Abstract #832

The Good, the Bad, and the Ugly: The Interaction of a Chronic Disease, a Behavior, and a Psychiatric Illness

Raja Shekhar Reddy Sappati Biyyani, MD, Arvind Y. Krishna, MD, FACE, Smita Battula, MBBS, Catherine Durishin, MD, Anil Singh, MD, MPH, Loren M. Kirchner, MD, Sanjiv Khullar, MD, FACP, and Suresh Uppalapu, MD

Background and Objective: Hepatic hyperglycogenosis is an uncommon problem associated with uncontrolled type 1 diabetes mellitus, usually in noncompliant patients. We describe a young woman with long-standing type 1 diabetes and anorexia nervosa, in whom severe hyperglycogenosis developed as a result of non-compliance with her insulin regimen because of “fear of gaining weight.”

Case Presentation: A 20-year-old white woman presented with diabetic ketoacidosis (DKA) and elevated results of liver function tests (LFTs). On examination, she was very thin and had pronounced hepatomegaly. The following laboratory values were noted (normal ranges shown in parentheses): aspartate aminotransferase 4,443 U/L (15 to 46); alanine aminotransferase 1,663 U/L (9 to 52); and alkaline phosphatase 165 U/L (28 to 126). Ultrasonography of the abdomen revealed diffuse hyperechogenicity, suggestive of an infiltrative process. On computed tomography, her liver measured 13 cm (anteroposterior dimension) by 21 cm (transverse) by 23.4 cm (craniocaudal). A liver biopsy revealed no evidence of inflammation but severe hyperglycogenosis. Laboratory evaluation for other causes of elevated results of LFTs was unremarkable (hepatitis A, B, and C, human immunodeficiency virus, Epstein-Barr virus, cytomegalovirus, anti-smooth muscle antibodies, antinuclear antibodies, ceruloplasmin, α1-antitrypsin, and rapid plasma reagin). The DKA corrected rapidly, and her LFT results returned to normal. This patient, however, appears to have perpetuated a pattern of having a poor body self-image, stopping eating, and discontinuing her insulin therapy because of fear of weight gain. This behavior has led to several admissions for DKA, each accompanied by elevated levels of liver enzymes. Despite attempts at aggressive diabetic and psychiatric care, the patient continues to be noncompliant, and her liver remains substantially enlarged.

Conclusion: Hepatic hyperglycogenosis, an uncommon finding, is usually seen in patients with uncontrolled type 1 diabetes. The condition is reversible and without long-term consequences if patients improve their diabetes control. This case highlights the unique interaction among a psychiatric illness (weight control is “the good” gone too
Exenatide is an incretin mimetic with glucoregulatory activities in patients with type 2 diabetes (T2DM). Subjects with T2DM were enrolled in two phase 2, randomized, triple-blind, placebo-controlled studies, which examined dose response (study 1) and the effects of exenatide monotherapy (study 2) on glucose control, determined by hemoglobin A1c (HbA1c) values during a period of 28 days.

**Methods:** Both studies began with a 2-week, single-blind, placebo lead-in, followed by 28 days of treatment. Study 1 consisted of 95 patients (52 women and 43 men) (age 52 ± 10 years, body mass index 34.8 ± 5.5 kg/m², HbA1c 7.5 ± 0.7%, and duration of diabetes 3.5 ± 3.2 years; all data, mean ± SD) who received placebo or 5 μg or 10 μg of exenatide subcutaneously twice a day for 28 days. Seventy-five percent of study subjects were taking metformin, whereas the other 25% were treated with diet and exercise only (no pharmacologic antidiabetic agents). All patients continued their treatments throughout the study. Study 2 consisted of 48 patients (29 women and 19 men) (age 54 ± 9 years, body mass index 33.9 ± 5.2 kg/m², HbA1c 7.9 ± 1.0%, and duration of diabetes 2.4 ± 1.7 years; all data, mean ± SD) who received placebo or 10 μg of exenatide subcutaneously twice a day for 28 days. Because the 75% of subjects taking orally administered antidiabetic agents discontinued their use 4 to 5 weeks before the triple-blind period, exenatide was tested in the absence of background antidiabetic therapy.

**Results:** In study 1, HbA1c changes from baseline to day 28 were comparable between the exenatide monotherapy arm (with diet and exercise) (mean ± SE: +0.1 ± 0.1%, -0.5 ± 0.2%, and -0.6 ± 0.1% in the placebo, 5-μg, and 10-μg arms, respectively) and the metformin + exenatide arm (mean ± SE: +0.1 ± 0.1%, -0.3 ± 0.1%, and -0.4 ± 0.1% in the placebo, 5-μg, and 10-μg arms, respectively). In study 2, HbA1c changes from baseline to day 28 showed decreases with exenatide treatment (mean ± SE: +0.2 ± 0.1% with placebo; -0.4 ± 0.1% with 10 μg of exenatide). In both studies, mild to moderate nausea was the most frequent adverse event.

**Discussion:** Treatment of patients who have T2DM with exenatide monotherapy for 28 days resulted in reductions in HbA1c comparable to those seen with addition of exenatide on a background of metformin. Overall, exenatide was generally well tolerated, with the most common adverse events being gastrointestinal symptoms, consistent with findings in prior studies.

**Conclusion:** Exenatide may be a potential treatment for patients with T2DM, either as an adjunctive therapy or as a monotherapy.

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**Abstract #834**

**Effect of Pramlintide on Hemoglobin A1c, Body Weight, and Insulin Use in Patients With Type 1 Diabetes Failing to Achieve Glycemic Targets With Insulin Therapy**

David G. Maggs, MD, MRCP, Richard A. Guthrie, MD, FAAP, FACE, Diane M. Karl, MD, FACE, Yan Wang, PhD, and Gayle Lorenz, RN

**Background and Objective:** When pramlintide (PRAM), an amylin analogue, was administered to patients with type 1 diabetes mellitus (T1DM), it reduced postprandial glucose excursions, hemoglobin A1c (HbA1c), and body weight in double-blind, placebo-controlled pivotal studies. This multicenter, open-label study examined the effects of PRAM on HbA1c, body weight, insulin use, 7-point glucose profile, and safety in a clinical setting.

**Methods:** In 265 patients with T1DM (age 43 ± 11 years, body mass index 29 ± 5 kg/m², HbA1c 8.0 ± 1.1%, and diabetes duration 21 ± 10 years; all data, mean ± SD), PRAM treatment was initiated by escalating from 15 to 60 μg, as tolerated, with a recommended 30% to 50% reduction in prandial insulin. The majority of the maintenance PRAM doses were 30 or 60 μg (three times a day or four times a day). After initiation of PRAM therapy, patients adjusted insulin use to achieve glycemic targets.

**Results:** At 26 weeks, there were significant \( P<0.05 \) reductions in mean HbA1c, body weight, and short-acting insulin dose of 0.18%, 3.0 kg, and 22%, respectively. Mean postprandial glucose levels trended lower (12 to 21 mg/dL) across all meals. The most common adverse events were nausea (mild to moderate in 38% and severe in 3%) and vomiting (mild to moderate in 8% and severe in <1%). The severe hypoglycemia event rate was 0.23 (0 to 6 months). Responses to a nonvalidated questionnaire indicated that many patients generally felt better; they perceived better control over blood glucose levels, weight, and ability to cope with their disease.

**Discussion:** Dose escalation of PRAM up to 60 μg as an adjunct to insulin therapy lowered HbA1c, body weight, insulin use, and daily glucose variation. Nausea incidence and hypoglycemia event rates were reduced in
Abstract #839

Improvements in Lipid and Glucose Abnormalities in Insulin-Resistant, Nondiabetic Patients Treated With Tesaglitazar

Ingrid Gause-Nilsson, MD, Björn Fagerberg, MD, Sion Edwards, MD, Tamas Halmos, MD, Jerzy Lopatynski, MD, Herbert Schuster, MD, Steen Stender, MD, Grethe Støa-Birketvedt, MD, Serena Tonstad, MD, and Peter Öhman, MD

Background and Objective: Insulin resistance (IR) is a key feature of type 2 diabetes and metabolic syndrome and is associated with abnormalities in both glucose and lipid metabolism that increase the risk of developing vascular disease. The Study in Insulin Resistance examined the effects of tesaglitazar, a novel dual-acting peroxisome proliferator-activated receptor-alpha/gamma agonist, on lipid and glucose abnormalities in nondiabetic patients with IR.

Methods: The efficacy and safety of tesaglitazar (0.1, 0.25, 0.5, and 1.0 mg once daily for 12 weeks) were compared with placebo in 390 patients (23% women) with manifestations of IR. The mean baseline characteristics (range) were as follows: age, 50 years (29 to 77); body mass index, 31 kg/m² (21 to 41); and triglycerides (TG), 266 mg/dL (151 to 638). Lipid and glucose variables were assessed, and low-density lipoprotein (LDL) particle size was measured by using nuclear magnetic resonance.

Placebo-Corrected Change From Baseline (%)

<table>
<thead>
<tr>
<th></th>
<th>0.1 mg (N = 60)</th>
<th>0.25 mg (N = 70)</th>
<th>0.5 mg (N = 58)</th>
<th>1.0 mg (N = 65)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TG</td>
<td>-10</td>
<td>-16*</td>
<td>-27*</td>
<td>-37*</td>
</tr>
<tr>
<td>HDL</td>
<td>4</td>
<td>1</td>
<td>11*</td>
<td>16*</td>
</tr>
<tr>
<td>TC</td>
<td>-1</td>
<td>-4</td>
<td>-3</td>
<td>-8*</td>
</tr>
<tr>
<td>FFA</td>
<td>-17</td>
<td>-18*</td>
<td>-21*</td>
<td>-40*</td>
</tr>
<tr>
<td>LDL</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>-3</td>
</tr>
<tr>
<td>Insulin</td>
<td>-9</td>
<td>-13*</td>
<td>-16*</td>
<td>-35*</td>
</tr>
<tr>
<td>HOMA</td>
<td>-6</td>
<td>-18*</td>
<td>-22*</td>
<td>-41*</td>
</tr>
</tbody>
</table>

*Significantly different from baseline.

Results: Tesaglitazar dose-dependently reduced fasting TG, total cholesterol (TC), and free fatty acids (FFA) and increased high-density lipoprotein (HDL) cholesterol. Compared with placebo, the 1-mg dose of tesaglitazar produced statistically significant improvements in all variables examined except LDL cholesterol. Although LDL cholesterol levels were unchanged, LDL particles were significantly and dose-dependently enlarged. Among patients who received the 1.0-mg dose of tesaglitazar and had pattern B (mean particle diameter up to 20.5 nm) at baseline, 79% (30 of 38) had a change to the less atherogenic pattern A (mean particle diameter greater than 20.5 nm). Tesaglitazar also produced significant and dose-dependent decreases in fasting plasma glucose (-5.9 mg/dL compared with baseline for the 1.0-mg dose), insulin, and homeostasis model assessment (HOMA); these improvements were significant for the three highest doses. No dose-dependent adverse events were seen.

Discussion: Tesaglitazar was well tolerated for a 12-week period and produced significant and dose-dependent improvements in lipid and glucose metabolism and insulin sensitivity in a nondiabetic population with manifestations of IR.

Conclusion: Improving these lipid and glucose variables may lead to reductions in macrovascular disease risk in this patient group.

Abstract #848

Exubera Leads to Greater Potential for Acceptance of Insulin Therapy in US Patients With Inadequately Controlled Type 2 Diabetes

Lawrence Blonde, MD, FACP, FACE, Nick Freemantle, PhD, and George E. Dailey III, MD, FACE

Objective: To examine the effect of the potential availability of Exubera, an inhaled insulin delivery system in development for the treatment of type 1 and type 2 diabetes mellitus (T2DM), on acceptance of insulin therapy in patients from US investigational sites of a previously reported multinational study.

Methods: This study consisted of 105 patients with inadequately controlled T2DM (hemoglobin A1c [HbA1c] ≥8%), on a diet and exercise regimen or receiving monotherapy or combination oral antidiabetic agents (OA), who were randomized into 2 groups. Group A (N = 51, mean age 58 years, 60% male, mean HbA1c 9.6%) received educational information on currently available treatment options for T2DM. Group B (N = 54, mean age 58 years, 43% male, mean HbA1c 9.9%) received educational information about Exubera as another potential therapy in addition to information about currently available treatment options. Patients, in consultation with their health-care professionals, were asked to make a choice regarding their future therapy. Choices could include making no change in their current therapy or adding or switching to any of the available treatment options (including
Exubera in group B). The primary outcome was the proportion of patients choosing insulin.

**Results:** In group B, 28% of patients chose a treatment option that included insulin, in comparison with 8% in group A (odds ratio 4.52; 95% confidence interval 1.28 to 19.97; \( P = 0.007 \)). The treatment choices are summarized as follows:

<table>
<thead>
<tr>
<th>Choice</th>
<th>Group A (N = 51)</th>
<th>Group B (N = 54)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>Did not choose insulin</td>
<td>47</td>
<td>92</td>
</tr>
<tr>
<td>No change</td>
<td>23</td>
<td>45</td>
</tr>
<tr>
<td>Add/replace OA</td>
<td>24</td>
<td>47</td>
</tr>
<tr>
<td>Chose insulin†</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>Subcutaneous</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>Inhaled</td>
<td>NA</td>
<td></td>
</tr>
</tbody>
</table>

*Missing data for 4 patients in group B.
†Add or change to insulin option.
‡\( P = 0.007 \).

**Discussion:** Many patients with T2DM and their health-care professionals are reluctant to initiate insulin therapy, even when noninsulin therapy fails to achieve target glycemia. Previous studies of Exubera have shown efficacy similar to that of subcutaneously administered insulin, along with improved patient satisfaction. This study demonstrated that theoretical availability of Exubera increased the choice of insulin therapy among patients with T2DM not at goal glycemia.

**Conclusion:** This US-specific subanalysis of a larger multinational study indicated that, among patients with T2DM with inadequate glycemic control despite diet and exercise or OA therapy, the availability of Exubera as a potential treatment option increased the willingness to add or change to more appropriate therapy, including insulin. Increasing the number of patients accepting insulin therapy may lead to improved glycemic control and health outcomes.

**Abstract #855**

Clinical Profile of Patients With Type 2 Diabetes Mellitus in Kaduna, Northern Nigeria

_Felicia Ohunene Anumah, MBBS, MWCP, FMCP_

**Objective:** To highlight the clinical characteristics of northern Nigerians with type 2 diabetes mellitus (DM) and to identify features that can be targeted for concerted action in reducing morbidity and mortality in patients with DM in Nigeria.

**Methods:** A descriptive study was undertaken during a 2-year period at the endocrinology clinic of Ahmadu Bello University Teaching Hospital in Kaduna, Nigeria. Consecutively attending patients with DM were recruited, and data were collected with use of a standard format and operational definitions. The patients’ clinical data were documented and analyzed.

**Results:** This study included a total of 278 patients; 117 (42.1%) were male and 161 (57.9%) were female subjects. The peak age at presentation was 51.0 ± 11.1 years, with a mean duration of diabetes of 49.3 ± 57.9 months.

Obesity was the predominant comorbidity, occurring in 182 (65.5%) of the 278 patients. The mean body mass index was 27.8 ± 5.8 kg/m². Hypertension was present in 173 (62.2%) of the study patients.

**Discussion:** The clinical profile shows that the age, sex distribution, and prevalence of hypertension were the same as in most other reported studies. Although obesity was a factor, the prevalence in these Nigerian study patients (65.5%) seemed to be lower in comparison with prevalence data from the developed world. The frequency of chronic complications at the time of initial assessment, however, was high in these study patients—a finding that could be attributable to the fact that Nigerian patients often seek medical assistance quite late in the course of their disease.

**Conclusion:** This study highlighted the association of obesity and hypertension in patients with DM. Among the common complications, neuropathy, nephropathy, diabetic eye disease, erectile dysfunction, and diabetic foot syndrome have been found to be the greatest problems. In light of the morbidity and mortality associated with these conditions, strategies for early prevention and control must be evolved.

**Abstract #860**

Glycemic Efficacy and Safety of Muraglitazar, a Novel Dual Peroxisome Proliferator-Activated Receptor-Alpha/Gamma Agonist, in Patients With Type 2 Diabetes: Results of a Double-Blind, Randomized, Parallel-Group, Dose-Comparison Study

_Cindy J. Rubin, MD, Kalyanee Viraswami-Appanna, PhD, and Fred T. Fiedorek, MD_

**Objective:** To assess the glycemic efficacy and safety of muraglitazar, a novel dual peroxisome proliferator-activated receptor-alpha/gamma agonist within the new “glitazar” class.

**Methods:** We conducted a double-blind, randomized, 24-week clinical trial in 1,477 drug-naive patients with type 2 diabetes who had inadequate glycemic control with use of a diet and exercise regimen. Patients received 1 of 5 doses of muraglitazar (ranging from 0.5 mg to 20 mg) or pioglitazone (15 mg once daily).

**Results:** Dose-dependent reductions in hemoglobin A1c (HbA1c) and fasting plasma glucose were observed
in the muraglitazar groups; the lowest dose (0.5 mg) showed minimal efficacy and served as the comparison group (control). At 24 weeks, muraglitazar in a dose of 5 mg produced clinically significant reductions in HbA1c (mean baseline HbA1c, 8.2%; mean change from baseline, −1.18%; P<0.0001 versus control) and fasting plasma glucose level (mean change, −40 mg/dL; P<0.0001 versus control). More patients receiving the 5-mg dose of muraglitazar achieved HbA1c values of ≤7% (62%) or ≤6.5% (43%) at 24 weeks than did those receiving 15 mg of pioglitazone daily (47% and 26%, respectively). In general, the glycemic efficacy of 15 mg of pioglitazone was comparable to the effect of 1.5 mg of muraglitazar, and muraglitazar was well tolerated. Incidence rates of adverse events (AEs) and serious AEs associated with muraglitazar doses of 5 mg or less and pioglitazone in a dose of 15 mg daily were comparable. Weight gain occurred with use of all efficacious muraglitazar doses, and edema was more common with the pioglitazone 15-mg dose than with any muraglitazar dose of 5 mg or less. There were no cases of congestive heart failure associated with the pioglitazone 15-mg dose or with muraglitazar doses of 5 mg or less.

Discussion: In this study, muraglitazar was generally well tolerated and efficacious in patients with type 2 diabetes at starting daily doses up to and including 5 mg.

Conclusion: Muraglitazar is a promising new treatment option for type 2 diabetes

Abstract #862

Screening for Gestational Diabetes Mellitus With Use of a 50-g Oral Glucose Load

Omololu Adegbola, MBBS, FWACS, FMCOG, and Godwin Olu Ajayi, MD, ASSP, FAGG, FRDMP, FWACS, FMCOG

Objective: To determine the predictive value of the 50-g oral glucose challenge test in the detection of gestational diabetes mellitus (GDM) in pregnant women.

Methods: At 24 to 28 weeks of gestation, 134 pregnant women attending the antenatal clinic of the Lagos University Teaching Hospital in Lagos, Nigeria, with risk factors for glucose intolerance were screened for GDM. Women known to have diabetes mellitus, those with multiple gestation, and those receiving drugs that affect glucose tolerance (such as salbutamol) were excluded from the study. Another consecutive 134 pregnant women, also at 24 to 28 weeks of gestation but without risk factors for glucose intolerance, served as control subjects after informed consent for study participation had been obtained. After an overnight fast, they were given 50 g of anhydrous glucose in 250 mL of water to drink within 5 minutes, and venous blood samples were obtained 1 hour later. All women with blood glucose levels of 130 mg/dL (7.2 mmol/L) or more in both groups were considered to have abnormal results and underwent a diagnostic 3-hour 100-g oral glucose tolerance test (OGTT) within 1 week, also after an overnight fast. A repeated 100-g OGTT was done at 30 to 32 weeks if the initial result was normal. Those women with a 50-g glucose challenge test value of less than 130 mg/dL underwent a diagnostic 3-hour 100-g OGTT at 30 to 32 weeks of gestation. The diagnosis of GDM was based on the criteria established by Carpenter and Coustan(1), who required at least two plasma glucose values after a 100-g OGTT to meet or exceed the following: 95 mg/dL fasting, 180 mg/dL at 1 hour, 155 mg/dL at 2 hours, and 140 mg/dL at 3 hours. These findings were analyzed in relationship to the proportion of those with a positive glucose challenge test result (plasma glucose level of 130 mg/dL or more 1 hour after a 50-g glucose load). The plasma glucose value was determined by the glucose oxidase method. The study commenced in May 2002 and ended in February 2003, spanning a period of 9 months. The institution’s ethics committee approved the study.

Results: Of the 134 women in the test group, 113 (84.3%) completed the study, as did 109 (81.3%) of the 134 women in the control group. The data from these women were analyzed. The mean age was 31.8 ± 4.1 years for the test group and 30.1 ± 3.9 years for the control group. The mean parity was 1.5 ± 1.2 for the test group and 1.0 ± 1.2 for the control group. No statistically significant difference was found in the age or parity between the 2 groups (P = 0.564546 and P = 0.999550, respectively). The mean blood glucose level 1 hour after a 50-g glucose load was 120.5 ± 21.4 mg/dL for the test group and 115.0 ± 21.8 mg/dL for the control group—no statistically significant difference (t value = 1.904888; P value = 0.847507).

The predictive values (that is, sensitivity, specificity, positive predictive value, and negative predictive value, respectively) of the 50-g glucose load at various screening values were as follows (test group versus control group): at a screening value of 130 mg/dL—100% versus 100%, 76.4% versus 88.5%, 21.9% versus 29.4%, and 100% versus 100%, respectively; at a screening value of 140 mg/dL—100% versus 100%, 88.7% versus 93.3%, 36.8% versus 41.7%, and 100% versus 100%, respectively; at a screening value of 150 mg/dL—71.4% versus 80%, 93.4% versus 98.1%, 41.7% versus 66.7%, and 98% versus 99%, respectively; and at a screening value of 160 mg/dL—42.9% versus 80%, 97.2% versus 99%, 50% versus 80%, and 96.3% versus 99%, respectively. Seven women in the test group and 5 women in the control group were diagnosed as having GDM with the 3-hour 100-g OGTT.

Discussion: This study was performed on a homogeneous group of women, inasmuch as the age and parity distributions were not statistically significantly different between the groups. GDM was found in 6.2% of the test group and 4.6% of the control group, an overall prevalence of 5.4% for the study. Among the patients with newly diagnosed GDM, 58% had risk factors for glucose intolerance, and 42% had no such risk factors. Therefore, propo-
ments of selective screening for GDM based on risk factors may need to reconsider their stance because this approach would have overlooked 42% of the women with GDM in this study. The sensitivity and negative predictive values were both 100% at screening values of 130 mg/dL and 140 mg/dL; however, at 140 mg/dL, the specificity improved. The low positive predictive value in this study resulted from the low overall prevalence of GDM (5.4%). The positive predictive value increases with increasing prevalence of a condition sought and also with improved specificity of the test used. In our study, the positive predictive value gradually increased as the screening value was increased; nevertheless, this improvement was at the expense of the sensitivity.

Conclusion: On that basis of our findings in this study, we would recommend that all pregnant women should be screened for GDM at 24 to 28 weeks of gestation with a 50-g oral glucose load and that there should be no selective screening based on risk factors. The screening value of 140 mg/dL (7.8 mmol/L) should be used because the sensitivity is 100% and, in addition, this value has a higher specificity than does the 130 mg/dL (7.2 mmol/L) screening value. GDM is unlikely to be present if the venous blood glucose level is less than 140 mg/dL 1 hour after administration of a 50-g oral glucose load because the negative predictive value at this screening level is 100%.

Reference


Abstract #865

A Practical Intravenous Insulin Infusion Protocol for Intense Management of Hyperglycemia in the Intensive Care Unit

Michael S. Balkin, MD, FACE, Charles Mascioli, MD, and Virginia Smith, RN

Objective: To design and then assess an insulin infusion protocol (IIP) with the following attributes: (1) yields good glucose control; (2) results in a low incidence of hypoglycemia; and (3) is practical, as determined by multiple factors including a low frequency of necessary glucose sampling.

Methods: We designed and then instituted an IIP for our medical intensive care unit (ICU) and our coronary care unit (CCU) for use in all patients not in diabetic ketoacidosis. The key elements of our protocol are three adjustment tables. The particular adjustment table to be used is based only on the current insulin infusion rate. Each adjustment table is a matrix that contains numbers, rather than instructions. Both the first vertical column and the first horizontal row list a series of blood glucose ranges from 75 mg/dL to >300 mg/dL. To use the table, a nurse locates the patient’s last blood glucose measurement in the first column and the current blood glucose value in the first row. The intersection of those two values is a cell containing the number of units, either positive or negative, by which the insulin infusion is to be changed. There are no further calculations to be made and no additional tables to consult.

Results: Currently, we have analyzed the results for the first 35 patients in whom our IIP has been used for at least 8 hours. No physician input was required for the administration of this IIP.

<table>
<thead>
<tr>
<th>Mean blood glucose value (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before initiation of IIP: 244.8 ± 95.3</td>
</tr>
<tr>
<td>With use of IIP: 132.7 ± 48.7</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Blood glucose values</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;60 mg/dL: 15 (0.9%)</td>
</tr>
<tr>
<td>75-140 mg/dL: 62.4%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patient hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>On IIP: 3,106</td>
</tr>
<tr>
<td>IIP stopped for hypoglycemia: 56.5 (1.8%)</td>
</tr>
</tbody>
</table>

| Mean frequency of glucose sampling: 113 min |

Discussion: A large, recently concluded intervention study demonstrated decreased mortality and morbidity in ICU patients with hyperglycemia who were treated with an intense insulin protocol (1). That protocol, however, resulted in a >5% rate of occurrence of severe hypoglycemia (<40 mg/dL) and necessitated substantial physician input. Our IIP resulted in minimal hypoglycemia and did not necessitate physician input, while achieving good glucose control. Our study also reports data not noted in other insulin protocol studies—frequency of glucose sampling and amount of time insulin was halted because of hypoglycemia.

Conclusion: We present a new IIP concept that is being used successfully in our community hospital’s ICU and CCU. It is effective and practical, in that the rate of associated hypoglycemia is very low and physician input has not been necessary. The frequency of required glucose sampling has been approximately every 2 hours, and the mean blood glucose level has been lowered from approximately 245 mg/dL to 133 mg/dL. Moreover, the infusion of insulin was halted for hypoglycemia only 1.8% of the total time.

Reference

Abstract #866

Glycemic Efficacy and Tolerability of Muraglitazar, a Novel Dual Peroxisome Proliferator-Activated Receptor-Alpha/Gamma Agonist, in Drug-Naive Patients With Type 2 Diabetes: A Randomized, Double-Blind, Placebo-Controlled Trial

Robert Frederich, MD, Kalyanee Viraswami-Appanna, PhD, and Cindy J. Rubin, MD

Objective: To evaluate the glycemic efficacy and tolerability of muraglitazar, a novel dual peroxisome proliferator-activated receptor-alpha/gamma agonist within the new “glitazar” class.

Methods: A double-blind, randomized, placebo-controlled, 24-week study was performed in 340 drug-naive patients with type 2 diabetes, who had had inadequate glycemic control with use of a diet and exercise regimen (mean hemoglobin A1c [HbA1c] at baseline, 8.0%). Mean change in HbA1c was the primary endpoint.

Results: Monotherapy with muraglitazar, 2.5 mg and 5 mg, reduced HbA1c (mean changes from baseline: −1.05% and −1.23%, respectively, versus −0.32% for placebo [P<0.0001]), with 72% of the 5-mg muraglitazar group achieving an HbA1c value of <7% at 24 weeks (58% and 30% of patients receiving 2.5 mg of muraglitazar or placebo, respectively, achieved the target). Fasting and postprandial plasma glucose levels and insulin levels improved during treatment with muraglitazar. In an open-label cohort within the same study, 109 patients with a mean baseline HbA1c of 10.7% were treated for 24 weeks with a 5-mg dose of muraglitazar. Among all patients initiating open-label treatment, muraglitazar in a dose of 5 mg reduced mean HbA1c by 2.6% from baseline. At week 24, 39% of these patients had achieved a final HbA1c value of <7%. In the open-label cohort, 62 patients completed all 24 weeks of open-label treatment and had a mean change from baseline HbA1c of −3.5%. At week 24, the mean change in body weight was 1.0 kg and 2.1 kg for the muraglitazar 2.5-mg and 5-mg groups, respectively, and −0.78 kg for those receiving placebo. Peripheral edema occurred in 8% of patients randomized to placebo or 2.5 mg of muraglitazar, in 11% of patients randomized to 5 mg of muraglitazar, and in 9% of patients receiving open-label muraglitazar in a dose of 5 mg. Except for 1 severe case in the placebo group, all edema was mild or moderate in intensity; all edema in the open-label cohort was mild. No cases of congestive heart failure occurred during double-blind therapy or in the open-label cohort.

Discussion: In this study, monotherapy with muraglitazar was generally well tolerated and provided pronounced HbA1c-lowering effects.

Conclusion: Muraglitazar, a novel dual PPAR-alpha/gamma agonist, is an effective monotherapy option for patients with type 2 diabetes.

Abstract #867

The GlycoMark Assay, an Index of Postprandial Hyperglycemia, Provides Additional Information to Achieve Optimal Glycemic Control

Bruce Sheldon Trippe, MD, FACE

Objective: To elucidate the general role of the GlycoMark assay as a reflective measure of postmeal glucose levels by describing three different relevant clinical scenarios.

Case Presentation: Case 1—Managing Postprandial Hyperglycemia in a Patient With Fluctuating Glucose Levels. A 19-year-old man with type 1 diabetes and a body mass index (BMI) of 18 kg/m² was managed with insulin infusion therapy. The patient’s hemoglobin A1c (HbA1c) levels were relatively stable, ranging from 6.7 to 7.5% during a 10-month period. His self-monitoring records showed highly variable blood glucose levels (from 130 to 257 mg/dL), which suggested that the highs and lows of individual blood glucose levels were being averaged into the “relatively stable” HbA1c values. His GlycoMark value was 4.3 µg/mL, which is indicative of hyperglycemia and suggests that this patient had poorly controlled blood glucose—consistent with the self-monitoring glucose records. The patient has been instructed to refine his blood glucose control to obtain HbA1c values below 6% with higher GlycoMark value targets—indicative of improved postprandial glucose control.

Case 2—Detecting Postprandial Hyperglycemia in a Patient With Suboptimal Control of Blood Glucose. A 13-year-old boy with type 1 diabetes and a BMI of 21 kg/m² was managed with insulin infusion therapy. His HbA1c levels showed improved control, decreasing from 8.9% to 7.6% during a 2-month period. Although preprandial glucose values were adequately controlled, this patient had documented elevated postprandial glucose levels, as determined by self-monitoring. Consistent with the presence of postprandial hyperglycemia, the GlycoMark value was 3.2 µg/mL. The patient is now monitoring postprandial glucose 2 hours after each meal, and GlycoMark will be measured to determine whether postprandial control has improved.

Case 3—Monitoring Postprandial Hyperglycemia in a Patient With Cardiovascular Complications. A 53-year-old man with a BMI of 29 kg/m² had had type 2 diabetes diagnosed at age 43 years, which was managed with rosiglitazone-metformin, insulin glargine, and insulin aspart before meals. This patient had a myocardial infarction in 1993 and has diabetic dyslipoproteinemic hypertension. HbA1c levels showed improved control, decreasing from 9.7% to 7.6% during a 3-month period. With a GlycoMark value of 5.4 µg/mL, however, significant postprandial excursions are suspected, with the concomitant cardiovascular risks. In light of the history of cardiovascular complications in this patient, monitoring postprandial hyperglycemia remains a high priority.
**Discussion:** GlycoMark is a new US Food and Drug Administration-approved glycemic test that measures 1,5-anhydroglucitol and captures the cumulative reflection of postmeal glucose levels in a single blood test. As an index of postprandial hyperglycemia, the GlycoMark assay in conjunction with the HbA1c test may be particularly useful as treatment targets are lowered and management of postmeal glucose levels becomes increasingly important.

**Conclusion:** Although HbA1c levels may indicate adequate metabolic control, postprandial hyperglycemia may be present. Because there is increasing evidence that postprandial hyperglycemia is implicated in the development of cardiovascular complications in patients with diabetes, a convenient measure of postmeal glucose levels, as provided by the GlycoMark assay, adds information to help achieve optimal glycemic control.

**Abstract #873**

**Association of Patterns in the Oral Glucose Tolerance Test and Different Clinical Features in Patients With Insulinoma**

*Fanny Rodriguez Vallejo, MD, Juan Manuel Rios Torres, MD, Francisco J. Gomez-Pérez, MD, Juan A. Rull Rodrigo, MD, and Bernardo Pérez Enriquez, MD*

**Objective:** To describe the association of various patterns on the oral glucose tolerance test (OGTT) and the different clinical features in patients with insulinoma.

**Methods:** We reviewed the OGTT results and different clinical findings in 13 patients with insulinoma who were encountered at our institution between 1994 and 2004. The patients were classified into two groups, depending on their response to the OGTT, and their clinical features were analyzed. The variables assessed in this study were age, body mass index (BMI), weight, evolution time, tumor localization and diameter, duration of the fasting test, and presence of syncope or seizures.

**Results:** Group 1, with a “hyper-hypo” curve OGTT pattern, consisted of 8 patients. They showed a maximal response of glucose at 60 minutes (serum glucose >200 mg/dL) and a minimal response at 300 minutes (serum glucose <80 mg/dL). Group 2, with a plane curve OGTT pattern, consisted of 5 patients. In these patients, the maximal glucose response occurred at 60 minutes (serum glucose >90 mg/dL) and the minimal response at 240 minutes (serum glucose <40 mg/dL).

For the 8 patients in group 1, the following mean values or data were recorded: age 33.3 years, BMI 30.5 kg/m², weight 85.18 kg, evolution time 34.25 months, localization of the insulinoma in the body or tail of the pancreas, diameter of the tumor 2.28 cm, duration of the fasting test 5.8 hours, occurrence of syncope 80%, and occurrence of seizures in 60%.

The values recorded for evolution time, BMI, weight, and serum glucose level on the OGTT response in group 1 exceeded those in group 2. The differences, however, were not significant.

**Conclusion:** We observed no autonomous patterns of the insulinomas in this study. The findings relative to insulinomas may depend on many factors, such as the molecular alterations of the insulin, the chronic hyperinsulinism, the chemical alterations of the insulin, the episodic secretion of the insulin, alterations in the counterregulatory mechanisms, or other currently unidentified variables.

**Abstract #884**

**Intrasubject Variability of Exubera Factors Comparable to Those for Subcutaneously Administered Regular Insulin in Patients With Type 2 Diabetes**

*Robert R. Henry, MD, Robert J. Fountaine, PharmD, Susan A. Willavize, PhD, Jeanine M. Fisher, MS, and David A. Fryburg, MD*

**Background and Objective:** Many deterrents to use of insulin exist, such as social stigma and fear of injection. Development of Exubera, an inhaled insulin delivery system, presents a new, noninvasive treatment option. Continual glycemic control without excessive hypoglycemic episodes is important. Therefore, any mode of administration of insulin must demonstrate practical reproducibility for consistent control.

**Methods:** A pharmacokinetic (PK) and pharmacodynamic (PD) study of 20 elderly obese patients (mean age, 72 years; mean body mass index, 33 kg/m²) with type 2 diabetes was conducted in a 4-way, randomized, crossover sequence consisting of 2 Exubera and 2 subcutaneously administered (SC) regular insulin sessions. Study subjects received either 4 mg of Exubera or a 12-IU SC injection of regular insulin. The variables of area under the curve (AUC) 0 to 2 hours, AUC 0 to 6 hours, Cmax, and tmax were determined for insulin (PK), as was the reduction in plasma glucose concentrations (PD) during the 6 hours after dose administration. Serum free insulin, C-peptide, and fasting plasma glucose levels were also measured.

**Results:** Exubera demonstrated a higher Cmax, earlier tmax, and greater AUC 0 to 2 hours than did an equivalent dose of SC regular insulin; however, total systemic insulin exposure during the 6-hour period after administration (AUC 0 to 6 hours) was similar. Consistent with the insulin PK results, early glucose lowering (AUC 0 to 2
hours) was greater with Exubera than with SC regular insulin. The intrasubject (within subject) variability for the determined PK variables was reduced for Exubera compared with SC insulin, with the reduction being significant for AUC 0 to 2 hours (P = 0.004) and max (P<0.001). The corresponding intrasubject variability of the glucose PD variables was also significantly lower for AUC 0 to 2 hours (P = 0.027) with Exubera treatment in comparison with SC insulin and was similar between treatment groups for Cmax and AUC 0 to 6 hours.

All adverse events were mild, except for 1 case of moderate hypoglycemia that occurred after treatment with SC insulin. The most common adverse event was mild hypoglycemia and associated symptoms, which were more prevalent after SC insulin therapy than after Exubera therapy. Respiratory safety and pulmonary function were maintained throughout the study period.

Discussion: The results of this study suggested that, at doses that produced comparable systemic insulin exposure for 6 hours, Exubera was absorbed more rapidly and had intrasubject variability similar to or less than that associated with SC insulin injection in elderly obese patients with type 2 diabetes who were inexperienced users of Exubera.

Conclusion: Overall, the PK profile of Exubera and its similar reproducibility to that of SC regular insulin make it well suited for use as a prandial insulin in patients with type 2 diabetes mellitus.

Abstract #886

Effects of Pioglitazone on Lipid Subparticle Profiles in Patients With Metformin or Insulin Therapy: A Double-Blind, Randomized Study of Pioglitazone Versus Placebo in Reducing or Eliminating Insulin Requirements

Mehmood Khan, MD, FACE, Allison Winokur, PhD, Alfonso Perez, MD, and Shawn Yu, PhD

Objective: To determine whether the insulin dose required to achieve glycemic control is reduced with pioglitazone hydrochloride (PIO) adjunct to metformin plus insulin or insulin alone in patients with type 2 diabetes and to examine the relative change in low-density lipoprotein (LDL) particle size.

Methods: This double-blind, randomized, placebo-controlled study included patients achieving fasting plasma glucose levels <140 mg/dL after insulin titration. Patients were randomly allocated to receive either 30 mg/day of PIO (N = 110) or placebo (N = 112), while receiving insulin and a stable dose of metformin, as applicable. Self-monitored blood glucose levels and direct clinical laboratory results were used to titrate the insulin dose needed to maintain a fasting plasma glucose level <140 mg/dL while avoiding hypoglycemia (<70 mg/dL). Lipid subparticle analysis was performed by using gradient gel electrophoresis.

Results: Baseline data and mean changes from baseline at week 20 are presented.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>Mean change (week 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin dose (U)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo group</td>
<td>57.74</td>
<td>0.75</td>
</tr>
<tr>
<td>PIO group</td>
<td>55.84</td>
<td>-11.99*</td>
</tr>
<tr>
<td>Hemoglobin A1c (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo group</td>
<td>8.59</td>
<td>-1.36</td>
</tr>
<tr>
<td>PIO group</td>
<td>8.37</td>
<td>-1.56</td>
</tr>
<tr>
<td>Large LDL (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo group</td>
<td>41.05</td>
<td>-2.50</td>
</tr>
<tr>
<td>PIO group</td>
<td>42.66</td>
<td>12.63*</td>
</tr>
<tr>
<td>Small LDL (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo group</td>
<td>38.52</td>
<td>2.97</td>
</tr>
<tr>
<td>PIO group</td>
<td>36.29</td>
<td>-10.61*</td>
</tr>
</tbody>
</table>

*P<0.001, PIO versus placebo.

Discussion: LDL subparticle distribution changed from predominantly small, dense particles (233 to 255 angstroms) to large, more buoyant particles (>206 angstroms).

Conclusion: In the presence of insulin, PIO in combination with metformin plus insulin significantly altered LDL subparticle distribution while still maintaining glycemic control and significantly reducing the insulin dosage required by patients.

Abstract #887

Effects of Pioglitazone on Lipid Levels in Patients With Metformin or Insulin Therapy: A Double-Blind, Randomized Study of Pioglitazone Versus Placebo in Reducing or Eliminating Insulin Requirements

Mehmood Khan, MD, FACE, John Whitbread, PhD, Alfonso Perez, MD, and Shawn Yu, PhD

Objective: To determine whether pioglitazone hydrochloride (PIO), in combination with metformin plus insulin or insulin alone, was efficacious in reducing the dosage of insulin required to achieve glycemic control in patients with type 2 diabetes and to examine changes in triglycerides (TG) and low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and total cholesterol (TC).

Methods: This double-blind, randomized, placebo-controlled study included patients achieving fasting plasma glucose levels <140 mg/dL after insulin titration. Patients received either 30 mg/day of PIO (N = 110) or placebo (N = 112), while receiving insulin and a stable dose of metformin, as applicable. Self-monitored blood glucose levels and direct clinical laboratory results were used to determine the appropriate insulin dose adjustments
needed to maintain a fasting plasma glucose level <140 mg/dL while avoiding hypoglycemia (<70 mg/dL). TG, LDL cholesterol, and HDL cholesterol were measured by using a 2-way analysis of covariance model, with treatment and center as the main effects and baseline value as a covariate.

**Results:** Baseline data and mean changes from baseline at week 20 are presented.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline (week 20)</th>
<th>Mean change (week 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin dose (U)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo group</td>
<td>57.74</td>
<td>0.75</td>
</tr>
<tr>
<td>PIO group</td>
<td>55.84</td>
<td>−11.99*</td>
</tr>
<tr>
<td>TC (mg/dL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo group</td>
<td>182.6</td>
<td>4.7</td>
</tr>
<tr>
<td>PIO group</td>
<td>177.5</td>
<td>5.7</td>
</tr>
<tr>
<td>HDL (mg/dL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo group</td>
<td>42.4</td>
<td>−0.2</td>
</tr>
<tr>
<td>PIO group</td>
<td>44.6</td>
<td>4.3*</td>
</tr>
<tr>
<td>LDL (mg/dL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo group</td>
<td>110.7</td>
<td>0.9</td>
</tr>
<tr>
<td>PIO group</td>
<td>106.9</td>
<td>4.0</td>
</tr>
<tr>
<td>TG (mg/dL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo group</td>
<td>140.9</td>
<td>43.7</td>
</tr>
<tr>
<td>PIO group</td>
<td>122.6</td>
<td>−0.2*</td>
</tr>
</tbody>
</table>

*P<0.001, PIO versus placebo.

**Discussion:** PIO in combination with metformin significantly increased HDL in the presence of insulin. PIO treatment also prevented increases in TG in patients with normal TG levels, while patients taking placebo showed significant increases in TG values.

**Conclusion:** Levels of HDL and TG, components of diabetic dyslipidemia, were significantly improved by the addition of PIO to metformin and insulin therapy, while glycemic control was maintained and the insulin dosage required by patients was significantly decreased.

**Abstract #890**

Atypical Antipsychotic Agents: The Incidence and Mean Time to Onset of Diabetes Mellitus

Shahzad Iqbal, MD, Faith X. Zhao, MD, Renuka Tunuguntla, MD, Deepak Thomas, MD, Mahboob A. Khan, MD, Kranti Purimetla, MD, Maria F. Renedo, MD, Zewge Deribe, MD, Nisarul Haque, MD, Gerald Posner, MD, Jochanan M. Weisenfreund, MD, Marina Kamenshchikov, MD, and Pranjal M. Agrawal, MD, MPH

**Background and Objective:** The relationship between atypical antipsychotic agents (AAPs) and hyperglycemia is not completely understood. Studies suggested an increased risk of treatment-related hyperglycemic adverse events in patients receiving AAP therapy. The purpose of this study was to investigate the incidence and mean time to onset of diabetes mellitus (DM) after initiation of treatment with AAPs.

**Methods:** We retrospectively reviewed the medical records of all patients who began AAP therapy while they were inpatients at the Interfaith Medical Center (New York) Department of Psychiatry between October 2003 and November 2004. Only patients with no prior history of DM were included in the study. Each patient’s demographics, medications, and blood glucose levels were recorded. The majority of the patients were African Americans.

**Results:** In 977 patients with no prior history of DM, AAP therapy was initiated during the indicated study period. The patients underwent follow-up for a mean of 15 weeks, during which time 6 patients were diagnosed with DM. The mean time to onset of DM after initiation of AAP treatment was 8 weeks (range, 2 to 15). The 15-week incidence of DM after onset of AAP therapy was 0.61%.

<table>
<thead>
<tr>
<th>Medication</th>
<th>Total patients</th>
<th>Developed DM No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aripiprazole</td>
<td>62</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Clozapine</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>219</td>
<td>2</td>
<td>0.91</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>177</td>
<td>1</td>
<td>0.56</td>
</tr>
<tr>
<td>Risperidone</td>
<td>259</td>
<td>1</td>
<td>0.39</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>53</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>≥2 medications</td>
<td>205</td>
<td>2*</td>
<td>0.98</td>
</tr>
<tr>
<td>Total</td>
<td>977</td>
<td>6</td>
<td>0.61</td>
</tr>
</tbody>
</table>

*Olanzapine + quetiapine and olanzapine + risperidone.

**Discussion:** In the National Health and Nutrition Examination Survey I Epidemiologic Follow-Up Study, the age-adjusted 16-year incidence of type 2 DM in the black population was 10.9% in male subjects and 15% in female subjects. On adjustment to 15 weeks, the incidence would be 0.19% and 0.27%, respectively. Hence, the 15-week incidence of DM after initiation of AAPs in our study (0.61%) is higher than that in the general population. The incidence was especially high with use of olanzapine (0.91%) and with use of a combination of AAPs.

**Conclusion:** The incidence of DM in patients who begin AAP therapy is higher than that in the general population. A particularly high incidence was found in association with olanzapine and combination AAP therapy. Further follow-up is needed to analyze the long-term incidence of DM during AAP treatment. In our study, the mean time to onset of DM was 8 weeks (range, 2 to 15). The frequency of occurrence of DM in this setting emphasizes the importance of monitoring fasting blood glucose.
levels before and at frequent intervals after initiation of AAP therapy.

**Abstract #891**

*Atypical Antipsychotic Agents and New-Onset Diabetes Mellitus: Clinical Presentation, Treatment, and Follow-Up*

Shahzad Iqbal, MD, Faith X. Zhao, MD, Renuka Tunuguntla, MD, Deepak Thomas, MD, Mahboob A. Khan, MD, Kranti Purimetla, MD, Zewge Deribe, MD, Pranjal M. Agrawal, MD, MPH, Nisarul Haque, MD, Jochanan M. Weisenfreund, MD, and Maria F. Renedo, MD

**Background and Objective:** Atypical antipsychotic agents (AAPs) are increasingly being associated with the development of diabetes mellitus (DM), and definite guidelines for treating DM in such cases are lacking. The purposes of this study were to determine the typical clinical presentation and to develop treatment recommendations for new-onset DM after initiation of AAP therapy.

**Methods:** In a retrospective study conducted at the Interfaith Medical Center (New York) Department of Psychiatry, we analyzed the medical records of all patients between October 2003 and November 2004 who were diagnosed with DM after beginning AAP treatment. Only patients with no prior history of DM were included in the study. Each patient’s demographics, blood glucose levels, hyperglycemic symptoms, and antihyperglycemic medications were recorded at the time of diagnosis of DM and at the end of the follow-up period.

**Results:** During the study period, 4 male and 2 female patients were diagnosed with DM after starting AAP therapy. Only 3 of the 6 patients (50%) were symptomatic at the time of diagnosis. Common presenting symptoms were polyuria, polydipsia, generalized weakness, and lethargy. At the time of diagnosis, the mean random blood glucose level was 414 mg/dL (range, 231 to 741). Use of AAPs was discontinued in 4 of the 6 patients (67%). Initial treatment was oral hypoglycemic agents in 2 patients (33%) and insulin in the other 4 patients (67%). At the end of the first month, the DM was well controlled with oral hypoglycemic therapy in 5 of the 6 patients (83%), but 1 patient was still receiving insulin.

The mean follow-up period was 4.5 months (range, 1.5 to 7). At the time of the last follow-up, 4 of the 6 patients (67%) had well-controlled DM with orally administered hypoglycemic medication. The other 2 patients had discontinued use of all medications on their own. On questioning, they admitted to having hyperglycemic symptoms but refused further testing.

<table>
<thead>
<tr>
<th>DM therapy</th>
<th>Total</th>
<th>Patients (no.)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Oral therapy</td>
</tr>
<tr>
<td>Beginning</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>At 1 mo</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>At 4.5 mo*</td>
<td>4</td>
<td>4</td>
</tr>
</tbody>
</table>

*2 patients stopped all medications—admitted to having hyperglycemic symptoms but refused further testing.

**Conclusion:** In this study, we found that only half of the patients had symptoms of hyperglycemia at the time of diagnosis of DM. Therefore, monitoring of the fasting blood glucose levels in all patients receiving AAPs is extremely important. At 4.5 months of follow-up, no remission of DM had occurred, whether or not the use of AAPs had been discontinued. Further long-term follow-up is needed to determine whether the DM will remit. In all patients, the DM was well controlled with oral hypoglycemic therapy at 4.5 months, irrespective of initial mode of treatment.

**Abstract #892**

*Common Characteristics of Patients in Whom Diabetes Mellitus Developed During Therapy With Atypical Antipsychotic Agents*

Shahzad Iqbal, MD, Faith X. Zhao, MD, Renuka Tunuguntla, MD, Mahboob A. Khan, MD, Deepak Thomas, MD, Kranti Purimetla, MD, Zewge Deribe, MD, Pranjal M. Agrawal, MD, MPH, Nisarul Haque, MD, Jochanan M. Weisenfreund, MD, and Maria F. Renedo, MD

**Objective:** To present a case analysis of patients in whom diabetes mellitus (DM) developed after initiation of therapy with atypical antipsychotic agents (AAPs).

**Methods:** In a retrospective study conducted at the Interfaith Medical Center (New York) Department of Psychiatry, we analyzed the medical records of all patients between October 2003 and November 2004 who were diagnosed with DM after starting treatment with AAPs. Only patients with no prior history of DM were included in the study. Each patient’s age, sex, race, baseline body mass index (BMI), prior history of hyperlipidemia, family history of DM, and weight gain since onset of AAP treatment were recorded.

**Results:** During the stipulated study period, DM was diagnosed in 6 patients (4 men and 2 women) after initiation of AAP therapy. The mean age of the study group was...
In this small study group, we found that the exact relationship between atypical antipsychotic agents (AAPs) and diabetes mellitus (DM) is not fully understood at present. Some studies, however, have suggested a possible association of weight gain and hyperglycemia with AAPs. The purpose of this study was to investigate the possible risk factors for development of new-onset DM after initiation of treatment with AAPs.

Methods: We undertook a retrospective case-control study at the Interfaith Medical Center (New York) Department of Psychiatry by analysis of the medical records of all patients who began AAP treatment between October 2003 and November 2004. The cases were patients who were diagnosed with DM after starting AAP therapy. The control subjects were those who were inpatients during November 2004 but did not develop DM. Only patients with no prior history of DM were included in the study. Each patient’s demographics, baseline body mass index (BMI), any increase in BMI, history of hyperlipidemia, and history of hypertension were recorded. The data were age and sex adjusted, and logistic regression analysis was performed (SAS version 8).

Results: In 6 patients (4 men and 2 women), DM developed after initiation of AAP therapy. The mean age of these patients was 40.8 years (range, 24 to 56). The control group consisted of 60 patients (33 men and 27 women), with a mean age of 45.4 years (range, 22 to 79). The mean duration of follow-up was 4.6 months (range, 0.5 to 14). The data were adjusted for age, sex, race, history of hyperlipidemia, and history of hypertension and were studied by logistic regression analysis.

We found that a ≥5% increase in BMI after initiation of AAP therapy had a statistically significant association with a risk of developing DM during such therapy (P = 0.02; odds ratio, 0.067; 95% confidence interval, 0.006 to 0.703). All other factors were not statistically significant.

Discussion: In our study, BMI increases ≥5% had a statistically significant association with a risk of developing DM after the onset of treatment with AAPs. Other factors were not statistically significant, perhaps because of the small number of patients in our study.

Conclusion: A ≥5% BMI increase is a possible risk factor for development of DM after initiation of AAP therapy. Thus, fasting blood glucose levels should be closely monitored in such patients. Further studies with larger numbers of patients should be conducted.

Abstract #894

Results of Implementation and Adherence to Diabetes Management Guidelines in an Endocrine Private Practice Setting

Pardis Dana, MD, Farhad Zangeneh, MD, Valerie Wrobel, MSN, CDE, and Ali M. Safa, MD, FACP, FACE

Background and Objective: Despite evidence-based guidelines for control of blood glucose, blood pressure (BP), and total cholesterol (TC) levels, recent data from the National Health and Nutrition Examination Survey (NHANES) IV indicated that only 7% of adults with diabetes in the United States met the target goals of hemoglobin A1c (HbA1c) <7.0%, BP <130/80 mm Hg, and TC <200 mg/dL. In view of this finding, we decided to compare the outcome of our patients with the reported results of NHANES IV. We also went one step further and reviewed our results following the American Diabetes Association (ADA) guidelines for management of dia-

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of hyperlipidemia</td>
<td>3 of 6</td>
</tr>
<tr>
<td>Family history of DM</td>
<td>3 of 6</td>
</tr>
<tr>
<td>Overweight (BMI ≥25 kg/m²)</td>
<td>5 of 6</td>
</tr>
<tr>
<td>Weight gain</td>
<td>6 of 6</td>
</tr>
</tbody>
</table>

Conclusion: In this small study group, we found that the traditional risk factors of DM such as hyperlipidemia and family history of DM were present in only 50% of the patients. Overweight and weight gain, especially ≥5% BMI increases, were common findings in these patients who were diagnosed with DM after starting AAP treatment. Additional studies with larger numbers of patients are needed, in which those with new-onset diabetes are compared with those without diabetes for the presence of the aforementioned risk factors.
betes mellitus: HbA1c <7%, BP <130/80 mm Hg, low-density lipoprotein (LDL) <100 mg/dL, high-density lipoprotein (HDL) >40 mg/dL, and triglycerides (TG) <150 mg/dL. The main objective of this study was to determine the results of implementation and adherence to these diabetes management guidelines in an endocrine private practice setting.

**Methods:** From January 2000 through December 2003, 584 patients with type 2 diabetes were referred to our practice. Of these, 334 patients (185 men and 149 women) who had at least three visits within 1 year were included in this study. Data were collected in a retrospective study from the review of the patients’ medical records. Results included the initial and the latest values of the HbA1c, systolic and diastolic BP, body mass index, LDL, HDL, TG, and the use of various antidiabetes, antihypertensive, and lipid-lowering agents.

**Results:** With use of a paired t test (alpha <0.05), the changes in the parameters were statistically significant for HbA1c (1.87%; P<0.001), systolic BP (2.56 mm Hg; P<0.001), TC (29.32 mg/dL; P<0.001), LDL (17.87 mg/dL; P<0.001), and TG (113.03 mg/dL; P<0.001); however, changes were statistically insignificant for diastolic BP (0.36 mm Hg; P=0.239), HDL (1.16 mg/dL; P=0.45), and body mass index (0.16 kg/m²; P=0.076). In their most recent office visits, 28.7% of the patients reached all the target goals of the NHANES IV study. With application of the ADA guidelines, however, 9.3% of the patients reached five, 27.8% reached four, 27.8% reached three, 21.6% reached two, 10.2% reached one, and 3.3% reached none of the target goals. Of the 334 patients, 59.3% were taking metformin, 39.8% insulin, 38% thiazolidinediones, 36.2% sulfonylurea drugs, 8.4% repaglinide, and 7.8% nateglinide. Of these, monotherapy was used in 24.9%, a two-drug regimen in 41.3%, a three-drug regimen in 22.5%, a three-drug regimen plus insulin in 6%, and lifestyle modification in 5.3%. With regard to the antihypertensive drugs, 53.3% of the patients were receiving angiotensin-converting enzyme inhibitors, 17.4% angiotensin receptor blockers, 12.4% calcium channel blockers, 13.5% β-adrenergic blocking agents, 27.7% diuretics, and 1% α-adrenergic blocking agents. Of these patients, 41.6% were taking one, 22.8% were taking two, 8.4% were taking three, and 3% were taking more than three drugs; 24.2% of the patients were not taking any hypertensive drug. In the lipid category, statins were taken by 60.8% of patients, fibrates by 9.9%, ezetimibe by 9%, and niacin by 0.6%. We found that 62.9% were receiving monotherapy, 9% were using two drugs, and 28.1% were not taking any lipid-lowering therapy.

**Discussion:** Our data show that the patients achieved a statistically significant decrease in the HbA1c levels by 1.87% (P<0.001). Furthermore, a statistically significant decrease of 2.56 mm Hg in the systolic BP was noted (P<0.001). The analyzed lipid profiles demonstrate statistically significant reductions in TC by 29.32 mg/dL (P<0.001), LDL by 17.87 mg/dL (P<0.001), and TG by 113.03 mg/dL (P<0.001). These patients were treated with a variety of antidiabetic, antihypertensive, and lipid-lowering agents. In each category, a significant percentage of patients were treated with multimodal therapy.

**Conclusion:** Our data reveal that, in a subspecialty endocrine practice, despite adherence to the ADA guidelines and use of a comprehensive approach to diabetes management with pharmacotherapy and diabetes education, the overall results were suboptimal. Clearly, a need exists for a more aggressive, detail-oriented management with use of far more resources and improved patient compliance, along with more efficacious and better tolerated pharmacologic considerations.

**Abstract #903**

**Anthropometric Variables and Glucose Intolerance Among Elderly Nigerians**

Ayoade Adedokun, MD

**Objective:** To assess various anthropometric variables in an elderly Nigerian population, to investigate blood glucose patterns in elderly Nigerians, and to observe any influence of the anthropometric indices on the blood glucose levels.

**Methods:** A total of 62 elderly Nigerians (20 men and 42 women) were included in this study. Any persons with cardiovascular or renal disease were excluded from the study. A Harpenden stadiometer was used to measure height, and weighing scales were used to measure weight. Circumferences were measured with flexible tapes to the nearest 0.1 cm. Blood glucose levels were measured in the hospital laboratory, during fasting and at 2 hours after a glucose load, with use of a standard spectrophotometer. The results were subjected to statistical analysis.

**Results:** The mean age of the study group was 66.6 ± 4.4 (SD) years and 68.0 ± 4.4 years for men and women, respectively. The mean body mass index (BMI) was 26.4 ± 5.3 kg/m² and 28.5 ± 9.9 kg/m² for men and women, respectively. We found a low positive correlation between age in men (but not in women) and 2-hour postprandial blood glucose level (r = 0.3; P<0.05). A weak positive correlation was also found between weight and fasting blood glucose level in men (r = 0.3; P<0.05). BMI was strongly correlated with 2-hour postprandial blood glucose level in the men. Mid upper arm circumference (MUAC) was found to have a significant positive correlation with 2-hour postprandial blood glucose levels in the men and a weak correlation in the women (r = 0.5 and P<0.05 for the men and r = 0.2 and P<0.05 for the women). The prevalence of diabetes mellitus (DM) in this study group was 6.5%.

**Discussion:** Anthropometric analysis is a simple non-invasive method of assessing body composition, which has been used with appreciable success in children and adults but not in the elderly population. Furthermore, the
influence of anthropometric variables on blood glucose levels had not previously been studied in elderly Nigerians. A trend for weight and height to decrease with advancing age was noted in this study. The 6.5% prevalence of DM was considered high for this population. Because BMI and MUAC had significant positive correlations with blood glucose levels, these variables could be good markers of body fat and potential insulin resistance in this Nigerian population.

**Conclusion:** Maintenance of normal anthropometric indices, particularly BMI and MUAC, could be recommended to caregivers of the elderly population as one method to help prevent insulin resistance syndrome.

**Abstract #912**

1,5-Anhydroglucitol and Postprandial Hyperglycemia as Measured by a Continuous Glucose Monitoring System in Patients With Inadequately Controlled Diabetes Mellitus

*John B. Buse, MD, PhD, CDE, FACE, Kathleen Marie Dungan, MD, Joseph Largay, PA-C, CDE, Steven Wittlin, MD, Shuhei Kato, BS, and Eric Button, MSc, MBA*

**Objective:** To demonstrate the relationship between serum 1,5-anhydroglucitol (1,5-AG) and the occurrence of postprandial hyperglycemia, as reflected by a continuous glucose monitoring system (CGMS) (Medtronic Gold), in patients with suboptimally controlled type 1 and type 2 diabetes mellitus (DM).

**Methods:** Volunteers, ranging in age from 18 to 75 years, with type 1 or type 2 DM and a hemoglobin A1c (HbA1c) value between 6.5 and 8% are being recruited from two sites. Inclusion and exclusion criteria ensure a study population with stable glycemic control, with use of regular home glucose monitoring and without significant confounding illness or complications. At baseline, mid-study, and end of the study, 1,5-AG, fructosamine, and HbA1c levels are determined. A CGMS is worn for two consecutive 72-hour periods. Area over the curve (AOC) for blood glucose >180 mg/dL and mean blood glucose as determined by CGMS over each 72-hour period will be compared with the mean and changes in individual levels of 1,5-AG, fructosamine, and HbA1c.

**Results:** Data for the first 3 study subjects are presented. Initial results demonstrate that, for each patient and each 3-day interval of study, CGMS variables (AOC >180 mg/dL and 72-hour mean glucose) indicating poor control are associated with a worsening (that is, reduction) in 1,5-AG, whereas more normal CGMS variables are associated with an improvement (that is, increase) in 1,5-AG. The changes in 1,5-AG between visits are proportionately greater than those seen with fructosamine and HbA1c. Results for a total of 40 participants are anticipated for this initial study. Subgroup analysis by type of diabetes, sex, and treatment method will be performed.

<table>
<thead>
<tr>
<th>Type of DM</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c (%)</td>
<td>7.5</td>
<td>7.2</td>
<td>9.0</td>
</tr>
<tr>
<td>1,5-AG (µg/dL)</td>
<td>3.0</td>
<td>5.5</td>
<td>4.1</td>
</tr>
<tr>
<td>Fructosamine (µmol/L)</td>
<td>301</td>
<td>331</td>
<td>323</td>
</tr>
<tr>
<td>Interval 1 AOC &gt;180 mg/dL (mg/dL × d)</td>
<td>32</td>
<td>20</td>
<td>8</td>
</tr>
<tr>
<td>Interval 1 72-hour mean glucose (mg/dL)</td>
<td>180</td>
<td>165</td>
<td>141</td>
</tr>
</tbody>
</table>

**Mid-study**

| HbA1c (%) | 7.4 | 7.2 | 9.1 |
| 1,5-AG (µg/dL) | 2.8 | 6.5 | 5.1 |
| Fructosamine (µmol/L) | 307 | 338 | 313 |
| Interval 2 AOC >180 mg/dL (mg/dL × d) | 7 | 20 | 10 |
| Interval 2 72-hour mean glucose (mg/dL) | 129 | 177 | 165 |

**End of study**

| HbA1c (%) | 7.5 | 7.5 | 9.0 |
| 1,5-AG (µg/dL) | 3.3 | 7.0 | 5.2 |
| Fructosamine (µmol/L) | 310 | 351 | 321 |

**Discussion:** Despite moderate overall glycemic control, significant postprandial hyperglycemia, as determined by CGMS, generally is present in patients with DM. Changes in 1,5-AG appear to reflect 72-hour glucose values more dynamically than HbA1c and fructosamine. This finding may allow for earlier and more precise fine-tuning of blood glucose control than would be possible with use of HbA1c alone.

**Conclusion:** In patients with substantial postprandial glucose excursions, 1,5-AG may be used as a complementary marker to HbA1c to determine the adequacy of glycemic control in patients with DM.
LIPID DISORDERS

Abstract #750

Efficacy and Safety of Micronized Fenofibrate-130 mg Taken With or Without Food Versus Placebo in Patients With Hypertriglyceridemia and Metabolic Syndrome—TRIMS Study (Triglyceride Reduction in Metabolic Syndrome)

Harold Bays, MD, Michael H. Davidson, MD, Evan A. Stein, MD, James M. Rhyne, MD, Keith S. Rotenberg, PhD, and Ralph T. Doyle, BA

Background: Some currently available fenofibrate formulations are recommended to be taken in conjunction with meals to optimize bioavailability. This multicenter, randomized, double-blind, double-dummy, placebo-controlled, parallel-group study included 146 patients with hypertriglyceridemia and metabolic syndrome (defined in accordance with the National Cholesterol Education Program Adult Treatment Panel III guidelines) who were randomized into 1 of the following 3 groups, each receiving 2 “pills” per day: (1) micronized fenofibrate-130 mg taken without food and placebo taken with food, (2) micronized fenofibrate-130 mg taken with food and placebo taken without food, or (3) placebo taken with food and placebo taken without food for 8 weeks.

Methods: Patients received dietary counseling and followed the Therapeutic Lifestyle Changes diet throughout the study. Baseline characteristics of all groups were similar, with mean baseline results reported as the average of the last 3 weekly fasting measurements during the 6-week, diet-only phase. The percentage change from baseline at the end of treatment (average of the last 2 weekly measurements in the 8-week treatment phase) for various lipids in the 3 study groups was summarized.

Results: Triglyceride and very-low-density lipoprotein cholesterol levels were significantly reduced and high-density lipoprotein cholesterol was significantly increased in both treatment groups in comparison with placebo.

Discussion: Eighteen of the 96 patients (19%) treated with micronized fenofibrate-130 mg and 8 of the 50 patients (16%) treated with placebo reported adverse events that were related to study drug. The most common adverse events reported by patients who received micronized fenofibrate-130 mg were gastrointestinal effects.

<table>
<thead>
<tr>
<th>Lipid (mg/dL)</th>
<th>Placebo† (N = 50)</th>
<th>MFB130 + food (N = 54)</th>
<th>MFB130; no food (N = 42)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triglycerides</td>
<td>0.7</td>
<td>-36.7‡</td>
<td>-36.6‡</td>
</tr>
<tr>
<td>TC</td>
<td>-0.8</td>
<td>-5.1</td>
<td>-3.4</td>
</tr>
<tr>
<td>HDL-C</td>
<td>0.8</td>
<td>13.7‡</td>
<td>14.3‡</td>
</tr>
<tr>
<td>LDL-C</td>
<td>3.2</td>
<td>15.4§</td>
<td>14.5</td>
</tr>
<tr>
<td>Non-HDL-C</td>
<td>-1.1</td>
<td>-8.2§</td>
<td>-6.6</td>
</tr>
<tr>
<td>VLDL-C</td>
<td>-1.6</td>
<td>-34.4‡</td>
<td>-30.4‡</td>
</tr>
<tr>
<td>RLP-C</td>
<td>12.3</td>
<td>-30.1§</td>
<td>-41.1‡</td>
</tr>
</tbody>
</table>

*HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; MFB130 = micronized fenofibrate-130 mg; RLP-C = remnant lipoprotein cholesterol; TC = total cholesterol; VLDL-C = very-low-density lipoprotein cholesterol.
†Taken with or without food.
‡P<0.0001 versus placebo.
§P≤0.01 versus placebo.

Conclusion: Micronized fenofibrate-130 mg, as an adjunct to diet, is equally effective when taken with or between meals at reducing elevated triglyceride levels in patients with metabolic syndrome.

Abstract #804

Adverse Interaction Between Simvastatin and Amiodarone Resulting in Rhabdomyolysis, Azotemia, and Hepatotoxicity

Basma M. Ricaurte, MD, Harris C. Taylor, MD, FACE, Akshey Bhanot, MD, and Amir Guirguis, MD

Objective: To describe the fourth reported case of a severe drug interaction between simvastatin and amiodarone and hypothesize inhibition of CYP3A4 as the major mechanism.

Case Presentation: A 72-year-old man with diabetes mellitus (DM), hyperlipidemia, hypertension, and mild azotemia was admitted to the hospital in September 2004 with complaints of thigh weakness, “achiness,” and dark urine for 7 days. A coronary artery bypass grafting procedure had been performed in July 2004, after which treatment with amiodarone, 200 mg daily, and simvastatin, 80 mg daily, had been initiated. He had previously taken pravastatin, 20 to 40 mg daily for 8 months, and then...
Simvastatin is frequently used by clinical practitioners due to its effectiveness in managing hyperlipidemia associated with DM. Myopathy and rhabdomyolysis, with or without azotemia and hepatotoxicity, are unusual, albeit well-recognized, AEs consequent to simvastatin monotherapy. More frequently, these AEs occur when simvastatin, which is metabolized by cytochrome P-450 CYP3A4, is used in combination with other drugs that inhibit CYP3A4. We report the 4th documented example (1-4) of a severe interaction between simvastatin and amiodarone, causing rhabdomyolysis, azotemia, and hepatotoxicity. An 80-mg dose of simvastatin causes a 15-fold increase in myopathy and rhabdomyolysis, in comparison with a 20-mg dose. In the postoperative state in a patient with DM and mild azotemia, we postulate that use of amiodarone, a known CYP3A4 inhibitor, and simvastatin, a drug metabolized by CYP3A4, resulted in toxic drug levels and more severe azotemia. This mechanism is consistent with absence of AEs with previous use of pravastatin (metabolized by sulfation) and fluvastatin (metabolized by CYP2C9) therapy. Awareness of this drug interaction is important because simvastatin was the third most prescribed drug by retail sales in 2003 and amiodarone is in the third most prescribed antiarrhythmic drug class.

Conclusions: Concurrent high-dose simvastatin and amiodarone therapy may be associated with severe muscle, kidney, and liver toxicity.

References

Abstract #846
Atorvastatin-Induced Isolated Ocular Myopathy
Niti Agarwal, MD,
Sachin Kumar Jain, MBBS, MD, DM, FACE, and
Ritesh Panwar, MD

Objective: To report the case of a patient who had diplopia as a manifestation of ocular myopathy with no other skeletal muscle symptoms during atorvastatin therapy and recurrence of this symptom after rechallenge with this drug.

Case Presentation: A 50-year-old man with diabetes and hypertension for 10 years had been maintained on glipizide, losartan, and aspirin. On a routine assessment of the patient, dyslipidemia was detected, with a total cholesterol level of 260 mg/dL, low-density lipoprotein of 160 mg/dL, and triglycerides of 195 mg/dL. His hypertension and diabetes were adequately controlled, with a hemoglobin A1c value of 6.9% and blood pressure of 116/74 mm Hg. Treatment was begun with atorvastatin, 10 mg daily. Three months later, he presented with complaints of binocular diplopia in variable gazes, without involvement of any other skeletal muscle or muscle groups. On examination, no obvious ocular muscle palsy was present. Moreover, no objective weakness or tenderness of any other muscles was noted. Bilaterally, the pupils were normal in size and reaction. Diplopia charting was inconclusive for any particular muscle involvement. Absence of weakness of any specific ocular muscle ruled out diabetic neuropathy. His serum creatine kinase and lactate dehydrogenase levels were within the reference ranges.

Initially, the symptoms were considered merely of psychologic origin, but they persisted and were a hindrance to performance of routine activities by the patient. On close reassessment of the history and examination, atorvastatin was identified as the only newly prescribed drug, which could potentially be the cause of the diplopia. Therefore, use of atorvastatin was discontinued. The patient’s vision improved during the next 4 to 6 weeks, without any residual diplopia.

Three months later, the patient was rechallenged with atorvastatin. Within 2 months, the diplopia recurred. After withdrawal of the drug, the symptom again disappeared.

Discussion: Statin-induced myotoxicity is well established, varying in severity from mild myopathy to fatal rhabdomyolysis, with or without an increase in creatine kinase levels. Although statin-associated myasthenia-like symptoms have been reported, statin-induced isolated ocular muscle toxicity has not been reported previously. In our patient described in this report, isolated ocular muscle weakness developed after initiation of atorvastatin therapy. Whether isolated ocular muscle involvement is a class effect or simply specific to atorvastatin is currently unknown.

Conclusion: Atorvastatin may lead to isolated ocular myopathy.
Abstract #864

Development of Type III Hyperlipoproteinemia With End-Stage Liver Disease and Effects of Liver Transplantation

Dima AbdelMannan, MD, and Byron J. Hoogwerf, MD, FACP, FACE

Background: Liver disease may be associated with abnormalities in lipids, lipoprotein patterns, and levels of apolipoprotein (apo) A-I and apo B. The liver is a major site of apolipoprotein synthesis as well as lipoprotein clearance. Patients with severe liver disease who undergo a liver transplantation may show changes in their serum lipids before and after liver transplantation. We describe a patient with a common apo E genotype (3/3) who manifested a type III lipoprotein pattern during her liver disease. After she underwent liver transplantation, her lipid profile reverted to a non-type III pattern.

Case Presentation: A 36-year-old woman had a history of ulcerative colitis and primary sclerosing cholangitis complicated by liver failure, for which she underwent an orthotopic liver transplantation in November 2000. Subsequent chronic organ rejection necessitated another orthotopic liver transplantation in December 2002. A summary of her liver enzymes and lipid profiles is presented.

After 1st liver transplantation:

<table>
<thead>
<tr>
<th>Component*</th>
<th>Jan-Sep 2001</th>
<th>Jan-Sep 2002</th>
</tr>
</thead>
<tbody>
<tr>
<td>T bili (0-1.5)</td>
<td>1.1-5.7</td>
<td>25-45</td>
</tr>
<tr>
<td>ALT (0-45)</td>
<td>39-125</td>
<td>90-1,094</td>
</tr>
<tr>
<td>AST (7-40)</td>
<td>21-46</td>
<td>405-1,318</td>
</tr>
<tr>
<td>TC (100-109)</td>
<td>...</td>
<td>239-614</td>
</tr>
<tr>
<td>TG (30-149)</td>
<td>...</td>
<td>439</td>
</tr>
<tr>
<td>HDL (&gt;55)</td>
<td>...</td>
<td>13</td>
</tr>
<tr>
<td>LDL (60-129)</td>
<td>...</td>
<td>54</td>
</tr>
<tr>
<td>Apo B (43-128)</td>
<td>...</td>
<td>270</td>
</tr>
</tbody>
</table>

*ALT = alanine aminotransferase; Apo B = apolipoprotein B; AST = aspartate aminotransferase; HDL = high-density lipoprotein; LDL = low-density lipoprotein; T bili = total bilirubin; TC = total cholesterol; TG = triglycerides.

After 2nd liver transplantation:

<table>
<thead>
<tr>
<th>Component*</th>
<th>Jan-Jun 2003</th>
<th>Jul-Dec 2003</th>
</tr>
</thead>
<tbody>
<tr>
<td>T bili (0-1.5)</td>
<td>14-20</td>
<td>0.4-1.3</td>
</tr>
<tr>
<td>ALT (0-45)</td>
<td>130-320</td>
<td>14-87</td>
</tr>
<tr>
<td>AST (7-40)</td>
<td>220-405</td>
<td>12-96</td>
</tr>
<tr>
<td>TC (100-109)</td>
<td>189-343</td>
<td>136-190</td>
</tr>
<tr>
<td>TG (30-149)</td>
<td>275-359</td>
<td>210-230</td>
</tr>
<tr>
<td>HDL (&gt;55)</td>
<td>11-16</td>
<td>11-22</td>
</tr>
<tr>
<td>LDL (60-129)</td>
<td>149-189</td>
<td>72-90</td>
</tr>
<tr>
<td>Apo B (43-128)</td>
<td>...</td>
<td>...</td>
</tr>
</tbody>
</table>

Discussion: The alterations in plasma lipids and lipoproteins in end-stage liver disease are attributable to complex abnormalities of lipoprotein synthesis. Cholesterol and lecithin molecules accumulate as hepatic secretion of lecithin-cholesterol acyltransferase decreases, and the arachidonate content, the precursor for eicosanoid production, is also reduced. Cholestasis is associated with hypercholesterolemia and the appearance of an abnormal lipoprotein (lipoprotein X), which represents biliary vesicles that are regurgitated into the plasma of patients with cholestasis. Extrahepatic cholestasis (bile duct ligation) in mice also results in an increase in cholesterol. After liver transplantation, some patients show a change in apoprotein phenotypes resembling those of the donor, consistent with the liver being the major site of production of these apoproteins.

Conclusion: The liver is the main site of apolipoprotein synthesis and lipoprotein clearance. Severe liver disease may be associated with lipid abnormalities, including changes in phenotypic pattern. These changes may result in a type III lipid pattern, even in patients who do not have the typical type III genotype. Reversion to a normal lipoprotein phenotype occurs after liver transplantation.

Abstract #879

Atherogenic Lipid Profile in Turner’s Syndrome

Vladimir K. Bakalov, MD, Phillip Van, MSc, and Carolyn A. Bondy, MD

Objective: To investigate X-chromosome gene dosage effects on serum lipids in women with ovarian failure.

Methods: In a cross-sectional, Clinical Research Center-based study, we evaluated 34 women with Turner’s syndrome (TS) and 50 women with spontaneous premature ovarian failure (POF). Women with TS had either monosomy X or one abnormal X chromosome in more than 70% of peripheral lymphocytes; women with POF had normal 46,XX karyotype. All study participants discontinued estrogen replacement therapy 2 weeks before onset of the study. Levels of fasting total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides were measured by an enzymatic assay that used Beckman-Coulter reagent; low-density lipoprotein (LDL) cholesterol level was measured by direct homogeneous assay (Genzyme N-geneous reagent); lipid particle size was determined by nuclear magnetic resonance spectroscopy; fasting insulin concentration was measured by chemiluminescence immunoassay on an Immulite 2000 analyzer; and fasting glucose level was measured by the glucose oxidase method.

Results: The two study groups (TS and POF) were similar in age, body mass index, and fasting insulin sensitivity, as assessed by the quantitative insulin sensitivity check index (QUICKI): TS (N = 34) – 34.5 ± 2 years,
27.2 ± 1 kg/m², and QUICKI 0.37 ± 0.4; POF (N = 50)—32.6 ± 1 years, 26.2 ± 1 kg/m², and QUICKI 0.37 ± 0.3.

LDL cholesterol levels (135 ± 41 mg/dL versus 113 ± 33 mg/dL) were significantly higher (P<0.003) whereas LDL particle size (21.2 ± 6.0 nm versus 21.8 ± 7.0 nm) was significantly smaller (P = 0.0002) in women with TS than in those with POF. HDL cholesterol levels were similar in the two groups (60.2 ± 14.7 mg/dL versus 61.8 ± 17.4 mg/dL; P = 0.6), but HDL particle size was smaller in women with TS than in those with POF (9.08 ± 4.4 nm versus 9.40 ± 4.9 nm; P = 0.002). Triglyceride levels were significantly higher in women with TS than in those with POF (122 ± 49 mg/dL versus 94 ± 47 mg/dL; P = 0.007).

**Discussion:** Young women with TS exhibit a distinctly atherogenic lipid profile in comparison with 46,XX women of the same age, gonadal status, body composition, and insulin sensitivity. Because these two groups are so similar in hormonal and behavioral factors influencing lipid metabolism, this atherogenic lipid profile in TS is unlikely to be a consequence of hypogonadism, excess adiposity, or low physical activity but may be caused by a deficit in X-chromosome gene dosage.

**Conclusion:** Because women with TS are likely to have an increased risk for coronary artery disease, they should be screened for lipids and other risk factors at a young age. Ongoing studies of patients with informative X-chromosome deletions are attempting to pinpoint X-chromosome genes involved in lipid metabolism.
Objective: To report a case of severe hypocalcemia and resulting acute confusion in an elderly patient who had received a dose of zoledronic acid for treatment of metastatic prostate cancer.

Case Presentation: An 83-year-old man was admitted with acute onset of confusion and repeated fist clenching. Recently, the patient had been diagnosed as having prostate carcinoma with metastatic lesions involving the spine. Pertinent medical history included chronic renal insufficiency and hypertension.

The patient’s total serum calcium concentration had decreased progressively from 6.2 mg/dL at the time of admission to 4.4 mg/dL on the day he was referred for consultation. The ionized calcium was 2.8 mg/dL. The serum phosphorus level was 2.5 mg/dL, the serum magnesium level was 1.7 mg/dL, and the serum albumin concentration was 1.2 g/dL. The patient had received zoledronic acid (4 mg intravenously) 2 weeks before the current consultation. His serum vitamin D levels, however, had not been assessed before this examination. Tests of calcitropic hormones revealed borderline low-normal 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D levels and a mildly increased intact serum parathyroid hormone level. The patient was initially given 10% calcium gluconate intravenously and subsequently was maintained with orally administered calcium and calcitriol supplementation. His serum calcium levels returned to the normal range during the subsequent 2 weeks, in conjunction with a gradual improvement of his mental status and a return to his baseline level of function.

Discussion: This case illustrates the deleterious effects of hypocalcemia due to high-potency intravenously administered bisphosphonates such as zoledronic acid. This problem can become especially severe in elderly patients, who often have deficient vitamin D stores attributed to various causes including malnutrition. Review of the literature shows similar presentations in younger patients, with and without malignant disease. With the increasing use of bisphosphonates to treat metastatic bone disease and as a prophylaxis against metastatic bone cancer, this problem may be seen more frequently in the future.

Conclusion: Severe hypocalcemia is especially a concern in elderly patients receiving zoledronic acid. Testing for adequate vitamin D stores before initiation of such treatments is recommended. Ensuring adequate replacement with calcium and vitamin D could prevent this complication.
detecting pseudofractures, particularly in the ribs and especially when such features are absent on conventional x-ray films. One explanation for the increased uptake in patients with osteomalacia could be the large “osteoid” pool as a result of the secondary hyperparathyroidism.

**Conclusion:** Corrections with high-dose ergocalciferol and a gluten-free diet led to normalization of the secondary hyperparathyroidism from osteomalacia, ultimately resulting in resolution of focal uptakes in the bone scan.

**Abstract #782**

**Sclerotic Bone Disease Attributable to Fluorosis Caused by Habitual Consumption of Tea**

*Julie Hallanger Johnson, MD, and Robert A. Wermers, MD, FACE*

**Objective:** To present the evaluation of sclerotic bone disease in a postmenopausal woman to highlight the differential diagnosis of this unusual condition and demonstrate how a thorough history and appropriate laboratory testing can lead to a cost-effective treatment.

**Case Presentation:** A 67-year-old woman had a 2-year history of stress fractures of the feet. Her medical history was significant for anorexia nervosa and ileal resection for volvulus complicated by renal calculi. Her lumbar total bone mineral density was 1.47 g/cm², the equivalent of a T-score of +2.3 and a Z-score of +4.7. The bone mineral density at the left femoral neck was 0.77 g/cm², with a T-score of −1.7 and a Z-score of +0.4. All the bones of the spine were diffusely increased in density, suggestive of sclerotic bone disease. A bone scan disclosed insufficiency fractures in the feet and increased uptake in L5. Laboratory studies showed an increased bone density in habitual tea drinkers. Tea is a readily available source of fluoride, which is often present in high levels in various teas. Fluoride treatment can cause pain in the lower extremities and gastrointestinal symptoms, both of which were present in our patient. Once we instructed the patient to limit her consumption of tea, her serum fluoride level steadily decreased. Alternatively, a different brand of tea with lower fluoride concentrations could be used.

**Conclusion:** Fluorosis is an important consideration in patients with dense bones or excessive consumption of tea.

**Abstract #795**

**High Use of Concomitant Medications Among Women With Postmenopausal Osteoporosis**

*E. Michael Lewiecki, MD, FACP, Mayur M. Amonkar, PhD, Sydney Lou Bonnick, MD, FACP, Mark P. Ettenger, MD, and Mone Zaidi, MD, PhD, FACE*

**Objective:** To assess concomitant medication (con-med) use among women with postmenopausal osteoporosis (PMO) receiving bisphosphonate therapy. PMO is a highly prevalent condition particularly among elderly women, who are also likely to have comorbid chronic conditions such as hypertension, hypercholesterolemia, and heart failure.

**Methods:** A Healthcare Insurance Portability and Accountability Act-compliant, longitudinal patient database (NDCHHealth, Atlanta, Georgia) was used to determine which medications or medication classes were used concomitantly with daily or weekly dosing of alendronate or risedronate and how many of these medications were used by each patient. Con-meds included prescription medicines administered orally, those taken by inhalation or intranasally, or those self-administered by parenteral injection. Prescription information covered 14,000 US retail pharmacies (~25% of US retail pharmacies) and a broad range of incomes and ages. Patient data were assessed on a monthly basis during a 56-month period (from November 1999 through June 2004) in women ≥50 years old receiving bisphosphonate therapy.

**Results:** The cohort of women eligible for analysis increased from 78,909 in November 1999 to 250,286 in June 2004. The mean number of con-meds used increased with advancing age and over time from 2.74 to 3.09 con-meds (for the 50- to 64-year-old group) compared with 3.16 to 3.97 con-meds (for the ≥75-year-old group) from November 1999 to June 2004, respectively. Although the percentage of patients receiving 1 to 5 con-meds remained relatively consistent throughout the observation period,
the percentage of patients receiving ≥6 con-meds increased substantially. By June 2004, 43.8% of women prescribed bisphosphonates were prescribed an additional 1 or 2 con-meds, 16.2% received 3 con-meds, 12.2% had 4 con-meds, 8.7% had 5 con-meds, and 19.1% had ≥6 con-meds. The most frequently prescribed con-meds were levothyroxine, atorvastatin, atenolol, furosemide, amlodipine, potassium chloride, hydrochlorothiazide, and lisinopril. The most common con-med classes included cholesterol-lowering agents, synthetic thyroid hormones, β-adrenergic blocking agents, calcium channel blockers, angiotensin-converting enzyme inhibitors, and systemic antiarthritic agents.

Discussion: Use of con-meds among women with PMO taking bisphosphonates orally is common, with the use of 6 or more con-meds increasing substantially during the observation period. Women prescribed daily bisphosphonates received more con-meds than did those prescribed weekly bisphosphonates.

Conclusion: Persistence with bisphosphonate therapy remains suboptimal (1). High con-med use may, in part, be a contributing factor (1). Development of more convenient dosing regimens may improve adherence and persistence.

Reference


Abstract #797

Better Oral Bisphosphonate Adherence With Once-Weekly Than With Once-Daily Regimens, but Still Suboptimal

E. Michael Lewiecki, MD, FACP, C. Conrad Johnston, Jr., MD, FACP, FACE, Rich Gallagher, MD, Mayur M. Amonkar, PhD, and Mark P. Ettinger, MD

Background and Objective: In patients with postmenopausal osteoporosis, studies have shown that good adherence (compliance and persistence) to bisphosphonate treatment is associated with greater bone mineral density increases, larger fracture risk reductions, and lower use of health care resources. Reduced dosing frequency is being explored as a means of improving medication adherence by enhancing the convenience of taking medication. We present an analysis of three large database studies (1-3) that have independently assessed bisphosphonate adherence with once-weekly versus once-daily dosing regimens.

Methods: One study from a claims database (Integrated Healthcare Information Services [IHCIS]) and two from a retail pharmacy database (NDCHealth) (total N = 214,029) compared once-weekly with once-daily alendronate or risedronate (or both) treatments for a period of 12 months. Refill compliance was assessed by using the medication possession ratio (MPR = days of supply/365 days) (1,2). Persistence was defined as the proportion of patients continuing therapy after 1 year (3) or with ≥30 days’ lapse for refill prescription from last dose (1).

Results: Refill compliance was substantially higher among patients with once-weekly compared with once-daily regimens (mean MPR 65.2% and 69.2%, versus 54.2% and 57.6%, in the NDCHealth and IHCIS cohorts, respectively). Mean MPR was significantly higher for the once-weekly dosing group regardless of payment method, age categories, or patterns of past medication use (NDCHealth). Overall, refill compliance was poor: the proportion of women with MPR ≥80%—an adherence level shown to be sufficient to ensure antifracture efficacy with bisphosphonate therapy (4)—was, at best, 55.3% (IHCIS weekly cohort) and, at worst, just 33.3% (NDCHealth daily cohort). Persistence was better with once-weekly compared with once-daily treatment. The 12-month persistence rates were 54.6% and 44.2% for once-weekly regimens versus 36.9% and 31.7% for once-daily regimens (NDCHealth and IHCIS, respectively).

Discussion: Persistence and refill compliance are better with weekly than with daily regimens of bisphosphonates. Even with weekly regimens, however, adherence is suboptimal.

Conclusion: Adherence may be further improved by less frequent (for example, monthly) dosing regimens. This strategy is currently under clinical investigation.

References

Use of Teriparatide in Osteogenesis Imperfecta

David M. Gorson, MD, FACE, and Suzanne Adler, MD

Objective: To describe the response of a patient with osteogenesis imperfecta to teriparatide therapy.

Case Presentation: A 47-year-old woman had a series of fractures beginning during childhood. Osteogenesis imperfecta had been diagnosed on skin biopsy in the remote past; details are unknown. At age 30 years, a seizure disorder developed, likely related to a cerebral arteriovenous malformation; it had been treated with a series of anticonvulsants (see below). At age 40 years, total abdominal hysterectomy-bilateral salpingectomy was performed for menometrorrhagia, and conjugated estrogen (Premarin) therapy was begun shortly thereafter.

Dual-energy x-ray absorptiometry (DXA) was first performed in 1997. A compression fracture was visible at L1, and the bone density at L2-4 was 0.950 g/cm², with a Z-score of −1.68 and a T-score of −2.09 (Lunar DPX-alpha). Bone density at the right femoral neck (the patient had a history of a fracture of the left femoral neck) was 0.793 g/cm², with a Z-score of −1.09 and a T-score of −1.56. Treatment with alendronate (Fosamax), 10 mg daily, was initiated by her primary care physician. Information about calcium and vitamin D supplementation at that time is unknown. Follow-up DXA in 1999 revealed no significant change at the lumbar spine or right femoral neck.

Another bone density study in 2001 revealed a significant reduction (7.8%) at the spine (bone mineral density 0.876 g/cm² and T-score now −2.70). No significant change was found at the right femoral neck.

The patient was referred for evaluation. At that time, her medications included the following: phenytoin (Dilantin), topiramate (Topamax), clonazepam (Klonopin), levetiracetam (Keppra), citalopram (Celsexa), Fosamax daily, Premarin, calcium (600 mg twice daily), calcitonin-salmon (Miacalcin) nasal spray, and a multivitamin. Results of routine hematology, serum chemistry, and thyroid function studies were unremarkable, with the exception of an alkaline phosphatase level of 145 U/L (normal range, 50 to 136). A 25-hydroxyvitamin D level was 31 ng/mL. A 24-hour urine study for calcium was 194 mg/day, and the 24-hour urine excretion of N-terminal telopeptide was 33 nmol/mmol creat. The Fosamax regimen was changed to weekly administration, and the patient was referred back to her neurologist to determine whether the Dilantin treatment could be discontinued. This was done, but not until 2003. During this time, the patient continued to have approximately one fracture per month. The longest duration without sustaining a fracture was 3 months, and fractures occurred independently of seizures.

In March 2003, follow-up DXA was performed. A further significant reduction (6.9%) in bone density of the lumbar spine was noted but no change in the femoral neck in comparison with 2001. Fosamax and Miacalcin treatments were discontinued, and therapy with teriparatide (20 μg daily) was begun. Use of Premarin was continued. Since that time (20 months), no further fractures have occurred. Another follow-up DXA scheduled to be performed.

Discussion: Osteogenesis imperfecta is an inherited disorder of type I collagen. It has a widely varying phenotypic expression, ranging from a mild variant with fractures from mild trauma to the lethal perinatal form. Therapeutic modalities include calcium and vitamin D supplementation, physical therapy, intramedullary rod placement and prostheses, and pharmacologic agents. Sodium fluoride, magnesium oxide, and anabolic steroids have been shown to be ineffective in reducing fractures (1-3). Cyclic intravenous administration of pamidronate has been shown to reduce bone resorption, increase bone density, and improve clinical outcomes in these patients (3,4). Other bisphosphonates have also been used, with some successful results (5,6). Alternatives such as growth hormone (7) and gene therapy (8,9) are also being investigated. One approach is to use a gene construct to target mutant mesenchymal cells in order to decrease the level of abnormal protein forming the subunits of type I collagen (8,9). Another approach is to perform a bone marrow transplantation, with the goal of permanent engraftment of normal osteoblasts. Although tantalizing, these investigative approaches are not yet clinically relevant for most patients.

In 2002, teriparatide was approved for use in osteoporosis in postmenopausal women at high risk for fractures and in men with primary or hypogonadal osteoporosis. To our knowledge, this is the first reported case of the use of this medication in a patient with osteogenesis imperfecta.

Conclusion: Although an apparent effect of teriparatide was seen in this patient, extrapolation to other cases of osteogenesis imperfecta is problematic for several reasons. Complicating factors include the prior use of antiepileptic drugs (which may have promoted osteomalacia), the prior combination of two antiresorptive agents, and the hormone replacement therapy. Although difficult to perform in light of the relatively rare prevalence of this disease, controlled clinical trials are needed to determine whether teriparatide should be used as an adjunct or alternative to currently used therapies for adult patients with this disorder. Because laboratory animals that have been administered teriparatide beginning at 2 months of age have been observed to develop osteosarcoma, the use of this medication in children without fully fused epiphyses is clearly contraindicated at this time.

References
Abstract #812

Prevalence of Established Diabetes Mellitus in Patients With Primary Hyperparathyroidism

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Background and Objective: Several studies have reported that patients with primary hyperparathyroidism (PHPT) have disorders of carbohydrate metabolism, including insulin resistance, hyperinsulinemia, and diabetes mellitus (DM). Nevertheless, whether the prevalence of DM is increased in patients with PHPT is unclear. Accordingly, we studied the prevalence of DM in PHPT, inasmuch as both conditions may adversely affect renal function and the presence of DM may explain the reported increased cardiovascular-related morbidity and mortality in patients with PHPT.

Methods: For assessment of the prevalence of DM in patients with PHPT, we conducted a retrospective cohort study of 609 patients with PHPT confirmed by surgical removal of one or more adenomas between 1992 and 2003. We looked for the presence of an established diagnosis of DM and compared the frequency with the American Diabetes Association published prevalence of DM in the general population of Michigan as control subjects.

Results: Of the PHPT study group, 38% were black patients, similar to the distribution in the Michigan population (36.6% black residents). The gender distribution, however, showed a male-to-female ratio of 1:4, differing from that in the general population (almost 1:1). This finding was not unexpected because PHPT is more prevalent in women than in men. The prevalence of DM among the patients with PHPT was 14.5%, significantly higher than the prevalence in the general population of Michigan (7.8%; P<0.001; 95% confidence interval, 11.8% to 17.5%). The prevalence of DM in various subgroups was as follows: blacks 20.4% (P<0.001), whites 11% (P<0.001), men 22.8% (P<0.001), and women 12.5% (P<0.001).

Discussion: The presentation of patients with PHPT has changed such that the classic manifestations are rare in contemporary cases of PHPT. Recently, attention has been directed toward nontraditional manifestations of PHPT, such as glucose intolerance, hyperlipidemia, and increased cardiovascular-associated morbidity and mortality. The reasons for the last-mentioned finding are not readily apparent but could be related to the increased prevalence of DM in patients with PHPT, as demonstrated by us in this retrospective cohort study of a large number of patients with surgically verified PHPT and by others. Although the treatment of choice for symptomatic PHPT is parathyroidectomy, the role of surgical intervention in asymptomatic PHPT is controversial. Because both DM and hypercalcemia of PHPT may adversely affect renal function, it may be prudent to consider parathyroidectomy in such asymptomatic patients with both conditions.

Conclusion: The prevalence of established DM in patients with PHPT is significantly higher than in the general population of Michigan. Because both DM and hypercalcemia may adversely affect renal function, parathyroidectomy may be considered in patients with both conditions.

Abstract #813

Prevalence of Vitamin D Inadequacy in North American Women Receiving Therapy for Osteoporosis

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Background and Objective: Vitamin D is essential for optimal bone health. Vitamin D inadequacy, however, may be overlooked by clinicians and thus lead to inadequate vitamin D supplementation in patients with osteoporosis. In this study, we evaluated serum 25-hydroxyvitamin D [25-(OH)D] concentrations in postmenopausal women currently receiving antiresorptive or anabolic therapies for osteoporosis and determined specific factors related to 25-(OH)D concentrations.

Methods: Between November 2003 and March 2004, 1,554 ambulatory, community-dwelling, postmenopausal women from 61 primary care physician practices in North America were recruited for this study. A serum 25-(OH)D level, intact parathyroid hormone value, and chemistry panel were obtained. A questionnaire was completed by patients to obtain information on factors that could influence vitamin D status. Potential factors for suboptimal 25-
(OH)D concentrations (<30 ng/mL) were evaluated with use of a multivariate logistic regression model.

Results: Of the 1,554 recruited patients, 1,536 completed the study. The mean age of the study participants was 71 years (range, 47 to 103), and 92% were white patients. Overall, 35% of subjects resided at a latitude greater than or equal to 42 degrees north (Boston, MA), and 24% resided below 35 degrees north (Memphis, TN). The overall mean (SD) serum 25-(OH)D was 30.4 (13.2) ng/mL. Serum 25-(OH)D was <20 ng/mL in 18%, <25 ng/mL in 36%, and <30 ng/mL in 52% of study subjects. A suboptimal 25-(OH)D concentration was present in 63% of subjects receiving <400 IU of vitamin D daily in comparison with 45% of those receiving greater than or equal to 400 IU of vitamin D daily (P<0.001). Factors related to vitamin D inadequacy [serum 25-(OH)D <30 ng/mL] that remained significant in the multivariate analysis included the following: age >80 years, race (nonwhite), body mass index >30 kg/m², use of medications affecting vitamin D metabolism, <400 IU/day of vitamin D supplementation, lack of exercise, education level less than grade 12, and absence of previous physician counseling regarding vitamin D.

Discussion: This study is the first to evaluate serum 25-(OH)D concentrations in a population of postmenopausal women currently receiving therapy for treatment or prevention of osteoporosis. Most of these women were healthy, ambulatory, community-dwelling, white women who were well educated. Despite these apparent advantages, more than half of these women (52%) had suboptimal (<30 ng/mL) 25-(OH)D concentrations.

Conclusion: These results underscore a need for improved physician and patient education regarding optimization of vitamin D status in the care of postmenopausal women with osteoporosis.

Abstract #817

Monthly Oral Ibandronate Therapy Is Effective and Safe in Women With Postmenopausal Osteoporosis: 1-Year Results From the MOBILE Study

Michael A. Bolognese, MD, Paul D. Miller, MD, Roberto Civitelli, MD, and E. Michael Lewiecki, MD, FACP

Background and Objective: Long-term adherence and persistence with oral bisphosphonate treatment are required for optimal outcomes in osteoporosis. With current daily and weekly oral regimens, however, adherence and persistence are poor, possibly because of the frequency of dosing and side effects. The MOBILE (Monthly Oral Ibandronate In LadiEs) study compares the efficacy and safety of monthly versus daily ibandronate, a novel nitrogen-containing bisphosphonate with proven antifracture efficacy.

Methods: MOBILE is a 2-year, double-blind, double-dummy, phase 3, noninferiority study involving 1,609 women (ages 55 to 80 years; ≥5 years since menopause) with postmenopausal osteoporosis (lumbar spine [L2-L4] bone mineral density [BMD] T-score less than −2.5). Participants were randomized to receive either monthly (50/50 mg [single doses on two consecutive days], 100 mg [single day], or 150 mg [single day]) or daily (2.5 mg) orally administered ibandronate. All participants received daily supplementation with calcium (500 to 1,500 mg) and vitamin D (400 IU). The primary endpoint was mean change from baseline in lumbar spine BMD after 1 year. Secondary endpoints included changes in hip BMD and biochemical markers of bone turnover (levels of serum C-telopeptide and bone-specific alkaline phosphatase).

Adverse events (AEs) were continuously monitored.

Results: After 1 year, substantial increases in lumbar spine BMD were observed in all treatment arms (range, 3.9 to 4.9%). Monthly regimens were at least as effective as daily administered ibandronate, and the 150-mg monthly regimen demonstrated superiority (P = 0.002). The observed increases in total hip BMD were 2.2%, 2.7%, and 3.1% for the 50/50-mg, 100-mg, and 150-mg monthly groups, respectively, and 2% for the daily group. Serum C-telopeptide was reduced by at least 60% from baseline (−62.8% to −75.8%) in all treatment arms, and substantial and similar decreases in level of bone-specific alkaline phosphatase were also observed for all regimens. The 150-mg monthly dose produced the strongest suppression of both biochemical markers. Orally administered ibandronate was well tolerated, and discontinuation related to AEs was infrequent (6.3%, 9.1%, and 7.8% in the monthly groups, respectively, and 9.1% in the daily group).

Discussion: Monthly oral ibandronate therapy is effective and safe for women with postmenopausal osteoporosis. Monthly regimens were proved noninferior to the daily regimen, with the 150-mg monthly dose demonstrating superiority. The incidence of AEs in the monthly treatment arms was low and similar to that with the daily regimen (which has previously shown placebo-level AE incidence).

Conclusion: Monthly oral ibandronate therapy provides a simplified dosing regimen for patients and may help to address poor adherence and persistence to conventional daily and weekly regimens.

Abstract #818

DIVA 1-Year Results: Extended-Interval Ibandronate Injections Are Superior to Daily Oral Ibandronate Therapy and Are Well Tolerated

Michael A. Bolognese, MD, Roberto Civitelli, MD, and Mone Zaidi, MD, PhD, FACE

Background and Objective: A well-tolerated intravenously administered bisphosphonate would be clinically valuable in those patients for whom oral bispho-
sphonate therapy is unsuitable. Ibandronate is a potent, nitrogen-containing bisphosphonate with proven antifracture efficacy in patients with postmenopausal osteoporosis (PMO) when administered orally, either daily or with an extended between-dose interval (>2 months). The DIVA (Dosing IntraVenous Administration) study is comparing the efficacy and tolerability of novel, intermittent injections of ibandronate with the proven 2.5-mg daily oral regimen of ibandronate, and the 1-year results are reported here.

Methods: DIVA is a randomized, double-blind, double-dummy, phase 3, noninferiority study, comparing the efficacy and tolerability of ibandronate injections (2 mg/2 mo, 3 mg/3 mo) with a 2.5-mg daily oral regimen of ibandronate in women with PMO. A total of 1,395 postmenopausal women (55 to 80 years old; ≥5 years since menopause) with osteoporosis (mean lumbar spine [L2-L4] bone mineral density [BMD] T-score less than −2.5) were randomized to treatment. Participants also received calcium (500 mg) and vitamin D (400 IU) daily. The mean percentage changes from baseline in the lumbar spine and proximal femur (total hip, femoral neck, and trochanter) BMD were measured after 1 year. Changes in serum C-telopeptide (a biochemical marker of bone turnover) were also analyzed. Adverse events (AEs), including influenza-like illness, renal AEs, and clinical fractures, were monitored throughout the study.

Results: Substantial increases in lumbar spine BMD were observed in all treatment arms. The BMD increases in the intravenous arms of the study were greater than those in the oral arm; superiority of the two intravenous treatment arms was prospectively demonstrated (P = 0.001). Increases in total hip BMD were 3.6% and 2.4% for the 2 mg/2 mo and 3 mg/3 mo intravenous groups, respectively, and 1.8% in the oral treatment arm (P < 0.05). At all sites, gains in BMD were greater in the intravenous treatment arms than in the oral treatment arm. Median percentage change from baseline in serum C-telopeptide was comparable (~58.6% to ~64.6%) in all treatment arms. Compared with the oral treatment arm, a similar overall incidence of AEs was observed in the intravenous ibandronate therapy arms. The incidence of influenza-like illness was low (3.3%, 3.2%, and 0.6% in the 2 mg/2 mo intravenous, 3 mg/3 mo intravenous, and daily oral arms, respectively), with no differences between the intravenous arms. The incidence of renal AEs was also low (≤3%) and comparable across all treatment arms of the study.

Discussion: Both the 2 mg/2 mo and the 3 mg/3 mo intravenous ibandronate injections demonstrated superiority in BMD endpoints compared with the daily oral ibandronate treatment. The intravenous preparations were equally well tolerated, and no concerns about renal toxicity were identified.

Conclusion: Extended-interval intravenous ibandronate injection offers a suitable alternative therapy for PMO in patients who are unable to take oral bisphosphonate treatments.

Abstract #850

Ectopic Parathyroid Adenoma of Neck Correctly Localized by Single-Photon Emission Computed Tomographic-Sestamibi Scan

Alejandro Martino-Morales, MD, and Vilma M. Rabell, MD, FACE

Objective: To present a case of ectopic parathyroid adenoma correctly localized by single-photon emission computed tomographic-sestamibi scan (SPECT-MIBI) after 4 previous unsuccessful neck explorations.

Case Presentation: A 39-year-old woman was incidentally found to have hypercalcemia on routine laboratory studies done 5 years previously (1999). At that time, the following laboratory results were reported: calcium, 14.9 mg/dL (normal, 8.5 to 10.5); phosphorus, 2.5 mg/dL (normal, 2.5 to 4.5); intact parathyroid hormone (PTH), 236.8 pg/mL (normal, 10 to 65); alkaline phosphatase, 131 U/L (normal, 36 to 92); and creatinine, 0.8 mg/dL (normal, 0.7 to 1.3). A 99mTc-sestamibi parathyroid scan done in August 1999 revealed a lesion highly suggestive of a functioning parathyroid adenoma immediately below the region corresponding to the lower pole of the right thyroid lobe.

In March 2000, the patient underwent an initial neck exploration, with pathology reports of total thyroidectomy with a nodular goiter, atrophic thymus, and parathyroid tissue with no significant pathologic changes. Postoperatively, the patient remained hypercalcemic (serum calcium, 13.9 mg/dL), and computed tomographic (CT) scans of the neck and thorax identified no parathyroid adenoma. In November 2001, repeated laboratory work-up showed the following: serum calcium 14.6 mg/dL, phosphorus 2.7 mg/dL, alkaline phosphatase 185 U/L, and intact PTH 584.6 pg/mL. In January 2002, dual-energy x-ray absorptiometry was done, showing a hip T-score of −1.9 and a spine T-score of −1.1. A 24-hour urine collection for calcium excretion reported 535 mg/day (normal, 100 to 300). At that time, the patient had symptoms of hyperparathyroidism, complaining of constipation, polyuria, and diffuse bone pain, but refused further operations.

In April 2003, the patient decided to undergo a second neck exploration, but the result was unsuccessful, with persistence of hypercalcemia. In December 2003, she presented with acute abdominal pain; on evaluation, acute pancreatitis and severe hypercalcemia (serum calcium, 15 mg/dL) were found. In January 2004, the patient underwent a third neck exploration, again without a successful resolution. Then in February 2004, she was transferred to a university district hospital for further evaluation and management. After review of all available information, the Surgery Department decided to perform a fourth neck exploration; that intervention again failed to disclose any lesion. A repeated 99mTc-sestamibi parathyroid scan in March 2004 showed the same lesion as found on the first
Ectopic parathyroid adenomas are uncommon, occurring in about 10% of all cases of hyperparathyroidism. Such adenomas can complicate the surgical treatment of primary hyperparathyroidism. In this case, even though the patient underwent a 99mTc-sestamibi parathyroid scan before the first neck exploration (which is not the usual standard of care preceding an initial neck exploration), which identified a suggestive parathyroid adenoma in the right lower neck area, it led to four unsuccessful neck explorations because the ectopic location of this parathyroid adenoma was not realized. The interventions were interpreted as inadequate neck explorations. The disadvantage of 99mTc-sestamibi planar images versus SPECT images is that the former do not provide information about the depth of an identified suspicious parathyroid adenoma within the tissue planes, in contrast with the latter. This lack of depth perception in planar images can result in unsuccessful neck explorations. When the SPECT-MIBI correctly localized the adenoma in the superior portion of the posterior mediastinum, a successful parathyroidectomy was accomplished in this patient. In this case, the CT scan also was ineffective in localizing the adenoma. This outcome is in accord with other investigators who have reported a lower sensitivity of CT scanning as compared with sestamibi imaging for localization of ectopic parathyroid adenomas.

Conclusion: In this report, we present the superiority of SPECT-MIBI for correct localization of ectopic parathyroid adenomas, even when an adenoma has been identified in a planar image of a 99mTc-sestamibi parathyroid scan. The advantage of the former study is that information about the depth of a lesion within the tissue planes can be obtained from SPECT-MIBI images but not from planar images.
cantly with PTH ($r = -0.354; P = 0.027$); however, partial correlation analysis showed the significance of this relationship to be slightly lower ($P = 0.067$). Additionally, in a partial and bivariate analysis we found that PTH was strongly correlated with UrCa ($r = -0.540; P = 0.021$) in this group. Although we did not find a direct correlation between 25-OHD and UrCa or spine BMD, 1,25-OHD showed a trend toward a significant association with UrCa ($r = 0.459; P = 0.064$) and spine BMD ($r = -0.356; P = 0.069$). No significant relationships were seen between ionized calcium or serum phosphorus and these other test results.

Discussion: In an attempt to “define” vitamin D deficiency, we analyzed the 25-OHD threshold at which the PTH levels of study patients began to increase and UrCa excretion began to decline. Using the $t$ test, we found the difference between the means of PTH above and below a 25-OHD level of 30 ng/mL to be significant. At 35 ng/mL, the significance was lost. For UrCa, the same vitamin D level of 30 ng/mL showed a significant difference between the means of UrCa for the patients with vitamin D values above and below that number. This relationship was also significant at 35 ng/mL and was lost at a vitamin D level of 40 ng/mL.

Conclusion: 25-OHD level of 30 ng/mL appears to define vitamin D deficiency. This was seen in 48% of patients. Our study indicated significant relationships between 25-OHD, PTH, UrCa, and BSAP. These tests are helpful in determining whether a patient is vitamin D deficient or replete.

Reference


Abstract #880

Greater Increases in Bone Mineral Density Do Not Relate to Greater Decreases in Nonvertebral Fracture Risk

Nelson B. Watts, MD, MACE, Piet Geusens, MD, Ian P. Barton, BSc, Dieter Felsenberg, MD, PhD

Background and Objective: Several studies suggest that greater bone mineral density (BMD) increases induced by osteoporosis therapy do not correlate with greater decreases in vertebral fracture risk. This study analyzed the relationship between BMD changes and osteoporosis-related nonvertebral fracture risk with use of individual patient data from postmenopausal women with osteoporosis receiving risedronate treatment.

Methods: We combined data from three pivotal risedronate fracture-endpoint trials—Vertebral Efficacy With Risedronate Therapy-North America (VERT-NA), Vertebral Efficacy With Risedronate Therapy-Multinational (VERT-MN), and the Hip Intervention Program (HIP). Women received 2.5 or 5 mg of risedronate (N = 2,561) or placebo (N = 1,418) daily for up to 3 years. BMD and nonvertebral fractures were assessed periodically. Osteoporosis-related nonvertebral fractures were defined prospectively as fractures of the hip, wrist, pelvis, humerus, clavicle, and leg, without regard for trauma. Patients were classified into 10 equal subgroups (deciles) on the basis of their change in BMD. The proportion of patients in each subgroup who sustained at least 1 incident nonvertebral fracture was plotted, and a “smoothing” curve was fitted through the data.

Results: The incidence of nonvertebral fractures during the 3-year study period was 10.9% in the placebo group in comparison with 7.7% in the risedronate group. These date reflect an estimated reduction in fracture risk in the risedronate-treated patients of 32% (hazard ratio = 0.68; 95% confidence interval [CI] = 0.54 to 0.85; $P<0.001$). The incidence of nonvertebral fractures in the risedronate group was lower than that in the placebo group across the distribution of percentage changes from baseline in BMD at both the lumbar spine and the femoral neck. The risk of nonvertebral fracture in risedronate-treated patients did not differ between patients whose BMD decreased and those whose BMD increased. The changes in lumbar spine and femoral neck BMD explained only 12% (95% CI, 2% to 21%; $P = 0.014$) and 7% (95% CI, 2% to 13%; $P = 0.005$), respectively, of the nonvertebral fracture efficacy of risedronate.

Discussion: Although absolute BMD is important in untreated patients, the reduction of risk of nonvertebral fractures must be mediated through other effects of risedronate treatment, not through change in BMD.

Conclusion: The size of treatment-related increases in BMD does not influence the magnitude of the effect of risedronate treatment on nonvertebral fractures.

Abstract #882

Humoral Hypercalcemia of Malignancy Associated With Malignant Ameloblastoma

Mario Skugor, MD, Adriana Gabriela Ioachimescu, MD, Leonid Trost, MD, and Chad Michael Silverberg, MD

Objective: To present a case report and review the literature about known cases of ameloblastomas, which are rarely malignant and even more rarely associated with hypercalcemia.

Case Presentation: An 84-year-old African American woman had a 12-year history of recurrent ameloblastoma originating in the right maxilla. The tumor was considered benign. After an initial operation, she underwent 3 resections for recurrent disease. A year before the latest recurrence, mild hypercalcemia (serum calcium level of 11.0 mg/dL) developed. The patient was asymptomatic, and no investigation was undertaken at the time. During the
hospitalization for the latest resection of recurrent ameloblastoma, the patient had an ionized calcium level of 1.55 mmol/L in conjunction with an intact parathyroid hormone (PTH) value of 12 pg/mL (normal, 10 to 60). Her PTH-related protein level was elevated to 1.7 pmol/L (normal, <0.4). Pathologic examination of resected tumor showed malignant transformation. No signs of metastatic disease were found.

**Discussion:** A search of the literature with use of MEDLINE revealed 9 additional cases of ameloblastoma associated with hypercalcemia. Seven of these patients had distant metastatic lesions in the lungs. Two cases had no apparent metastatic involvement but were considered malignant. In most cases, hypercalcemia was humoral (associated with intact PTH in 2 cases and with PTH-related protein in 6 cases). In one case, the reason for the hypercalcemia was not disclosed.

**Conclusion:** Development of hypercalcemia in a patient with ameloblastoma signifies malignant potential, and aggressive treatment is warranted even before apparent recurrence. In addition, in these patients, the probability of metastatic lesions—especially in the lungs—is very high, and a thorough search for metastatic disease should be undertaken before formulation of the therapeutic strategy.

**Abstract #885**

**Safety and Efficacy of Paricalcitol Capsule for Treatment of Secondary Hyperparathyroidism in Patients With Diabetes and Stage 3 or 4 Chronic Kidney Disease**

Joel Zachary Melnick, MD, Ping Qiu, MD, Daniel Coyne, MD, Dennis Andress, MD, Laura A. Williams, MD, and Stuart M. Sprague, DO

**Background and Objective:** Diabetes mellitus is the most common cause of chronic kidney disease (CKD) in adults. In CKD, secondary hyperparathyroidism develops early, often preceding abnormalities of serum calcium and phosphorus, and advances with progressive decline of kidney function. A major factor in the development and progression of secondary hyperparathyroidism is diminished synthesis of calcitriol by the failing kidneys. Oral calcitriol therapy can decrease elevated parathyroid hormone (PTH) levels, but its use has been associated with increased risk of hypercalcemia, hypercalciuria, and hyperphosphatemia. Paricalcitol is a third-generation vitamin D analogue, a selective vitamin D receptor activator, which has been shown to have a wider therapeutic index (significantly decreasing PTH levels while minimally affecting serum calcium and phosphorus concentrations). We examined the reported effect of treatment with paricalcitol capsule in patients with diabetes and stage 3 or 4 CKD who had secondary hyperparathyroidism.

**Methods:** Paricalcitol capsule therapy was studied in three double-blind, placebo-controlled, randomized (1:1), multicenter studies that involved 220 patients with stage 3 or 4 CKD. Across the three studies, 129 of 220 patients (59%) had diabetes; 64 received paricalcitol and 65 received placebo. Patients took study drug 3 times per week or once daily for up to 24 weeks. The initial doses were based on baseline intact PTH (iPTH) levels (2 or 4 µg 3 times a week or 1 or 2 µg daily). Doses were titrated thereafter on the basis of serum iPTH, calcium, and phosphorus levels.

**Results:** Overall among the patients with diabetes, 90% of those receiving paricalcitol achieved the primary efficacy endpoint of two consecutive ≥30% iPTH reductions from baseline compared with 16% of patients receiving placebo. The significant iPTH reduction in the paricalcitol-treated patients was achieved with no significant difference in the incidence of hypercalcemia or hyperphosphatemia in comparison with the placebo group. No difference was detected in the change of urinary calcium excretion between the two treatment groups.

<table>
<thead>
<tr>
<th>Primary endpoints</th>
<th>Paricalcitol</th>
<th>Placebo</th>
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<tbody>
<tr>
<td>2 consecutive: ≥30% decreases from baseline iPTH</td>
<td>55/61 (90%)*</td>
<td>10/61 (16%)</td>
</tr>
<tr>
<td>Serum calcium levels &gt;10.5 mg/dL</td>
<td>2/61 (3%)</td>
<td>0/63 (0%)</td>
</tr>
<tr>
<td>Serum phosphorus levels &gt;5.5 mg/dL</td>
<td>10/61 (16%)</td>
<td>8/63 (13%)</td>
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*Significantly different (P<0.001) from placebo.

**Discussion:** Similar to findings in patients with other baseline etiologic factors accounting for the development of CKD, paricalcitol capsule provides significant reduction of iPTH with minimal effect on serum calcium and phosphorus metabolism in patients with diabetes and stage 3 or 4 CKD.

**Conclusion:** Paricalcitol capsule is an effective new treatment option for patients with diabetes mellitus and secondary hyperparathyroidism who have early-stage CKD.

**Abstract #898**

**Mixed Primary and Secondary Hyperparathyroidism**

Stephanie Painter, MD, Mary Ann Emanuele, MD, Steven De Jong, MD, FACS, FACE, and Fadi A. Nabhan, MD

**Objective:** To summarize the clinical course of a patient with primary and secondary hyperparathyroidism.
Case Presentation: A 60-year-old man with hyperlipidemia was referred for further evaluation of increased serum alkaline phosphatase and intact parathyroid hormone (PTH) levels. The increased alkaline phosphatase had been noted on routine laboratory studies, which prompted further work-up. Results of this work-up included an intact PTH level of 755 pg/mL, an alkaline phosphatase level of 379 U/L (bone fraction, 341), and a bone scan with increased uptake at the left sacroiliac joint. At the time of his initial visit, he complained of low back pain. He was not taking lithium, thiazide diuretics, or calcium supplements.

Findings on physical examination were significant for mild kyphosis. Results of laboratory studies done at that time were as follows: intact PTH 972 pg/mL, 25-hydroxyvitamin D (25-OHD) <5 ng/mL, 1,25-dihydroxyvitamin D₃ 29 pg/mL, alkaline phosphatase 408 U/L, phosphorus 2.2 mg/dL, ionized calcium 1.35 mmol/L, and urine calcium excretion 258 mg/24 h (calcium/creatinine ratio 0.012). A ⁹⁹ᵐTc-sestamibi parathyroid scan revealed a likely parathyroid adenoma. The bone lesion was found to be a brown tumor. A dual-energy x-ray absorptiometry scan was consistent with osteopenia. In light of the profound vitamin D deficiency, the degree of which was not consistent with primary hyperparathyroidism alone, he was cautiously given vitamin D supplements, 400 U twice a day, before surgical treatment.

After 1 month of vitamin D replacement, the patient’s intact PTH level decreased to 814 pg/mL; however, his serum phosphorus was unchanged at 2.2 mg/dL and his ionized calcium level increased to 1.44 mmol/L. The vitamin D replacement was then discontinued. He underwent subtotal parathyroidectomy about 1 week later. His intact PTH levels decreased from 993 to 74 pg/mL intraoperatively. Postoperatively, treatment was initiated with calcitriol (0.25 µg daily) and calcium (600 mg twice a day). One week later, his ionized calcium and phosphorus levels had normalized.

One month after operative intervention, the patient’s 25-OHD level had increased slightly to 6 ng/mL, and his ionized calcium remained within the normal range at 1.23 mmol/L, but his intact PTH level increased to 289 pg/mL. At that time, his vitamin D replacement was switched to ergocalciferol, 50,000 U twice a week. Two months later, his ionized calcium, 25-OHD, and intact PTH levels were within normal limits.

Discussion: The concomitant existence of primary and secondary hyperparathyroidism is an uncommon, but possible, scenario.

Conclusion: Vitamin D status is an important aspect in the work-up of a patient with primary hyperparathyroidism. This information has clinical and therapeutic ramifications.

Abstract #908
A Comparison of Primary Care and Specialty Physicians’ Approach to Diagnosis and Treatment of Osteoporosis

Tiffany Anya Karas, MD, Cinthia Leman, MS, James Sinacore, PhD, Pauline M. Camacho, MD, FACE

Objective: To analyze the approach to screening, diagnosis, and treatment of osteoporosis among male and female physicians in various demographic locations, practice settings, and specialties that encounter high-risk patients, including primary care, endocrinology, rheumatology, geriatrics, orthopedic surgery, and gynecology.

Methods: We analyzed the responses to a cross-sectional survey, developed in the form of a Likert scale, to assess the practice of osteoporosis screening, diagnosis, and treatment among physicians of various specialties. In addition, we compared the approach to screening, diagnosis, and treatment of osteoporosis among six specialty groups of physicians and attempted to determine whether sex, years in medical practice, and practice setting affect the strategies used for screening, diagnosis, and treatment of osteoporosis within each group of specialists and among all the physicians surveyed.

Results: Overall, 122 surveys were returned electronically, including 27 from geriatrics, 25 from endocrinology, 23 from obstetrics-gynecology, 20 from rheumatology, 19 from primary care, and 8 from orthopedics. In reference to screening for osteoporosis, 94.4% of all physicians surveyed would be likely to perform dual-energy x-ray absorptiometry (DEXA) scanning if a patient had 2 or more risk factors, 93.0% for height loss, and 89.0% for long-term use of prednisone. Only 59.9% of all responding practitioners would order a DEXA scan in an elderly male patient with low serum testosterone levels. Physicians in all specialties would likely order DEXA scanning in the setting of vertebral deformities in both male patients (62 to 92%) and female patients (70 to 100%), the one exception being that only 43.5% of obstetricians-gynecologists would order DEXA for male patients with vertebral deformities. Each specialty was least likely to perform screening in elderly male patients with low testosterone levels. Overall, endocrinologists and rheumatologists were more likely to use DEXA given any risk factor or patient scenario in comparison with physicians in the other 4 specialties, and orthopedic surgeons were least likely. Regarding adherence to National Osteoporosis Foundation (NOF) guidelines for treatment of osteoporosis, rheumatologists were most likely to initiate treatment in patients with indications, followed by endocrinologists, geriatricians, primary care physicians,
and obstetricians-gynecologists. Patients were most likely to be screened, diagnosed, and treated for osteoporosis by female physicians practicing in urban, academic settings who had been in practice for more than 6 years.

**Discussion:** Osteoporosis is a disease characterized by low bone mass and loss of bone microarchitecture that gives it strength. Data from the NOF indicate that more than 7.8 million people have osteoporosis and almost 22 million women have low bone density at the hip. This condition will lead to hip fracture in one of every two women. Hip fractures result in decreased functionality, loss of quality of life, and increased health-care costs.

**Conclusion:** Osteoporosis is a common disease that is underdiagnosed and undertreated, despite published guidelines for management. This survey can be used to focus educational efforts on physicians in various specialties who are most likely to provide medical care for patients at high risk for this disease.

**Abstract #919**

**Whole-Body $^{99m}$Tc-Sestamibi Scintigraphy to Localize Tumors Causing Oncogenic Osteomalacia**

Peter Tebben, MD, Stephen F. Hodgson, MD, MACE, Bart L. Clarke, MD, FACE, Brian P. Mullan, MD, William P. Cooney III, MD, and Thomas J. Shives, MD

**Objective:** To describe three patients with surgically proven oncogenic osteomalacia whose tumors were localized preoperatively with use of whole-body $^{99m}$Tc-sestamibi scintigraphy.

**Case Presentation:**

**Case 1:** A 71-year-old woman had a 4-month history of proximal muscle weakness and pain in her thighs, groin, and back. A skeletal survey revealed several vertebral compression fractures, a fracture of the right inferior pubic ramus, and a right rib fracture. Her serum phosphorus concentration was 1.5 mg/dL (normal, 2.5 to 4.5). Her bone-specific alkaline phosphatase (BAP) level was increased, and her 1,25-dihydroxyvitamin D value was inappropriately low. Whole-body $^{99m}$Tc-sestamibi scintigraphy localized a lesion in her right wrist. Magnetic resonance imaging (MRI) confirmed the presence of the lesion. After removal of the tumor, her serum phosphorus level returned to normal (4.0 mg/dL), and her symptoms resolved.

**Case 2:** A 50-year-old man had a 12-month history of bilateral shoulder and right ankle pain. He had multiple rib fractures and a tibial fracture. His serum phosphorus concentration was 1.6 mg/dL. He had an increased BAP level and inappropriately low serum 1,25-dihydroxyvitamin D. His clinical presentation and biochemical profile suggested the diagnosis of oncogenic osteomalacia, but conventional imaging failed to locate the tumor. Five years later, a nodular lesion was found in the lateral aspect of his right ankle on a whole-body $^{99m}$Tc-sestamibi scan and was subsequently confirmed by MRI. After surgical removal of the tumor, his serum phosphorus level increased to 2.7 mg/dL and his symptoms completely resolved.

**Case 3:** A 66-year-old woman had had progressive back pain and weakness for many years. Because of an elevated BAP level, she had been treated with monthly infusions of pamidronate for presumed Paget’s disease. She had multiple rib fractures, thoracic compression fractures, pelvic fractures, a left hip fracture, and a fracture of the sternum. Her serum phosphorus concentration was 1.0 mg/dL. She had an increased BAP value, and an inappropriately low serum 1,25-dihydroxyvitamin D level. Whole-body $^{99m}$Tc-sestamibi scan showed a subtle area of uptake in her right upper arm that was initially thought to be artifact. A subsequent MRI showed a lesion in the same location. After removal of the tumor, her serum phosphorus level increased to 5.4 mg/dL, and her symptoms gradually improved.

**Discussion:** Oncogenic osteomalacia is a rare condition causing hypophosphatemia, hyperphosphaturia, and osteomalacia. If the inciting tumor is removed, the biochemical and clinical abnormalities resolve. These tumors are typically small, difficult to locate, and often undetectable. In these three cases, the offending tumor was localized preoperatively with whole-body $^{99m}$Tc-sestamibi scintigraphy, which ultimately led to a curative surgical procedure for each patient.

**Conclusion:** Whole-body $^{99m}$Tc-sestamibi scintigraphy should be considered early during assessment of patients with a diagnosis of oncogenic osteomalacia and may be an important and cost-effective strategy in localizing peripheral tumors.
OBESITY

Abstract #739

Correlation of C-Reactive Protein Levels With Various Indices of Obesity and Lipid Factors in a Healthy North Indian Population

Sachin Kumar Jain, MBBS, MD, DM, FACE, Niti Agarwal, MD, and Ritesh Panwar, MD

Objective: To study the correlation of C-reactive protein (CRP) levels with various indices of obesity and lipid parameters in a healthy North Indian population.

Methods: The study group consisted of 100 healthy adults (50 men and 50 women) who were 20 to 55 years old. CRP levels were measured by a quantitative immunoturbidimetric method. The following indices of obesity were determined: body mass index (BMI), waist circumference (WC), hip circumference (HC), waist-to-hip ratio (WHR), total skinfold thickness (TSF, a sum of biceps thickness, triceps thickness, subscapular thickness, and suprailiac thickness), and percentage body fat [%BF, determined by an equation reported by Durnin and Womersley (1)]. Fasting lipids were measured in all study subjects.

Results: The mean CRP level was 5.57 mg/L (SD + 3.00; range, 0.8 to 15.4). CRP levels were positively correlated with all indices of obesity: BMI (r = 0.852; P < 0.0001), WC (r = 0.644; P < 0.0001), HC (r = 0.724; P < 0.0001), WHR (r = 0.272; P < 0.0001), %BF (r = 0.509; P < 0.0001), and TSF (r = 0.669; P < 0.0001). In addition, CRP was positively correlated with total cholesterol (TC) (r = 0.258; P < 0.05), low-density lipoprotein cholesterol (LDL-C) (r = 0.299; P < 0.005), triglycerides (TG) (r = 0.201; P < 0.05), and very-low-density lipoprotein cholesterol (VLDL-C) (r = 0.220; P < 0.05), but it was negatively correlated with high-density lipoprotein cholesterol (HDL-C) (r = -0.229; P < 0.005). When the study population was divided into quartiles on the basis of CRP levels, the various indices of obesity and all lipid parameters except HDL-C increased across the quartiles of the CRP levels.

Discussion: In our study, CRP, a sensitive marker of inflammation, was positively correlated with BMI and also various indices of body fat distribution in normal healthy North Indian subjects. CRP levels were also positively correlated with all lipid variables studied except HDL-C, with which it showed a negative correlation. Similar findings have been reported in the Western population.

Conclusion: Chronic subclinical inflammation may be one of the important pathophysiologic mechanisms for atherosclerotic disease, together with increasing adiposity and adverse lipid profile.

Reference


Abstract #902

Situs Inversus in Bardet-Biedl Syndrome

Urooj Mansoor, MD

Objective: To report a case of situs inversus in a patient with Bardet-Biedl syndrome.

Case Presentation: A 24-year-old man with a history of Bardet-Biedl syndrome presented to the endocrine clinic for continued management of congenital hypogonadism. Recently, erythrocytosis had been detected, and his current testosterone dose was being reevaluated. Physical examination revealed an alert, well-oriented, and cooperative man who was 180.3 cm tall and weighed 104.3 kg. He had a normal masculine body hair pattern. His eyes showed constant jerky movements bilaterally. He had small genitalia. Results of laboratory studies showed a hematocrit of 55%, normal electrolytes, blood urea nitrogen of 12 mg/dL, and serum creatinine of 1.2 mg/dL. An ophthalmoscopic examination 1 year previously had shown bilateral bull’s-eye-appearing macular lesions with waxy disk pallor, attenuated retinal vessels, and mid to peripheral bone spicule pigment clumping in each eye.

<table>
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<th>Lipid factor</th>
<th>CRP quartile (mg/L)</th>
<th>0.8-3.5</th>
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<th>4.9-6.3</th>
<th>6.4-15.4</th>
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<td>104.6</td>
<td>118.3</td>
<td>125.7</td>
<td>137.9</td>
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</table>

*Data are shown in mg/dL.

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He had been born by cesarean section because of failure of progression of labor, causing fetal distress. At the time of his birth, the father and mother were 35 and 38 years old, respectively, with no significant past medical history. The family history was unremarkable. A brother of the patient was in good health. Microgenitalism and polydactyly of the left foot of the patient had been noted at birth, and the polydactyly had been treated surgically. As a child, the patient had undergone evaluation for obesity, incomplete puberty, and visual problems. At that time, his work-up revealed central hypogonadism and retinitis pigmentosa; therefore, the diagnosis of Bardet-Biedl syndrome was made. Treatment was initiated with testosterone supplements. A few months before the current consultation, erythrocytosis had been noted; the leukocyte and platelet counts were normal, as was the erythropoietin level. A sleep study was performed, which was negative for hypoxemia. Ultrasonography of the abdomen showed situs inversus, two splenic loculi, and slight malrotation of the right kidney.

**Discussion:** Bardet-Biedl syndrome is inherited as an autosomal recessive condition with heterogeneity. It is characterized by a wide spectrum of clinical manifestations. The generally accepted components of this syndrome are retinopathy, obesity, mental retardation, polydactyly, hypogonadism, and renal abnormalities.

Various published reports have described different disorders in patients with Bardet-Biedl syndrome, including cerebellar vermis hypoplasia (1), lymphangioma (2), and Hirschsprung’s disease (congenital megacolon) (3). To my knowledge, only two previous reports have mentioned the presence of situs inversus in patients with Bardet-Biedl syndrome (3,4).

**Conclusion:** The occurrence of various anomalies in patients with Bardet-Biedl syndrome might be incidental; however, this syndrome has been shown to be clinically and genotypically heterogeneous. The current case and the two previously reported cases of situs inversus in patients with Bardet-Biedl syndrome suggest a possible common cause of both malformations.

**References**

PITUITARY DISORDERS

Abstract #723

Incidence and Clinical Significance of Elevated Macroprolactin Levels in Patients With Hyperprolactinemia

Abel Alfonso, DO, and Robert Vigersky, MD

Objective: To determine the incidence and clinical characteristics of patients with macroprolactinemia in an endocrinology practice at a tertiary care center.

Methods: We reviewed the medical records of 46 patients who had been referred by their primary care providers because of hyperprolactinemia (range of total serum prolactin levels, 22 to 293 ng/mL; mean, 96). The macroprolactin levels in these patients had been determined between June 2003 and August 2004.

Results: Of the 46 patients, 18 (9 male and 9 female) (39%) had an elevated macroprolactin level (50 to 94% of the total prolactin; mean, 75%). The demographic characteristics of these patients were similar to those of patients with elevated monomeric prolactin. The majority of men with macroprolactinemia (78%) had erectile dysfunction as the presenting complaint, whereas the most common symptom in women was menstrual irregularities (67%). Fifty percent of the patients had no identifiable cause for their presenting complaint other than macroprolactinemia. Of the 18 patients with macroprolactinemia, 16 underwent magnetic resonance imaging (MRI) of the pituitary, of whom 56% had normal findings, 25% had a microadenoma, and 19% had either an atrophic hypophysis or a prominent anterior lobe. No statistically significant relationship was found between the MRI findings or symptoms and the presence of elevated macroprolactin levels. In 39% of patients, treatment with a dopamine agonist was initiated.

Discussion: For many years, the clinical significance of macroprolactin has been a controversial subject. Early studies suggested that macroprolactin was generally biologically inactive, and patients were thought to be asymptomatic. Recent evidence suggests, however, that macroprolactin is mainly an IgG-monomeric prolactin complex, and patients frequently present with signs and symptoms consistent with hyperprolactinemia, such as menstrual irregularities, infertiltiy, and galactorrhea in women and erectile dysfunction in men. In our study, 50% of the patients with hyperprolactinemia had no explanation for the presenting symptoms other than the presence of macroprolactinemia.

Conclusion: Macroprolactin is commonly found in patients with hyperprolactinemia. Neither symptoms nor MRI findings are useful in predicting the presence of macroprolactinemia. Macroprolactin may be biologically active.

Abstract #742

Erythrocytosis as a Presenting Feature of Acromegaly

Julia Kaplun, MD, LiSen Liu, MD, and Leonid Poretsky, MD

Objective: To describe a patient with erythrocytosis as the initial manifestation of acromegaly.

Case Presentation: A 65-year-old man was under follow-up surveillance by a hematologist for erythrocytosis. Because of decreased libido, serum testosterone was assessed and found to be 137 ng/dL. Inasmuch as androgen replacement was thought to be relatively contraindicated in the presence of erythrocytosis, the patient was referred to an endocrinologist for further evaluation. His laboratory values were as follows: luteinizing hormone 1.1 mIU/mL, follicle-stimulating hormone 3.1 mIU/mL, prolactin 9.2 ng/mL, growth hormone (GH) 4.0 ng/mL, insulin-like growth factor-I (IGF-I) 902 ng/mL, growth hormone (GH) 4.0 ng/mL, insulin-like growth factor-I (IGF-I) 902 ng/mL, urine free cortisol 58.7 ng/mL, morning cortisol 1.0 µg/dL after administration of 1 mg of dexamethasone the night before, hemoglobin 17.1 g/dL, and red blood cell (erythrocyte) count 5.73 x 10⁶/µL. An oral glucose tolerance test confirmed a diagnosis of acromegaly (GH values [ng/mL]: 5.8 at baseline, 4.5 at 30 minutes, 5.7 at 60 minutes, 5.8 at 120 minutes, and 5.1 at 180 minutes).

Magnetic resonance imaging (MRI) of the pituitary showed a macroadenoma (1.4 by 2.3 cm). The patient underwent transsphenoidal hypophysectomy. Because the MRI revealed residual tumor, he later underwent stereotactic radiosurgery. Relevant preoperative and postoperative laboratory data are presented:

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<td>GH</td>
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<tr>
<td>GH</td>
<td>4.0</td>
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<tr>
<td>RBC</td>
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</table>

*Normal ranges: GH = growth hormone (<10 ng/mL); Hb = hemoglobin (14-17 g/dL); Hct = hematocrit (41-51%); IGF-I = insulin-like growth factor-I (90-360 ng/mL); RBC = red blood cells (4.2-5.9 x 10⁶/µL).
Discussion: The mean preoperative hemoglobin concentration was 18.3 ± 0.9 g/dL (N = 5, October 2002 to April 2004). The mean posttreatment hemoglobin value was 14.7 ± 0.5 g/dL (N = 5, June 2004 to November 2004) (P = 0.0003).

Conclusion: To our knowledge, this is the first reported case in which erythrocytosis resolved after treatment of acromegaly. This effect may be explained by a postoperative resolution of GH- or IGF-I-induced stimulation of erythropoiesis (1).

Reference

Abstract #758

Cyclic Cushing’s Disease: 11-Year Delay in Diagnosis

Maria Fleseriu, MD, Amir H. Hamrahian, MD, Nancy J. Lazarescu, MD, Ali Usmani, MD, Maria M. Pineyro, MD, and Charles Faiman, MD, MACE

Objective: To present a challenging case of Cushing’s disease with intermittent hypercortisolism and delayed diagnosis.

Case Presentation: A 17-year-old girl with a history of more than a 45.4-kg weight gain during an 11-year period was referred to our Pituitary Clinic. She had a normal, healthy childhood until the age of 6 years, when she began to gain weight rapidly. At age 8 years, a morning cortisol value of 0.9 µg/dL after a 1-mg overnight dexamethasone suppression test was interpreted as ruling out Cushing’s syndrome. At puberty, the patient continued to gain weight and had oligomenorrhea, muscle weakness, and acanthosis nigricans. She was diagnosed as having polycystic ovary syndrome and advised to lose weight; oral contraception (OC) and spironolactone therapy were initiated. A 24-hour urine free cortisol (UFC) of 1,354 µg (normal, 20 to 100) at age 14 years prompted a referral to an academic endocrinology center. Findings on physical examination were not deemed to be impressive for Cushing’s syndrome. The high UFC was attributed to the OC, apparently supported by the finding of a normal 24-hour UFC excretion of 54 µg after its discontinuation. Further weight gain prompted a referral to our medical center. A midnight salivary cortisol of 2,136 ng/dL (normal, <100) and a 24-hour UFC of 723 µg were both dramatically increased. Magnetic resonance imaging of the pituitary was inconclusive for the presence of an adenoma, but inferior petrosal sinus sampling was consistent with a pituitary source of adrenocorticotropic hormone (ACTH).

A microadenoma, identified and resected during a transsphenoidal pituitary operation, showed immunostaining only for ACTH. Although the patient had a temporary remission postoperatively, the disease recurred after 4 months, followed by an unsuccessful second transsphenoidal surgical procedure. She is currently under evaluation for gamma knife radiotherapy.

Discussion: This case is remarkable for the prolonged, intermittent hypercortisolism, the reliance on the result of an overnight 1-mg dexamethasone suppression test in a pediatric patient to rule out Cushing’s syndrome, and the false presumption that use of OC results in elevated UFC values.

Conclusion: Clinicians must keep in mind the limitations of different screening tests for Cushing’s syndrome as well as the potential existence of cyclic Cushing’s syndrome as a major challenge to achieving an accurate, timely diagnosis.

Abstract #762

Treatment of Recurrent Cushing’s Disease

Daniel K. Short, MD, PhD, and William F. Young, Jr., MD, FACE

Objective: To review the appropriate treatment of recurrent Cushing’s disease.

Case Presentation: A 42-year-old man with a prior history of Cushing’s disease was referred to our medical center from an outside hospital with chest pain and retrosternal hematoma after undergoing a third pituitary surgical procedure. He had never been considered for bilateral adrenalectomy despite his multiple recurrences, substantially and persistently elevated 24-hour urine cortisol levels, and pronounced signs and symptoms of hypercortisolism. At the time of our assessment, his morning serum cortisol concentration was 38 µg/dL (normal, 7 to 25), plasma adrenocorticotropic hormone (ACTH) concentration was 320 pg/mL (normal, 10 to 60), and 24-hour urine free cortisol was 4,797 µg (normal, 3.5 to 45).

Discussion: The patient had had a stroke and had a large saddle pulmonary embolism as consequences of his recent surgical procedure. His medical status was extremely precarious, and he was deemed not to be a surgical candidate for bilateral adrenalectomy at that time. Treatment was initiated with ketoconazole, 600 mg twice daily, and his 24-hour urine free cortisol level decreased to 30 µg after 3 weeks of therapy.

Conclusion: When the source of excess ACTH secretion cannot be resected, patients should be considered for bilateral laparoscopic adrenalectomy. Failure to do so can expose the patient to appreciable morbidity and even mortality attributable to the effects of excess glucocorticoids. Repeated surgical interventions can likewise be associated with increased risk for significant morbidity, as in the
current case. Therefore, such a recommendation should be carefully considered before a patient is subjected to operative treatment that does not have curative potential. In cases in which bilateral laparoscopic adrenalectomy is contraindicated because of the patient’s medical status, ketoconazole may sometimes be very effective as a temporizing measure.

Abstract #767

“Red Herrings” and the Syndrome of Inappropriate Antidiuretic Hormone Secretion

Richard W. Pinsker, MD, FACE, Kaushik Doshi, MD, Kartik Desai, MD, and Dhimant Dani, MD

Objective: To report an interesting “red herring” case of hyponatremia.

Case Presentation: A 75-year-old African American woman presented with a 2-week history of increasing nausea and vomiting, progressive lethargy during the previous week, and colicky lower abdominal pain in conjunction with diarrhea for 3 days. The patient’s family related that she had undergone some type of pituitary surgical procedure twice during the preceding 6 months but could provide few details. Since then, she had been taking several “pills” but currently was taking only levothyroxine and hydrochlorothiazide. Laboratory studies showed the following: serum sodium 114 mEq/L, chloride 73 mEq/L, potassium 2.6 mEq/L, bicarbonate 29 mEq/L, blood urea nitrogen 5 mg/dL, and creatinine 0.7 mg/dL. Urine sodium was 32 mEq and the specific gravity was 1.013, but no osmolarity was reported. In the emergency department, the patient was thought to have the syndrome of inappropriate antidiuretic hormone secretion (SIADH), and fluid restriction was initiated. Eventually, hypertonic saline was added, but the serum sodium concentration continued to decline, and she became more lethargic. An endocrine consultation prompted measurement of a cortisol level, which was only 3.26 µg/dL. The blood pressure at that time was 120/60 mm Hg, and the pulse was 84 beats/min. The consultant found the patient to be very lethargic and unable to provide any history. Intravenous administration of hydrocortisone rapidly corrected the serum sodium level. The patient’s mental status rapidly improved, and she then related taking cortisone orally but stopping a few months previously. After her condition improved, she was dismissed from the hospital with an oral maintenance regimen of cortisone and levothyroxine.

Discussion: Cortisol deficiency due to a pituitary deficit of adrenocorticotropic hormone can cause hyponatremia on the basis of water retention and inability to excrete a water load, but it is not accompanied by hyperkalemia because aldosterone secretion is usually preserved. This patient was considered as having SIADH until an endocrinologist noted the patient’s history of pituitary surgical procedures and only levothyroxine replacement therapy. No further endocrine work-up was deemed necessary, and replacement corticosteroid therapy was initiated.

Conclusion: SIADH is often a “red herring” diagnosis. Isolated glucocorticoid deficiency must always be excluded in the appropriate clinical scenario.

Abstract #779

Prolactinoma Diagnosed Incidentally on Positron Emission Tomographic Scan

Helen Karakelides, MD, Val J. Lowe, MD, and Dana Erickson, MD, FACE

Objective: To present the case of a 73-year-old man found to have a prolactinoma incidentally on a positron emission tomographic (PET) scan during an evaluation for an esophageal malignant lesion.

Case Presentation: The patient had recently been diagnosed with grade 4 esophageal carcinoma, and a PET scan was done for staging purposes. Focal, intense 18F-2-deoxy-2-fluoro-D-glucose (FDG) accumulation in the right aspect of the sella turcica, extending laterally into the region of the right cavernous sinus, was noted on the PET scan. Magnetic resonance imaging of the brain revealed that this hypermetabolic sellar mass was a 1.2-cm pituitary mass that involved the right side of the sella and extended inferolaterally along the right lateral cavernous sinus. The patient denied having any visual changes, headaches, galactorrhea, or other symptoms of hormonal excess; however, he did have decreased libido and erectile dysfunction. Further endocrine hormonal evaluation showed a substantially increased prolactin level of 771 ng/mL (normal, 4 to 23), appreciable secondary hypogonadism, but normal thyroid, growth hormone, and adrenal axis. A diagnosis of macroprolactinoma was made.

The patient was treated with cabergoline, 0.25 mg twice weekly, and he tolerated this regimen well. Approximately 2 months after institution of cabergoline therapy, his prolactin level had decreased substantially to 39.4 ng/mL. In the interim, he had undergone surgical treatment of his esophageal cancer, and multiple complications from his cancer arose during the next 2 months. Unfortunately, the patient died of the complications from his esophageal cancer within a few weeks after his follow-up.

Discussion: After detailed review of the literature, we conclude that this is apparently the first reported incidentally found prolactin-secreting macroadenoma detected by FDG PET scanning. Normal pituitary glands usually do not accumulate FDG and are therefore not visualized by FDG PET scans. In a case series of 24 patients with known pituitary macroadenomas, of which 5 were prolactinomas, 32 FDG PET scans were performed and showed a sensitivity of 100% for detection of all types of macroadenomas. In another case series of 4 patients with known
macroprolactinomas, however, the sensitivity of FDG PET scanning was nil. One published case report has described an adrenocorticotropic hormone-producing tumor incidentally detected on a PET scan.

**Conclusion:** FDG PET scanning may incidentally show pituitary tumors, including prolactinomas. Published studies on the diagnosis of pituitary tumors with PET scans are scant, and various tracers have been used in case series. Therefore, further studies regarding PET scans and their diagnostic usefulness for pituitary tumors are warranted.

**Abstract #815**

**Massive Polyuria Due to Ewing’s Sarcoma-Associated Central Nervous System Disease**

Farah Dawood-Farah, MD, Maryann Mugo, MD, and Stephen A. Brietzke, MD, FACE

**Objective:** To describe a rare cause of central diabetes insipidus.

**Case Presentation:** A 39-year-old white woman presented to the hospital with new-onset diabetes insipidus, which was partially but incompletely responsive to desmopressin. The baseline urine volume was 12 to 15 L/24 h, with an osmolality of 65 mOsm/kg H₂O, compared with a serum osmolality of 304 mOsm/kg H₂O and a serum sodium level of 147 mEq/L. Therapy with hydrochlorothiazide produced a decrement in urine volume to 4 to 5 L daily, and symptoms resolved. Because the patient had a concurrent medical history of Ewing’s sarcoma, which had been initially diagnosed and treated 4 years earlier, and multiple paraspinal recurrences within the past year, neuroimaging (magnetic resonance imaging) was performed. A partially rim-enhancing mass lesion (2 by 2 cm) was identified in the hypothalamus. Medical oncologists and neuro-oncologists agreed that surgical resection of the hypothalamic lesion was unfeasible because of the poor overall prognosis. The patient was discharged from the hospital to outpatient hospice care and given hydrochlorothiazide therapy for palliation of her diabetes insipidus.

**Discussion:** A literature review identified no case of Ewing’s sarcoma causing diabetes insipidus. Central nervous system metastatic lesions occur in approximately 3% of cases, and if any disorder of water metabolism is observed, it has historically been attributable to the syndrome of inappropriate antidiuretic hormone secretion. Hence, the current case is extremely unusual and emphasizes the importance of neuroimaging in cases of deranged water metabolism in patients with a known malignant tumor.

**Conclusion:** Hypothalamic metastatic lesions from Ewing’s sarcoma can cause central diabetes insipidus. Neuroimaging in patients with cancer and diabetes insipidus should include the suprasellar region.

**Abstract #829**

A Rare Magnetic Resonance Imaging Presentation in Adult Endocrinology: The Pituitary Stalk Transection Syndrome—From Ontogeny to Clinical Picture

Adriana Gabriela Ioachimescu, MD, and Robert S. Zimmerman, MD

**Objective:** To present a case of panhypopituitarism caused by abnormal formation of the pituitary gland, compatible with the pituitary stalk transection syndrome, and discuss the importance of magnetic resonance imaging (MRI) in understanding pituitary function.

**Case Presentation:** A 19-year-old male college student presented for his first consultation with an adult endocrinologist. He had been diagnosed as having growth hormone (GH) deficiency at age 4 years and took GH replacement until age 18 years. At 7 years of age, thyroid hormone replacement therapy was instituted. No sexual development occurred until testosterone therapy was initiated at age 15 years. He had had a surgical procedure on the upper respiratory tract at age 2 years and orchiopexy at 11 years, with no corticosteroid treatment or adverse events. Findings on examination by the adult endocrinologist were remarkable for small testes (3 cm³) and lack of facial hair. Hormonal evaluation showed the following: insulin-like growth factor-1 42 ng/mL (normal, 182 to 780), thyrotropin 0.032 mIU/mL, thyroxine 7.9 µg/dL, free thyroxine index 7.1 µg/dL (while taking levothyroxine, 150 µg/day), and prolactin 22.7 µg/mL (normal, 2.0 to 14.0). A cosyntropin stimulation test (250 µg) showed plasma cortisol responses of 1.6, 4.4, and 5.3 µg/dL at 0, 30, and 60 minutes. MRI of the pituitary gland disclosed an abnormal signal intensity posterior to the optic chiasm on precontrast T1-weighted images, with minimal postcontrast enhancement (ectopic pituitary). The pituitary stalk was not identified on either precontrast or postcontrast images. A small amount of enhancing soft tissue was identified in the pituitary fossa.

**Discussion:** Our patient’s MRI illustrated the pituitary stalk transection syndrome, characterized by an ectopic posterior pituitary lobe, absence of the pituitary stalk, and hypoplasia of the anterior hypophysis. Clinically, the syndrome includes GH, thyrotropin, follicle-stimulating hormone, luteinizing hormone, and adrenocorticotropic hormone deficiencies, as well as hyperprolactinemia and normal posterior pituitary function. In children presenting with short stature, those with pituitary stalk transection have earlier onset of and more severe hypopituitarism. Patients with a visible pituitary stalk will more likely have isolated GH deficiency. In contrast, patients with PROP1 gene mutations, the most common heritable cause of hypopituitarism, exhibit deficiencies of all anterior pituitary hormones, including prolactin, and normal posterior pituitary function. Among the interesting features in our case are ectopic location of
the posterior pituitary lobe and delayed development of adrenal insufficiency in the setting of pituitary stalk transection.

**Conclusion:** The MRI appearance in association with the clinical and biochemical findings may elucidate the cause of hypopituitarism in children with short stature. In adults, the pituitary stalk transection syndrome is a rare cause of hypopituitarism, characterized by anterior hypopituitarism, hyperprolactinemia, and normal posterior pituitary function. As in our case, delay in development of adrenal insufficiency can occur.

**Abstract #835**

**Therapeutic Potential of the Novel Multiligand Somatostatin Analogue, SOM230, for Patients With Cushing’s Disease**

*Ly-Le Tran, MD, A. Silva, PhD, J. E. Glusman, MD, and H. A. Schmid, PhD*

**Background:** SOM230 is a novel multiligand somatostatin analogue with high binding affinity to four somatostatin receptor subtypes, sst1, sst2, sst3, and sst5. This characteristic contrasts with the analogue octreotide, which binds preferentially to sst2 receptors and has only weak affinity for sst3 and sst5 receptors. Of note, sst1 receptors are expressed by one in three adrenocorticotropin hormone (ACTH)-secreting tumors, whereas sst3 and sst5 receptors are expressed by one in two ACTH-secreting tumors. Cushing’s disease, which is characterized by hypersecretion of ACTH and subsequently corticosterone, currently has no approved medical therapy.

**Methods:** Preclinical studies with SOM230 in several animal species have evaluated the effect of this novel agent on the secretion of various hormones, including ACTH.

**Results:** In vitro evaluation showed a high expression by messenger RNA of sst5 receptors but few sst2 receptors in a mouse corticotroph adenoma cell line (AtT-20 cells); thus, the expression profile of human corticotroph adenomas was mimicked. Furthermore, the binding affinity, stimulation of GTPyS on AtT-20 cell membranes, and inhibition of cyclic adenosine monophosphate production in AtT-20 cells were stronger with SOM230 than with octreotide. In vivo evaluation in rats demonstrated that a single subcutaneous pretreatment dose of 3 or 10 µg/kg of SOM230 led to effective inhibition of both ACTH release (46% and 54%, respectively) and corticosterone release (43% and 27%, respectively). In contrast, octreotide in a dose of 10 µg/kg had a comparatively small effect on ACTH release (35%) and had no effect on corticosterone release.

**Discussion:** The binding profile of SOM230 and the high expression of sst5 receptors in human corticotroph adenomas suggest that this novel agent may have a greater inhibitory effect on ACTH secretion than current somatostatin analogues such as octreotide. Indeed, the demonstration by preclinical data of significant inhibition of ACTH release in vitro and in vivo suggests that SOM230 has considerable potential as effective medical therapy for patients with Cushing’s disease.

**Conclusion:** Phase 2 studies with SOM230 in Cushing’s disease are ongoing, and early results are encouraging.

**Abstract #836**

**Preclinical and Clinical Experience With the Novel Multiligand Somatostatin Analogue, SOM230**

*Ly-Le Tran, MD, and H. A. Schmid, PhD*

**Background:** SOM230 is a novel multiligand somatostatin analogue that exhibits high binding affinity to four of the five somatostatin receptor subtypes: sst1, sst2, sst3, and sst5. In comparison with octreotide, SOM230 has 30, 5, and 40 times greater affinity for sst1, sst3, and sst5 receptors, respectively, and a comparable affinity for sst2 receptors. Because of its unique multiligand profile, SOM230 potentially offers therapeutic benefits, not only in the “classic” somatostatin analogue indications such as acromegaly and neuroendocrine tumors but also in conditions in which sst subtypes other than sst2 are important. Such conditions include Cushing’s disease, which is characterized by overproduction of adrenocorticotropin hormone, and tumors that express sst1, sst3, and sst5, such as metastatic carcinoid tumors.

**Methods:** Preclinical and phase 1 clinical studies have been conducted, and SOM230 is currently under investigation in phase 2 studies in patients with metastatic carcinoid tumors and in Cushing’s disease.

**Results:** In vitro evaluation highlighted the potential for SOM230 to inhibit hormone release by different types of secreting pituitary adenomas. SOM230 had a stronger inhibitory effect on cyclic adenosine monophosphate production of mouse pituitary corticotroph adenoma cells (AtT-20 cells) and caused a stronger inhibition of growth hormone secretion from rat somatotroph cells in comparison with octreotide. In animal models, SOM230 demonstrated greater potency than octreotide in inhibiting growth hormone and insulin-like growth factor-I secretion. In humans, SOM230 has been studied in single or multiple doses up to 1,500 µg/day as well as administered by continuous infusion at doses up to 2,250 µg/day. In healthy male subjects, SOM230 given once or twice a day was well tolerated even at higher doses, adverse effects being generally mild. The most common adverse effects noted were loose stools and mild, transient elevation of blood glucose levels at higher doses. Most adverse effects were transient and did not necessitate treatment.

**Discussion:** Early phase 2 data from trials with SOM230 in patients with metastatic carcinoid tumors and...
in patients with Cushing’s disease have shown encouraging results.

**Conclusion:** Preclinical and early clinical data show that, because of its novel multiligand binding profile, SOM230 has potential efficacy in the treatment of conditions for which no effective medical therapy is currently available, such as octreotide-resistant metastatic carcinoid tumors and Cushing’s disease. SOM230 is well tolerated in humans.

**Abstract #852**

**There and Back Again: A Perplexing Prolactinoma’s Tale**

Khurshid Ahmad Khan, MD, Candi Nobles-James, MD, and Stephen A. Brietzke, MD, FACE

**Objective:** To document spontaneous remission and late recurrence of hyperprolactinemia when prolactinoma is complicated by pituitary apoplexy.

**Case Presentation:** A 38-year-old African-American woman was originally diagnosed with microprolactinoma in 1998 after presentation with oligomenorrhea and galactorrhea. The serum prolactin level was 157 ng/mL, and magnetic resonance imaging (MRI) of the sella revealed an 8- by 5-mm adenoma. For 3 years, the serum prolactin level was suppressed to <18 ng/mL by bromocriptine therapy, with restoration of normal menses and resolution of galactorrhea. In 2001, despite continued therapy, hyperprolactinemia recurred. Neither escalation of the dose of bromocriptine nor treatment with cabergoline suppressed the prolactin level. The hyperprolactinemia persisted for 2 years, until the patient had acute onset of headache, nausea, and photophobia in 2003. MRI demonstrated a microhemorrhage within the 8- by 5-mm adenoma; the serum prolactin value at the time of the clinical apoplexy event was 135 ng/mL. The headache resolved with conservative management; 2 weeks after the event, the serum prolactin level was 9 ng/mL. Despite continued therapy with bromocriptine (10 to 15 mg daily), hyperprolactinemia gradually recurred during the subsequent 18 months, without associated enlargement of the sellar mass, visual field changes, or headache. In the fall of 2004, the serum prolactin concentration was 48 ng/mL during treatment.

**Discussion:** This intriguing case appears to reflect an initially ergot-responsive microprolactinoma, which gradually lost suppressibility over time, presumably because of loss of dopamine D2 receptors (described in 5 to 18% of prolactinomas, as an explanation for resistance to dopamine agonists). A clinical apoplexy event, which was associated with a characteristic small intrasellar hemorrhage, led to transient remission of hyperprolactinemia, perhaps as a result of infarction-related loss of critical tumor cell mass. Late recurrence of hyperprolactinemia likely reflects clonal regeneration of adenomatous tissue.

**Conclusion:** Pituitary apoplexy may be associated with transient remission of hyperprolactinemia, which may later recur, presumably attributable to regeneration of the secretory capacity of the adenoma. Thus, long-term follow-up of patients with apparent remission of hyperprolactinemia is advisable.

**Abstract #854**

**Pituitary Infarction and Hypopituitarism in Diabetes Mellitus—Report of 2 Cases and Review of a Little-Known Complication**

Roshni Kundranda, MD, and Harris C. Taylor, MD, FACE

**Objective:** To report one case of pathologically verified pituitary infarction in a patient with diabetes mellitus (DM) and a second presumptive case with documented hypopituitarism and to review the subject comprehensively for the first time since 1969.

**Case Presentation:** In the first case, a 31-year-old man with type 1 DM for 11 years, treated with 40 U of NPH insulin, was hospitalized because of weakness, vomiting, and diarrhea. Septicemia, renal failure, and recurrent hypoglycemic episodes resulted in discontinuation of insulin therapy and ultimately death. Autopsy demonstrated recent pituitary infarction involving 70% of the adenohypophysis. In the second case, a 65-year-old woman with type 1 DM had episodes of recurrent neuroglycopenia and hyponatremia attributed to the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Secondary hypogonadism (luteinizing hormone 5.4 mIU/mL and follicle-stimulating hormone 8.0 mIU/mL), secondary hypoadrenalism with normal results of a 0.25-mg cosyntropin test—baseline cortisol 13.5 µg/dL and aldosterone 2.9 ng/dL, which increased to 23.8 µg/dL and 15.9 ng/dL, respectively, at 60 minutes—but abnormal results of a metyrapone test, with a serum cortisol level <1 µg/dL but inadequate levels of 11-deoxycortisol of 3.2 µg/dL (normal, 7 to 18) and adrenocorticotropic hormone of 79 pg/mL (normal, 112 to 466), were found. Results of thyroid function tests were normal: free thyroxine index 5.5 (normal, 4.4 to 11.2) and thyrotropin 2.9 µIU/mL (normal, 0.3 to 5.0). Magnetic resonance imaging showed a normally sized empty sella. Hydrocortisone, 10 mg twice daily, and insulin dosage adjustment eliminated the SIADH, recurrent hypoglycemia, and emergency department visits.

**Discussion:** In the English-language medical literature, 70 cases of pituitary infarction/necrosis or hypopituitarism in adults with DM have been reported. The autopsy incidence of pituitary infarction and necrosis in patients with DM, however, is 4 times that in the general population. Both acute onset and insidious onset of pituitary insufficiency in patients with diabetes have been described, occurring in settings such as after delivery, with and without hemorrhage (in 13 cases), before childbirth.
Pituitary infarction and necrosis should affect the degree of damage associated with infarction and the remaining pituitary reserve. Generally, at least 75% of the anterior pituitary lobe must be destroyed to cause clinically apparent hypopituitarism. Our 2 patients differed in age, sex, acuity of onset, and clinical course; these features exemplify the varied nature of this condition. The first patient had septicemia and shock, perhaps causing pituitary infarction and necrosis, whereas the second patient had no known precipitating factor.

**Conclusion:** Pituitary infarction and necrosis should be considered when patients with diabetes present with unexplained hypoglycemia or other endocrine abnormalities.

**Abstract #869**

**Xanthoma Disseminatum—A Rare Cause of Central Diabetes Insipidus**

**Muhammad Houri, MD, and Afshin Salsali, MD**

**Objective:** To present a case of xanthoma disseminatum (XD), a rare cause of central diabetes insipidus (DI), with its associated clinical manifestations.

**Case Presentation:** A 61-year-old man was referred for evaluation because of polyuria and polydipsia of 3 months’ duration. He also complained of hoarseness, fatigue, and somnolence. His medical history was significant for XD (confirmed by skin biopsy 2 years previously) and coronary artery disease.

Physical examination was remarkable for a rash involving the face and upper torso. Thorough evaluation revealed XD involvement of the conjunctivae, upper respiratory tract, pituitary gland, and possibly the pericardium (pericardial effusion of unknown cause). A water deprivation test confirmed the diagnosis of central DI. Magnetic resonance imaging of the head revealed enlargement of the pituitary gland and pituitary stalk, with uniform enhancement. Complete evaluation of the anterior pituitary function showed central hypogonadism. A fasting lipid profile included a triglyceride level of 179 mg/dL and low-density lipoprotein cholesterol level of 173 mg/dL.

Treatment with desmopressin for the central DI yielded considerably diminished symptoms. He declined treatment for hypogonadism. For the XD, he was treated with a 6-week course of cladribine (a synthetic antineoplastic agent), which ameliorated his skin and upper airway disease.

**Discussion:** XD is a rare, non-Langerhans cell, histiocytic syndrome. The condition seems to occur sporadically; the preponderance of cases are in young men. The patients have normal lipid levels and present with xanthomas involving the skin, upper respiratory tract, pituitary gland, and other organs.

The initial manifestations are usually red-yellow papules and nodules, often in flexural sites such as the axillae, which enlarge over a period of years to form confluent xanthomatous plaques. Mucous membrane involvement develops in 40 to 60% of patients, most commonly affecting the oropharynx (dysphagia), larynx (hoarseness or dyspnea), corneas, and conjunctivae.

Systemic involvement may result in substantial morbidity. Death as a result of airway obstruction or massive intracranial involvement has been reported. Occasional cases of XD have been associated with osteolytic lesions, monoclonal gammopathy, and multiple myeloma.

Central DI develops in 40% of patients because of lesions involving the pituitary fossa. DI may precede the appearance of the rash; in some cases, the rash has appeared a few years after the diagnosis of idiopathic DI. In some patients, the DI may resolve spontaneously.

**Conclusion:** XD is a rare disorder. Affected patients have normal lipid profiles and xanthomas involving the skin and upper respiratory tract. Systemic involvement may result in appreciable morbidity. Central DI develops in 40% of the patients and may precede the skin lesions. Therefore, physician should look for manifestations of XD when a patient has no apparent cause for DI.

**Abstract #878**

**Pituitary Apoplexy After Administration of Leuprolide**

**Anu Bhalla Davis, MD, Shefali Goel, MD, Michalis K. Picolos, MD, Min Wang, MD, PhD, and Victor Lavis, MD**

**Objective:** To report a case of pituitary apoplexy occurring after administration of leuprolide for treatment of prostate cancer.

**Case Presentation:** A 61-year-old man visited the emergency department because of onset of a frontal headache a few hours after he received his first injection of leuprolide for treatment of prostate cancer. Brain computed tomography without use of a contrast agent revealed no abnormalities, and the patient was discharged home. His symptoms persisted, and nausea, vomiting, and ptosis of the left eye developed over the next 4 days, leading to a second emergency department visit. Vital signs were normal, and physical examination revealed a well-developed
man with no clinical findings of hypogonadism or functional pituitary adenoma. Findings on neurologic examination were consistent with a palsy of cranial nerve III. Visual field examination showed bitemporal field cuts. Laboratory studies showed normal electrolytes and renal function, low levels of luteinizing hormone, follicle-stimulating hormone, and testosterone, a normal free thyroxine index, and a normal level of prolactin. Magnetic resonance imaging of the head disclosed a hemorrhagic sellar mass (20 by 18 by 14 mm). The patient received stress dose corticosteroids and underwent transsphenoidal hypophysectomy. The pathology report indicated findings consistent with pituitary apoplexy, immunohistochemically suggestive of an infarction of a preexisting gonadotroph cell adenoma.

**Discussion:** Pituitary apoplexy is a potentially life-threatening medical emergency. Most commonly, it occurs spontaneously, but it may occur in response to pituitary stimulation by gonadotropin-releasing hormone or gonadotropin-releasing hormone agonists.

**Conclusion:** The possibility of acute pituitary hemorrhage must not be overlooked in patients in whom headache develops after leuprolide therapy. Initial stimulatory effects of gonadotropin-releasing hormone analogue may induce pituitary apoplexy in patients with asymptomatic gonadotroph adenomas.

**Abstract #888**

**Unique Association of Thrombotic Thrombocytopenic Purpura and Diabetes Insipidus**

Richard W. Pinsker, MD, FACE, Mahpara Qureshi, MD, Naveen Pathak, MD, Nadezhda Badalova, MD, Shetra Sivamurthy, MD, and Mohammed Babury, MD

**Objective:** To describe an unusual case of thrombotic thrombocytopenic purpura (TTP) that led to central diabetes insipidus, necessitating desmopressin therapy—itself a complicating factor in platelet maintenance.

**Case Presentation:** A 47-year-old African American woman presented with crampy abdominal pain and nausea. The patient had tachycardia, fever, and hypotension. Laboratory studies showed the following: hematocrit 29.8%, leukocytes 15.0 × 10³/µL, platelets 29 × 10³/µL, blood urea nitrogen 27 mg/dL, serum creatinine 1.9 mg/dL, lipase 802 mIU/mL, amylase 308 U/L, lactate dehydrogenase 1,318 U/L, reticulocytes 4.6%, and troponin I 3.77 mg/mL. Ultrasonography suggested pancreatitis and cholecystitis. Subsequently, the patient became confused and had a seizure, and her renal function deteriorated. Bone marrow showed adequate megakaryocytes, but a peripheral smear revealed severe thrombocytopenia, polychromasia, and schistocytes. TTP was diagnosed, and plasmapheresis was initiated. Mechanical ventilation was required.

Over the next few days, severe polyuria developed, and the serum sodium concentration increased to 171 mEq/L. Central diabetes insipidus was diagnosed, and desmopressin was administered, with prompt reduction of urine output and of the serum sodium level. Desmopressin therapy, however, had to be discontinued several times because of worsening thrombocytopenia, likely due to stimulated release of von Willebrand factor multimers. The serum sodium level again increased, and the patient died.

**Discussion:** Review of the literature revealed only one published case report of TTP and central diabetes insipidus. Our case is the first in which desmopressin was used in such a setting.

**Conclusion:** Treatment of diabetes insipidus with desmopressin in a setting of TTP is extremely challenging.

**Abstract #889**

**Congenital Dysgenesis of the Pituitary Gland as a Cause of Developmental Delay**

Omar Mtaweh Murad, MD, Shahed A. Quyumi, MD, and Jeffrey G. Rothman, MD, FACP, FACE

**Objective:** To report a case of untreated panhypopituitarism attributable to congenital pituitary dysgenesis.

**Case Presentation:** A 43-year-old man had a history of lifelong short stature and delay of growth. The patient had not been treated until the age of 20 years. He had no history of trauma to the head, a surgical procedure involving the brain, or radiation therapy. His medications included levothyroxine (100 µg daily) and prednisone (7.5 mg daily).

A review of the patient’s medical records showed that he had received growth hormone for 4 years from age 20 to 24 years with no change in height. Testosterone treatment elicited a mild growth of pubic hair and an unsustainable erection. A bone density test, done in 1999, revealed a low bone mineral density with a T-score of ~4, which was treated with calcium and vitamin D. On a follow-up visit in our clinic, the patient was offered further growth hormone stimulation testing and treatment, but he refused this option.

On physical examination, the patient had an adolescent appearance, cushingoid face, and no facial hair. His weight was 52 kg, and his height was 137 cm. He had prominent gynecomastia. Genital examination showed Tanner stage 2 development.

Laboratory studies showed the following (normal ranges indicated in parentheses): insulin-like growth factor-I 45 ng/mL (90 to 360), luteinizing hormone 0.11 mIU/mL (2 to 18), follicle-stimulating hormone 0.92 mIU/mL (1.6 to 18.1), free testosterone 1.4 pg/mL (50 to 210), total testosterone 10 ng/dL (260 to 1,000 for an adult male patient), prolactin 3.4 ng/mL (3.0 to 16.0), and total thyroxine 8.1 µg/dL.
Magnetic resonance imaging of the pituitary disclosed a hypoplastic sella turcica and anterior lobe of the pituitary gland, with maximal height of the latter of 2 mm (normal, 8 to 10 mm for an adult male patient). The pituitary stalk was bulbous and did not communicate with the gland. The bone age of the patient was consistent with 15 years of age.

Discussion: In the medical literature, reports of 7 similar cases of untreated panhypopituitarism were found and reviewed. The patients in those reports had varied growth patterns. Some patients remained dwarfed throughout life, whereas others had a surge in their growth later during adulthood. Speculations about potential reasons for this variability include the possible presence of an unknown growth factor, an abnormal concentration of an insulin-like growth factor-binding protein, and the growth effect of insulin, prolactin, and estrogen.

Conclusion: Pituitary dysgenesis is a cause of panhypopituitarism that can result in developmental delay. The survival and development of this patient whose panhypopituitarism was not treated during the first 20 years of his life raise questions regarding physiologic mechanisms that allow for survival into adult life.

Abstract #896
Hypothalamic-Pituitary-Adrenal Axis Testing With Use of a 25-µg Cosyntropin Stimulation Test
Ali Usmani, MD, Antoine Makdissi, MD, Amir H. Hamrahan, MD, S. Sethu K. Reddy, MD, MBA, FACE, Robert J. Weil, MD, and Charles Faiman, MD, MACE

Background: A 1-µg or 250-µg cosyntropin stimulation test (CST) is used as a screening study for evaluation of the hypothalamic-pituitary-adrenal (HPA) axis, with each test having its proponents and critics. The subcutaneous administration of 20 µg and 30 µg of cosyntropin results in peak mean adrenocorticotropic hormone levels of about 200 and 350 pg/mL, respectively, approximating values achieved during the insulin tolerance test (ITT) and metyrapone test. Accordingly, we selected the 25-µg subcutaneous CST for evaluation of the HPA axis and report on its diagnostic accuracy.

Methods: The 25-µg CST has been used in our Pituitary Clinic for the past 2 years. The serum cortisol level is measured before and at 30 and 60 minutes after administration of cosyntropin. A 250-µg cosyntropin vial is reconstituted in 1 mL of saline. The 25-µg dose (0.1 mL) is given subcutaneously with use of an insulin syringe. The reconstituted vial can be stored for up to 1 month in the refrigerator before being discarded.

Results: Twenty patients with a presumably normal HPA axis and no history of a pituitary surgical procedure served as control subjects. Magnetic resonance imaging of the pituitary showed normal findings in 14 patients and a microadenoma (2 to 6 mm) in 6. The median (range) cortisol levels at 30 and 60 minutes were 19.9 µg/dL (17.2 to 35.8) and 18.6 µg/dL (11.1 to 46.5), respectively. The peak value occurred at 30 minutes in 15 of the 20 patients. Forty-three patients underwent the CST and either an ITT (N = 26) or metyrapone test (N = 17). Of these 43 patients, 16 passed and 27 failed the ITT or a metyrapone test. Most of these patients (31 of 43) had a pituitary macroadenoma. In those patients who underwent a pituitary surgical procedure, all tests were done at least 4 weeks postoperatively. Receiver operating characteristic curve analysis of the 30-minute and 60-minute data from the 20 control subjects and 43 patients was performed. A cortisol cutoff value of 18.0 µg/dL at 30 minutes resulted in the best combination of sensitivity and specificity of 88.9% and 59.5%, respectively. Of the 27 patients who failed the ITT or metyrapone test, 3 passed the 25-µg CST. Two of these 3 patients did not benefit from glucocorticoid therapy, which was subsequently discontinued without sequelae.

Discussion: The 25-µg CST offers an alternative to current provocative testing of HPA reserve. It affords reasonable sensitivity. Although the specificity in our retrospective data analysis was somewhat lower than in reported studies that have used the 1-µg or 250-µg cosyntropin test, this result may be due to the relatively small number of patients with a documented normal HPA axis in the current study.

Conclusion: The 25-µg CST seems to be convenient and reliable for evaluation of the HPA axis. Determining whether it will prove superior to the 1-µg or 250-µg CST will necessitate direct head-to-head studies.

Abstract #909
Transient Ischemic Attack as the Initial Presentation of Macroprolactinoma: Resolution With Dopamine Agonist Therapy
Judith Michelle Dickert, MD, Martha Girz, MD, John A. Poremba, MD, FACE, Linda S. Krook, MD, FACE, and Capt. K. M. Mohamed Shakir, MD, FRCP, FACP, FACE

Objective: To report the first case describing a transient ischemic attack as the initial manifestation of a macroprolactinoma.

Case Presentation: A 59-year-old man presented with a history of transient right hand numbness, right visual loss, right face paresis, and slurred speech lasting less than 12 hours. This scenario was preceded by 2 weeks of atypical global headaches, 8 months of profound fatigue, and a 10-year history of erectile dysfunction. He denied having heat or cold intolerance, orthostatic symptoms, breast enlargement or discharge, or changes in facial features or ring or shoe size. His prior medical history was significant for controlled hypertension (with lisinopril and clonidine therapy), depression, and acid reflux. On physi-
cal examination performed at presentation, but after resolution of symptoms, a superior temporal quadrantanopia was noted as the only neurologic defect. He had no gynecomastia. His testes were 25 cc bilaterally and soft, and he had normal male hair distribution.

Computed tomography of the head revealed a large sellar mass causing bony erosion of the anterior and posterior clinoid and clival bones. Magnetic resonance imaging of the sella further delineated a 3.6-cm T1-enhancing mass involving the entire sella and bilateral parasellar regions, with bilateral carotid encasement, cavernous sinus involvement, and suprasellar extension with deviation of the optic chiasm. A 2.5-cm cystic mass projected into the right frontal sinus at the level of the foramen but did not involve the brainstem or basilar arteries. Because of his presenting symptoms, carotid artery ultrasonography, echocardiography, and 36 hours of telemetry were performed, and the findings were normal.

Laboratory studies showed low levels for the following analytes (normal ranges shown parenthetically): luteinizing hormone 2.61 mIU/mL (0.97 to 10.2), follicle-stimulating hormone 2.7 mIU/mL (1 to 18), total testosterone 180 ng/dL (260 to 1,000), and human growth hormone <0.1 ng/mL. Alpha subunit was 0.5 ng/mL (0.0 to 0.9), insulin-like growth factor-I was 164 ng/mL (71 to 290), and baseline morning cortisol was 10.8 µg/dL (all normal). Results of an adrenocorticotropic hormone stimulation test were normal. A serum prolactin level was elevated at 13,600 ng/mL (normal, 1.61 to 18.77). By 28 months after treatment with dopamine agonists, his visual deficits had resolved, the prolactin level had normalized, and the prior macroadenoma measured 6 by 5 by 4 mm. All presenting symptoms ultimately resolved.

Discussion: To our knowledge, this is the first case describing a macroprolactinoma manifesting as a transient ischemic attack without evidence of pituitary hemorrhage or apoplexy. Neurologic symptoms associated with a macroprolactinoma are rare. A hemorrhage in the tumor can produce frontal or vertex headaches, which may be followed by visual and other clinically significant neurologic symptoms. Prolactinomas have also been associated with cluster headaches, including short-lasting unilateral neuralgiform pain with conjunctival injection and tearing, but not with strokelike symptoms. In the absence of other etiologic factors to explain the neurologic symptoms, we propose the likely cause was compression of the internal carotid artery by the tumor. A case report of strokelike symptoms involving the internal carotid artery territory after pituitary hemorrhage in a patient with acromegaly has been described, but none due to the mass effect of the pituitary adenoma itself.

Conclusion: This is a unique case of strokelike neurologic symptoms, without accompanying hemorrhage, that were the presenting clinical feature of a macroprolactinoma. Mass effect of a pituitary tumor in the absence of hemorrhage or apoplexy should be included in the differential diagnosis when a patient presents with symptoms of a stroke.
Abstract #714

**Idiopathic Hypogonadotropic Hypogonadism**

Maria Patricia Deanna Delfin Maningat, MD, and Cecile A. Jimeno, MD

**Objective:** To present a case of a 29-year-old man in whom secondary sexual characteristics failed to develop and to discuss the evaluation and treatment options for a patient with hypogonadotropic hypogonadism.

**Case Presentation:** A 29-year-old man requested a medical consultation because of underdeveloped genitalia. He had no other comorbidities. There was no history of maternal drug intake while the patient was in utero, and no similar disorder was present in the family. The patient had been at par with classmates of the same age in both physical and mental health. At age 20 years, he became aware of absence of facial, pubic, and axillary hair growth and, more importantly, no penile enlargement. On a routine preemployment examination, he was advised to seek an endocrine consultation. Pertinent features were eunuchoid body proportions, a high-pitched voice, and absence of facial hair. The patient also had bilateral gynecomastia. Pubic hair was graded at Tanner stage 1. His testes, which were 2.5 cm long and 1.5 cm wide, were bilaterally descended. His penis was 4 cm long and 2 cm wide, with no urethral abnormalities. There were no midline abnormalities. Findings on neurologic examination were normal, and he had an intact sense of smell. Levels of testosterone, follicle-stimulating hormone (FSH), and luteinizing hormone (LH) were all low. The serum prolactin value was normal. Gonadotropin-releasing hormone (GnRH) testing was done, and LH and FSH responses were normal. Normal findings on cranial magnetic resonance imaging ruled out an organic pathologic disorder. These findings suggest a central cause of hypogonadism, more likely at the hypothalamic level.

**Discussion:** Idiopathic hypogonadotropic hypogonadism is a rare but treatable disease, with an incidence of 1 in 10,000 to 1 in 86,000. Only 2 cases of Kallmann’s syndrome (hypogonadotropic hypogonadism with anosmia) have been reported at the Philippine General Hospital. Patients with this disorder may have low morale and self-esteem because of lack of sexual development. Other medical conditions, such as decreased bone density and lipid abnormalities, may occur if the disorder is left untreated. Options for treatment include pulse GnRH therapy to precipitate the onset of puberty, maintain virilization and sexual function, and initiate spermatogenesis. (GnRH therapy is not available in the Philippines.) If fertility is not of utmost importance, treatment with testosterone preparations may be given for development of secondary sexual characteristics. Treatment should also include psychologic counseling as the patient adjusts to physical and emotional changes during treatment. Unfortunately, our patient has not been able to secure sufficient funds to begin treatment.

**Conclusion:** Sexual dysfunction is a quality-of-life issue for both men and women. It may have both physiologic and psychologic causes and consequences. The detailed work-up necessary to localize the source of the problem is crucial to institute the proper treatment. Patients with idiopathic hypogonadotropic hypogonadism should be aware of the full potential for fertility if appropriate treatment is received. We recommend further research into the link between neuronal migration and hypogonadotropic hypogonadism. We also recommend further case finding to establish prevalence and linkage data in the Philippines.

Abstract #728

**Androgen Insufficiency and Oral Contraceptives: A Pathophysiologic Mechanism**

Claudia Panzer, MD, Sarah Wise, MS, Ricardo Munarriz, MD, and Irwin Goldstein, MD

**Background:** Oral contraceptive agents (OCs) have been the preferred method of birth control because of their high rate of effectiveness and personal control over fertility. Despite their benefits, OC use has been associated with sexual dysfunction and androgen insufficiency. OCs are known to decrease serum testosterone levels by decreasing ovarian production of testosterone and by increasing production of sex hormone-binding globulin (SHBG) from the liver. It has been assumed that these changes are reversible after discontinuation of OC use. We have anecdotally observed, however, that SHBG levels can remain elevated for prolonged periods. Therefore, we investigated the natural history of SHBG levels after discontinuation of OC use.

**Methods:** This was a retrospective, institutional review board-approved study of 102 premenopausal women with female sexual dysfunction who either were taking OCs (“users”; N = 62; mean age, 37 years) or had discontinued the use of OCs at some point during their treatment of female sexual dysfunction (N = 40; mean age, 33 years). Serving as a control group were 23 women who had never taken OCs (“never-users”; mean age, 36 years). We measured and compared SHBG values in all three groups at baseline and at certain time intervals after discontinuing the use of OCs (<90 days, 90 to 180 days, and >180 days). All SHBG values were expressed as a percentage of the laboratory range. P values <0.05 were considered significant.
Results: SHBG values in the OC user group were 7 times higher than those in the never-user group (mean 135 ± 57% versus 19 ± 16%; P<0.01). Despite a decrease in SHBG values after discontinuation of OC use, SHBG levels remained elevated in comparison with those in the control group (P<0.01 for <90 days, P<0.05 for 90 to 180 days, and P<0.01 for >180 days).

Discussion: OCs lower the free androgen index, in part, by substantially increasing SHBG levels. Despite discontinuation of OC use, SHBG levels remained continuously elevated for up to 1 year.

Conclusion: These results suggest that the hormonal changes induced by OCs are not immediately reversible after discontinuation of OC use. The free androgen index may remain low for a prolonged period.

Abstract #746

Hirsutism in a Postmenopausal Woman With Ovarian Teratoma and Hyperthecosis

Maria Fleseriu, MD, and Elias S. Siraj, MD, FACE

Objective: To report a case of rapidly progressing hirsutism in a postmenopausal woman who was ultimately found to have ovarian teratoma and hyperthecosis and to review similar cases in the literature.

Case Presentation: A 72-year-old African American woman of Jamaican extraction presented with severe hirsutism on her face, neck, breasts, and abdomen associated with intermittent vaginal bleeding, which had developed during the preceding 2 years. She had no other symptoms of androgen excess, such as change in voice, acne, or male pattern baldness. Her medical history was significant for multinodular goiter, for which she had undergone a left hemithyroidectomy 15 years previously. Her remaining thyroid tissue had grown, leading to a recurrence of the multinodular goiter. She also had recently been diagnosed as having diabetes mellitus, which was controlled with diet.

Hormonal evaluation showed a substantially increased serum testosterone level of 138 ng/dL (normal, 20 to 70), an elevated free testosterone value of 22.6 pg/mL (normal, 1 to 9), and a slightly suppressed thyrotropin level of 0.393 µIU/mL (normal, 0.4 to 5.5). Androstenedione, dehydroepiandrosterone sulfate, free triiodothyronine, and free thyroxine values were all within normal limits.

Because of the very high serum testosterone level as well as the rapidly progressive hirsutism, further investigations were undertaken in an attempt to identify the cause. Computed tomographic scanning and magnetic resonance imaging evaluation showed a 6- to 7-cm mixed cystic and solid mass on the right ovary, with multiple small fluid loculations and solid components. The patient underwent surgical resection of this mass. The pathology report showed mature teratoma with extensive struma ovarii and prominent peripheral multifocal stromal luteinization, consistent with hyperthecosis. Two months postoperatively, the patient had complete normalization of her testosterone level but only minimal improvement of her hirsutism.

Discussion: This case is interesting for the unusual manifestation of a mature teratoma combined with peripheral multifocal stromal luteinization (hyperthecosis) that accounted for the hyperandrogenism. The presence of extensive struma ovarii may have contributed to the subclinical hyperthyroidism noted in the patient, even though it may as well have been attributable to the multinodular goiter. On review of previously reported cases of mature cystic teratoma showing hyperthecosis and associated with androgen excess in the English-language literature, almost all cases occurred in postmenopausal women with obesity, insulin resistance, type 2 diabetes, or some combination of these findings. Elevated postmenopausal gonadotropin levels and insulin resistance may act synergistically at insulin-like growth factor-I receptor sites to increase androgen secretion.

Conclusion: Hyperthecosis can coexist with ovarian tumors and is a major cause of postmenopausal hyperandrogenism. Patients benefit from early identification and treatment of this disorder.

Abstract #751

Effects of Quinine on Testicular Testosterone and Malondialdehyde and Sperm Quality in the Rat

Abraham Adewale Osinubi, MBBS, MSc, Cressie C. Noronha, MD, and Abayomi O. Okanlawon, MD

Objective: To determine changes in the testicular levels of testosterone (TT) and malondialdehyde (MDA) attributable to administration of quinine and ascorbic acid (AA) in rats.

Methods: In this study, 30 adult male Sprague-Dawley rats weighing 180 to 200 g were divided into 3 groups of 10 rats each. Group 1 rats received quinine (10 mg/kg intramuscularly), group 2 rats received both quinine (10 mg/kg intramuscularly) and AA (0.1 mg/kg intramuscularly), and group 3 animals constituted the control group and received an equal volume of distilled water (intramuscularly). Each treatment was for 8 weeks, and all the animals were sacrificed at the end of 8 weeks. Seminal analysis was done on tubular fluid from caudal epididymides. The testes were excised, and both TT and MDA levels were determined in the supernatants of the testicular homogenates. The TT levels were determined by enzyme immunoassay, and MDA was determined by the modified method of Buege and Aust. Testicular specimens were processed for histologic and morphometric analyses.

Results: Our results showed a significant (P<0.05 to 0.001) reduction of TT and elevation of MDA levels in the
testicular homogenates of rats treated with quinine only in comparison with those of the control group and those treated with a combination of quinine and AA. The semen of rats treated only with quinine demonstrated a significantly \( P<0.001 \) lower sperm concentration and motility in comparison with the control animals and those treated with quinine plus AA. Morphometry also showed that AA partly protects against quinine-induced testicular toxicity.

**Discussion:** Elevation of MDA levels is a reflection of increased oxidative stress and provides evidence of lipid peroxidation. Free radicals react with cellular macromolecules. The initiated chain reaction caused by free radicals leads to the formation of a variety of degradation products that induce changes in membrane structure and function. These degradation products increase the rigidity of membranes. Furthermore, after they migrate out of the membranes, they react with proteins and nucleic acids and thereby contribute to DNA damage. The reduction in TT level and reduction of the absolute volume of the interstitium suggest a disruption in the function of the Leydig cell as well.

**Conclusion:** We conclude that quinine-induced testicular toxicity occurs at least partly through a disturbance or depression in the testicular oxidant status and partly through a disruption of Leydig cell function.

Abstract #753

**Klinefelter’s Syndrome Manifesting in Conjunction With Hypogonadotropic Hypogonadism**

*Dima AbdelMannan, MD, and Elias S. Siraj, MD, FACE*

**Background:** Patients with Klinefelter’s syndrome typically have primary testicular failure, with the chromosomal defect expressing itself primarily in the gonads and resulting in raised circulating levels of both follicle-stimulating hormone (FSH) and luteinizing hormone (LH). In a few published reports, however, patients with Klinefelter’s syndrome have shown paradoxically decreased gonadotropin secretion associated with abnormalities of hypothalamopituitary regulation. We describe a patient with Klinefelter’s syndrome who had hypogonadotropic hypogonadism in the absence of other identifiable pituitary disease and who was later diagnosed as having hereditary hemochromatosis.

**Case Presentation:** A 23-year-old man presented initially for evaluation of syncope associated with generalized weakness. Cardiac evaluation included an echocardiogram that showed only mild ventricular dysfunction, which could not entirely explain the patient’s symptoms. The patient stated that he had always been slim and tall, with an absence of body hair. Apparently, his sense of smell had been normal (but had never been formally evaluated). He had experienced some learning and behavioral problems beginning in puberty. Evaluation by his local physician revealed a low serum testosterone level, and a trial of testosterone injections ameliorated his symptoms.

Physical examination revealed a tall, thin man who weighed 61.2 kg and was 193 cm tall. His genital examination revealed a normal-sized adult penis, very limited pubic hair, and small testicles that were 10 cc bilaterally and soft in consistency. Laboratory tests showed undetectable FSH and LH; results of other pituitary function tests were within normal limits. Magnetic resonance imaging of the pituitary showed normal findings. Genetic studies confirmed the diagnosis of Klinefelter’s syndrome. Results of liver function tests were abnormal, and a transthoracic liver biopsy showed findings consistent with the diagnosis of hemochromatosis. In addition, a DNA sample was interpreted as positive for the H63D mutation of hereditary hemochromatosis.

**Discussion:** The chromosomal defect of Klinefelter’s syndrome expresses itself primarily in the gonads and leads to hypogonadism, typically characterized by high levels of FSH and LH. Hypogonadism occurs in 19 to 75% of men with hereditary hemochromatosis. The hypogonadism in hemochromatosis most commonly results from central damage (pituitary or hypothalamic) and therefore is characterized by low FSH and LH levels, but gonadal failure with preserved pituitary function has also been described.

**Conclusion:** This case depicts a rare manifestation of Klinefelter’s syndrome together with hemochromatosis, leading to hypogonadotropic hypogonadism.

Abstract #777

**Situs Inversus Totalis Associated With SRY Gene Translocation to an X Chromosome in a 46XX Male Patient**

*Maria Paliou, MD, Jonathan Schlosser, DO, and Leonid Poretsky, MD*

**Objective:** To report a case of a 43-year-old 46XX male patient with SRY gene translocation and situs inversus totalis.

**Case Presentation:** A 43-year-old man was referred to the endocrine clinic for treatment of hyperthyroidism. His medical history included testicular trauma at a young age, gynecomastia since age 18 years, and dextrocardia. He related a 6-year history of decreased libido and erectile dysfunction.

**Discussion:** Physical examination revealed a diffusely enlarged thyroid and bilateral symmetric gynecomastia. Genital examination showed an underdeveloped penis and small atrophic testicles. A summary of the laboratory data is presented: 123I 24-hour uptake and scan of the thyroid revealed a 60% diffuse uptake. A diagnosis of Graves’ disease was made, and 10 mCi of 131I was administered. Because of hypogonadism and gynecomastia, chromosomal analysis
was performed. It revealed a 46XX karyotype. A fluorescent in situ hybridization study with an SRY probe detected SRY gene translocation to the short arm of one X chromosome. Scrotal ultrasonography showed no signs of a malignant lesion and bilateral small atrophic testicles. Computed tomography of the abdomen and pelvis disclosed situs inversus totalis and was negative for gonadal remnants. Mammography revealed predominantly fatty breasts with a small amount of asymmetric glandular tissue in the bilateral retroareolar regions, without evidence of a mass. The patient underwent genetic counseling and is being treated with testosterone supplementation.

### Abstract #781

**Association Between the Polycystic Ovary Syndrome and the Metabolic Syndrome in Women in Puerto Rico**

Marielsa Rabelo, MD, and Margarita Ramírez, MD

**Objective:** To determine the prevalence of obesity and features of the metabolic syndrome (hypertension, hypertriglyceridemia, abnormal glucose metabolism, and low levels of high-density lipoprotein [HDL] cholesterol) in Puerto Rican women with the polycystic ovary syndrome (PCOS).

**Methods:** This study was conducted through review of medical records of the Endocrinology Section at the University of Puerto Rico. From the records of patients with polycystic ovary syndrome (PCOS), the following data were gathered: age, weight, height, blood pressure, triglyceride levels, HDL cholesterol levels, fasting blood glucose levels, and levels of blood glucose after a 2-hour 75-g glucose tolerance test. Metabolic syndrome was defined as the presence of two or more of the following findings: (1) abnormal level of plasma glucose—fasting value >100 mg/dL or 120-minute post 75-g glucose challenge value >140 mg/dL; (2) triglyceride level >150 mg/dL; (3) HDL cholesterol level <50 mg/dL; and (4) blood pressure >130/85 mm Hg.

**Results:** The medical records of 39 women with PCOS were identified. Their mean age was 29.4 years and mean body mass index was 36 kg/m². Of these 39 women, 89.5% were obese, 43% had triglyceride levels >150 mg/dL, 71% had HDL cholesterol levels <50 mg/dL, and 36% had blood pressure measurements >130/85 mm Hg. Impaired fasting plasma glucose levels or impaired glucose tolerance was identified in 10%, and type 2 diabetes mellitus was present in 37%. Abnormal glucose metabolism was present in 47% of women with PCOS. The metabolic syndrome was identified in 44% of sampled women with PCOS.

**Discussion:** In this sample of Puerto Rican women with PCOS, obesity was almost universally present. Almost half of sampled patients with PCOS had abnormal glucose metabolism. Because PCOS has a high prevalence in the United States, especially among the Latino population, many women are at high risk of type 2 diabetes mellitus at a young age. More than two thirds of patients with PCOS had low levels of HDL cholesterol, more than a third had hypertriglyceridemia, and more than a third had hypertension, all of which increase the risk of cardiovascular disease in this group of young women. The metabolic syndrome was identified in 44% of sampled women with PCOS. This is a considerably higher prevalence than that found in the general population (30% in Americans and 36% in the Latino population).

**Conclusion:** Patients with PCOS from Puerto Rico have a higher prevalence of obesity, impaired glucose metabolism, and the metabolic syndrome than the rest of the population. Patients with PCOS are at high risk of cardiovascular disease at a young age.

### Abstract #787

**Effect of Antihypertensive Therapy on Pituitary-Testicular Axis in Men With Arterial Hypertension**

Richard Allen Dickey, MD, FACP, FACE, Nikita V. Ivanov, MD, Natalia V. Vorokhobina, MD, PhD, and Elena A. Volkova, MD, PhD

**Objective:** To determine the level of insulin, main steroids, and pituitary hormones in men with arterial hypertension (AH) given antihypertensive therapy and to discuss the role of hyperinsulinemia in the pathogenesis of
the low androgen level in partial androgen deficiency in the aging male (PADAM) syndrome, which is a contributing factor in the diseases associated with insulin resistance (AH, diabetes mellitus).

**Methods:** The study included 91 previously untreated male patients with hypertension. Serum free testosterone (FT), dehydroepiandrosterone sulfate (DHEAS), estradiol, cortisol, luteinizing hormone, follicle-stimulating hormone, and prolactin were measured both before and after 30 days of therapy with calcium channel blockers (CCB), angiotensin-converting enzyme (ACE) inhibitors, or β-adrenergic blocking agents (BB).

**Results:** After 30 days of treatment, men who received CCB or ACE inhibitors demonstrated a reduced insulin level and increased concentrations of serum FT and DHEAS. The BB treatment was associated with an increase in fasting serum insulin and decreased levels of main androgens. The levels of gonadotropin hormones, estradiol, and cortisol were unaffected after the treatment, and their concentrations were the same in all groups of patients. Hormonal changes in treated male patients correlated with the presence of a family history of AH.

**Conclusion:** These findings provide evidence that insulin acts as a physiologic regulator of androgen metabolism and lowers circulating FT and DHEAS concentrations in men with AH. Therapy with CCB and ACE inhibitors induced a reduction in circulating insulin, accompanied by an increase in androgen level. The BB treatment resulted in the opposite changes.

**Abstract #790**

**Association of Testosterone Deficiency and Symptoms With Diabetes, Hypertension, and Hyperlipidemia: Data From the Hypogonadism in Males (HIM) Study**

*Sherwyn Leon Schwartz, MD*

**Objective:** Hypogonadism—defined biochemically as total testosterone (TT) level <300 ng/dL—is a complex syndrome of signs and symptoms, usually accompanied by decreased quality of life. The goal of this study was to estimate the prevalence of hypogonadism in men presenting to primary care practices, particularly in relationship to the presence of recognized components of the metabolic syndrome.

**Methods:** Men 45 years of age or older and providing written informed consent were recruited from 95 primary care centers. Blood samples obtained between 8 AM and 12 PM were assayed for TT, free testosterone, and bioavailable testosterone. Patient characteristics (comorbid conditions, demographics, and reason for presenting to a physician) were recorded. Patients were queried about the presence of common symptoms associated with hypogonadism, including sexual dysfunction, fatigue or weakness, and mood changes. Prevalence rates were estimated for the total sample and for specific subsets.

**Results:** The crude prevalence rate of hypogonadism based on the aforementioned definition of TT was 38.7%. Similar trends were observed for free testosterone and bioavailable testosterone. Of 2,162 patients enrolled in the study with evaluable TT, 836 had hypogonadism, with 80 receiving testosterone treatment. Among men not receiving testosterone, 756 (36.3%) had TT ≤300 ng/dL. The prevalence rate of hypogonadism was 50% (237 of 474) in patients with a history of diabetes, 42% (499 of 1,177) in patients with a history of hypertension, and 40% (455 of 1,125) in patients with a history of hyperlipidemia. For all patients, a decrease in ability or frequency of sexual performance was reported by 65.5%, 55.8%, and 52.0% of hypogonadal men with diabetes, hypertension, and hyperlipidemia, respectively. These rates were statistically significantly different for hypogonadal versus eugonadal men in all 3 groups (P≤0.014). Differences in sexual desire or libido (P≤0.014) and physical exhaustion or lacking vitality (P≤0.023) were statistically significant for hypogonadal versus eugonadal men who were also diagnosed with diabetes or hyperlipidemia. A decline in general feeling of well-being was significantly different in hypogonadal men with hyperlipidemia versus eugonadal men (P = 0.011).

**Discussion:** Among men presenting to a primary care office, those with a history of diabetes, hypertension, or hyperlipidemia have a higher crude prevalence of hypogonadism than the general population of patients seen in this setting.

**Conclusion:** Hypogonadism is significantly associated with sexual dysfunction and physical fatigue in patients with certain metabolic syndrome risk factors. On the basis of these data, it may be prudent to evaluate testosterone in these patients.

**Abstract #838**

**Female Sex Hormones Cause Beneficial Effect on Reactivity of Intramural Coronary Arteries**

*Attila Nemeth, MD, PhD, MBA, and Béla Székács, PhD*

**Background:** In age-matched groups, cardiovascular morbidity and mortality are higher in men than in women. This finding could be explained partially by gender-specific differences in the reactivity of small branches of coronary arteries. Thus far, several studies have been conducted on the more accessible epicardial vessels, whereas the intramural small arteries—which necessitate more delicate preparations—have proved difficult to investigate in vitro. In the current experimental study, we focused on notable sex-related differences in the vasoconstriction or endothelium-dependent vasodilatation potentially attributable to the role of estrogen.

**Methods:** We tested 4 different groups of Sprague-Dawley rats (weighing 250 to 270 g): intact males, intact females, females subjected to bilateral ovariectomy
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The inner radius of the coronary artery segments branching from the left anterior descending coronary artery were isolated, cannulated, and studied by microarteriography. The intraluminal pressure was increased stepwise (2 to 90 mm Hg), and the steady-state, passive diameter was measured at each point in Ca²⁺-free Krebs solution. The evaluation was repeated in the presence of U46619 (a thromboxane A₂ [TXA₂] receptor agonist, at a concentration of 10⁻⁶ M) and bradykinin (at a concentration of 10⁻⁶ M) in normal Krebs-Ringer solution. A continuous superfusion was applied at a rate of 2.4 mL/min. Pressure and diameter signals were digitalized by an analog/digital converter and transmitted into an IBM Pentium PC for data storage and processing.

Results: The inner radius of the coronary artery segments was similar between normal male and female rats in both solutions; however, the wall thickness was greater in the male rats. The elastic modulus in segments from male animals was lower, especially in higher pressure ranges. The vasoconstrictive response at 50 mm Hg induced by U46619 was significantly stronger in male versus female rats (30.9 ± 6.6% versus 14.5 ± 3.3%; P<0.001, analysis of variance). Nevertheless, no gender-dependent difference was observed in the bradykinin-induced relaxation. The ratio of wall thickness/vessel radius (WT/VR), a determinant of vascular resistance, was highest in BLO females. The TXA₂-induced vasoconstriction was 1.7 to 2.2 times stronger at each pressure gradient in male animals than in the females. The bradykinin-induced relaxation was substantially smaller. These effects were eliminated by HRT, and the spontaneous myogenic tone of the coronary arteries was normalized.

Discussion: Some recent randomized controlled trials of HRT were disappointing in terms of vascular (especially coronary) protective effects of combined HRT. Despite the lack of protective effect in these trials, evidence is available for beneficial effects of estrogen on the biomechanical properties of the vascular system in both animal and human studies. Both estrogen and combined HRT showed favorable effects on the biomechanical characteristics of small peripheral arteries. Most of the studies of HRT were performed on aorta and carotid artery segments, although some involved extramural coronary segments. Intramural coronary arteries have never been studied before in this respect because of the difficulties in preparation of these arteries. The importance of studying the intramural coronary arteries lies in the fact that pharmacologic reactivity and flow conditions are considerably different in various serially connected segments of their network. Mechanical properties of intramural segments are of special importance; as a consequence of the cardiac pumping function, these vessels are subjected to long-term cyclic mechanical compression.

Conclusion: At the intramural small coronary vessel level, we found that the pharmacologic and biomechanical properties of these small branches are influenced by sex hormones. In male and BLO female rats, the TXA₂ analogue-induced WT/VR ratio was higher than in control female rats. The intracoronary-activated platelet-released TXA₂ reveals the clinical relevance of these findings, inasmuch as no difference was noted in bradykinin-induced vasodilatation whereas the increased contractility seen in the BLO group in response to TXA₂ agonist was depressed back to the control level in the HRT group. The key role of estrogen in these experiments was strongly substantiated: the lack of estrogen increased the TXA₂-induced vasoconstriction, which could be attributed to direct myogenic TXA₂ sensitivity versus simply WT/VR geometric changes. Accordingly, the HRT reversed the TXA₂-induced deleterious responses. It could be inferred that, in both sexes, the endothelium-derived vasodilatation is a result of more intricate interactions (that is, different effects of bradykinin and TXA₂ analogue) because estrogen itself significantly increased the relaxation of the intramural small coronary arteries.

Abstract #897

Turner’s Syndrome: Report of 2 Cases

Anthonia Okeoghene Ogbera, MBBS, FMCP

Background: Turner’s syndrome (or Bonnevie-Ullrich syndrome) is a disorder of gonadal dysgenesis characterized by sexual infantilism, short stature, and somatic anomalies. The classic features of Turner’s syndrome may not be evident in early childhood; thus, the diagnosis may be missed at that time. As a result, some potentially remediable somatic complications of this syndrome may be detected too late for correction. Turner’s syndrome is infrequently reported in Nigerians. Accordingly, this report serves to describe the pattern of presentation, somatic abnormalities, and other complications as seen in our locality.

Case Presentation: Two female patients, 17 and 21 years old, respectively, presented with sexual infantilism and short stature. The 21-year-old patient had a history of a “pathologic” fracture of the left lower limb and clinical and biochemical features suggestive of Hashimoto’s disease. The 17-year-old girl had bifid collecting ducts detected on routine radiologic examination. Both patients had poorer academic performance than did their siblings. In the 21-year-old patient, a buccal smear result was compatible with the mosaic form of Turner’s syndrome, whereas the other patient had a 45XO karyotype pattern on chromosomal analysis. They both attained some sexual development, including menarche, after female hormonal replacement.

Discussion: In some areas in Africa, medical help is often not sought for female children when they have ail-
ments that appear non-life-threatening. The parents of both of the current patients were not disturbed about the short stature of their children, but they became concerned when they thought that the reproductive ability of their daughters was threatened. This attitude contributed to the delay in seeking medical assistance. At the time of the initial assessment, the bone epiphyses were already fused. Therefore, attainment of further height even by administration of growth hormone was not possible.

**Conclusion:** Awareness of the somatic complications of Turner’s syndrome should prompt physicians or caregivers to screen for manifestations of this disorder early enough so that treatment can be offered for abnormalities that are potentially treatable. Education and counseling of the patients and family members are helpful factors in making informed decisions about available treatment options.
THYROID DISEASE

Abstract #709

Absence of Congenital Defects After Maternal Exposure to Methimazole Early in Twin Gestation

John Charles Parker, MD

Objective: To describe a patient with thyrotoxicosis who had been treated with methimazole during the first trimester of pregnancy and the absence of congenital defects in the products of a monochorionic twin gestation.

Case Presentation: A 33-year-old woman presented with suppression of thyroid-stimulating hormone and clinical thyrotoxicosis from Graves’ disease. At the time of consultation, she was taking methimazole. Subsequently, she was found to have an intrauterine twin pregnancy. In retrospect, she had been treated with methimazole from gestational weeks 5 to 13. She had previously undergone bilateral tubal ligation. Propylthiouracil was substituted for methimazole at week 13 and continued through week 27, when administration was discontinued because of the presence of euthyroidism. Healthy twins were delivered at term. Since delivery, euthyroidism has been maintained in the mother.

Discussion: Although methimazole-related embryopathy is of concern to clinicians caring for patients with thyrotoxicosis during pregnancy, early gestational exposure to methimazole, putatively when the risk of teratogenicity is greatest, was not associated with any deleterious effects on the neonates in this case.

Conclusion: Even though propylthiouracil holds rank as the “standard of care” thyrostatic drug therapy for thyrotoxicosis during pregnancy, the absence of congenital defects in the twin offspring of a mother treated with methimazole during the first trimester of pregnancy provides evidence of the safe use of methimazole during pregnancy.

Abstract #711

Torsades de Pointes as a Manifestation of Severe Primary Hypothyroidism

Ali Abbas Rizvi, MD, FACE, John B. Schenck, MD, and Tu Lin, MD

Objective: To describe a case of severe, untreated hypothyroidism in a patient presenting with myxedema psychosis, bradycardia, syncope, and polymorphic ventricular tachycardia (torsades).

Case Presentation: A 55-year-old woman was brought to the emergency department after a single-vehicle accident resulting from a syncopal episode. She was confused, disoriented, and unable to provide any history. Her family stated that, during the prior 6 months, the patient had experienced progressive confusion, behavioral and memory changes, constipation, weight gain, dizziness, chest pain, and episodes of near-syncope. The patient had been diagnosed with primary hypothyroidism 10 years previously and was prescribed levothyroxine therapy; however, she had been noncompliant with the medication. Instead, she was taking laxatives, sucralfate, and vitamins C and E. A 99mTc sestamibi stress test 1 year previously had revealed no evidence of cardiac ischemia.

Examination showed a puffy face and sallow appearance, a husky voice, blood pressure of 87/55 mm Hg, pulse rate of 48 beats/min, dry skin, slow deep-tendon reflexes, absence of thyromegaly, and disorientation. Pertinent laboratory studies revealed the following (normal ranges shown parenthetically): thyroid-stimulating hormone, 249 µIU/mL (0.35 to 5.50) and a repeated test showing 224 µIU/mL; free thyroxine, 0.12 ng/dL (0.89 to 1.76); free triiodothyronine, 1.0 pg/mL (2.3 to 4.2); cortisol, 34.2 µg/dL; and creatine kinase, 6,559 U/L with a predominant MM fraction. Serum electrolytes were normal, except for a slightly decreased potassium of 3.4 mEq/L. A computed tomographic scan of the brain showed no acute damage or chronic changes. Electrocardiography disclosed a low-voltage baseline bradycardia of 48 beats/min, first-degree atrioventricular block, a prolonged QT interval of 560 ms, and episodes of polymorphic ventricular tachycardia (torsades de pointes) occurring every 5 to 10 minutes. An echocardiogram revealed normal left ventricular function with an ejection fraction of 60% and a small pericardial effusion.

The patient was admitted to the intensive care unit and placed under cardiac monitoring. She was treated with intravenously administered magnesium, amiodarone, and lidocaine drip. Therapy with hydrocortisone (100 mg every 8 hours) and levothyroxine (100 µg intravenously daily) was initiated. With hormone therapy, the patient’s general, neurologic, and cardiac conditions improved dramatically. The corticosteroids were tapered, and the administration of levothyroxine was switched to the oral route. The patient showed no evidence of cardiac arrhythmia after 48 hours of therapy, and she was transferred out of the cardiac care unit in stable condition.

Discussion: The cardiac effects of hypothyroidism include bradycardia, delayed conduction, heart block, pericardial effusion, decreased ejection fraction, and impaired mechanical efficiency. The resulting prolonged QT interval uniquely predisposes the patient to the polymorphic form of ventricular tachycardia, also known as torsades de pointes. An extensive review of the English-language literature revealed only 10 reported cases. The current patient had no other cause usually associated with this tachycardia (such as electrolyte abnormalities, coronary ischemia, or infarction). Intravenous administration of levothyroxine promptly eliminated the arrhythmia. Delayed ventricular repolarization by electrophysiologic methods has been shown previously in patients with hypothyroidism presenting with torsades. Some investiga-
tors have suggested a compounding of risk attributable to subtle metabolic and ischemic changes. Therefore, it is probable that numerous factors in advanced hypothyroid states, predominantly the occurrence of QT prolongation, increase the propensity for occurrence of a malignant ventricular arrhythmia. This potentially fatal condition is probably underdiagnosed and underreported; indeed, it may be a more significant cause of morbidity and mortality in patients with hypothyroidism than is currently recognized.

**Conclusion:** Pathophysiologic, metabolic, and conduction system abnormalities in thyroid hormone deficiency can predispose to ventricular arrhythmias. Clinicians should keep in mind that torsades de pointes is a relatively rare but potentially lethal cardiac manifestation of undiagnosed or untreated severe hypothyroidism.

**Abstract #716**

**Hürthle Cell Carcinoma of the Thyroid: A Rare Familial Occurrence**

*Abid Yaqub, MBBS, and Bruce S. Chertow, MD, FACE, FACP*

**Objective:** To describe a rare familial occurrence of Hürthle cell carcinoma (HCC) of the thyroid in a brother and sister pair and discuss recent advances in understanding of the genetic basis of sporadic and familial forms of the disease.

**Case Presentation:** A brother and sister with HCC had striking similarities in their initial manifestations and the progression of disease. Both patients had the disease diagnosed during later years of life (beyond 50 years of age), both had cold thyroid nodules for 4 to 5 years before histologic diagnosis, and both had local recurrence after thyroidectomy and postoperative radiiodine ablation. The local occurrence was treated with external irradiation in each patient, and both of them had persistent elevation of serum thyroglobulin levels in the setting of negative diagnostic whole-body $^{131}$I and bone scans. Subsequently, pulmonary metastatic disease was documented in each patient. The family history was pertinent for a deceased sister with “goiter” and a living sister with multinodular goiter and oxyphil tumors (one member had HCC), and a gene was mapped to chromosome 19p13.2. Beckner et al (2) mentioned two mother and daughter pairs with HCC in their series of cases.

HCC is characterized by distinctive eosinophilic cytoplasm owing to an abundance of abnormal mitochondria. Maximo and Sobrino-Simoes (3) reported the deletion of mitochondrial DNA associated with development of sporadic HCC. Farrand et al (4) described a potential tumor suppressor gene mapped to chromosome 17p13 in sporadic HCC. Recently, gains on certain chromosomes have been observed to be associated with disease recurrence in HCC. Originally thought to be a variant of follicular carcinoma, recent identification of RET/PTC rearrangements in a subset of HCC suggests its subclassification into HCC and HCPTC (with RET/PTC).

**Conclusion:** HCC is a rare type of thyroid cancer. Several recent observations have provided new insight into the pathogenesis of sporadic HCC; however, the search for a gene that predisposes to familial HCC continues. Our report describes a rare familial occurrence of this malignant disease and suggests the role of an unidentified specific germline mutation.

**References**


**Abstract #738**

**Outcomes of Calculated-Dose Radioiodine for the Treatment of Hyperthyroidism: Preliminary Results**

*Maria Patricia Deanna Delfin Maningat, MD, Cecile A. Jimeno, MD, and Gabriel V. Jasul, MD*

**Objective:** To determine the 6-month outcome of treatment of hyperthyroidism with use of calculated-dose radiiodine (RAI) and, more specifically, to determine the thyroid status of patients within 6 months after RAI therapy, the characteristics of patients associated with persistent hyperthyroidism, and the approximate time to occurrence of hypothyroidism.
Methods: We conducted a prospective cohort study. The study group had a calculated sample size of 96 participants, based on a failure rate of 10% and a level of error of 6%. Considered for inclusion in the study were patients who met the following criteria: adult patients (>18 years old), with a diagnosis of diffuse toxic goiter based on an elevated free thyroxine level, a suppressed thyrotropin level, and a diffuse goiter on physical examination and imaging, undergoing RAI treatment for the first time based on a thyroid scan and a 24-hour RAI uptake study, and given a dose within 1 mCi of the calculated dose. The exclusion criteria were as follows: no thyroid scan or RAI uptake study, the presence of a nodular toxic goiter, a previous thyroid surgical procedure, previous RAI treatment, or concomitant thyroid carcinoma.

The RAI dose used was calculated on the basis of the thyroid scan and a 24-hour RAI uptake study. $^{131}$I was administered in capsule form. Patients were advised to have repeated free thyroxine and thyrotropin determinations every 2 months for the subsequent 6 months. Follow-up was left to the discretion of the fellow-in-charge.

Results: Of the 113 patients included in the study, 25 were still under observation, 18 had been lost to follow-up, and 70 had analyzable data at the time this report was written. At 6 months, 60% of the patients were hypothyroid and 24% were euthyroid; 16% still had hyperthyroidism. No baseline characteristic was significantly associated with persistent hyperthyroidism. By 4 months after RAI therapy, 54% of patients were hypothyroid.

Discussion: Currently, no consensus exists about the optimal dose calculation to ensure success of treatment with RAI. Although a wide range of doses have been advocated, no dose achieves 100% cure. Most studies have been performed in countries with iodine sufficiency; thus, their results may not be applicable in our setting in the Philippines. At our institution, we aim to deliver a dose of 160 µCi/g of thyroid tissue based on a 24-hour RAI uptake to approximate iodine accumulation and on a thyroid scan to approximate thyroid volume. We found that 60% of our patients were hypothyroid and 24% were euthyroid by 6 months after RAI treatment, comparable to the 40 to 90% success rate reported in most published works. Possibly because of the limited sample size, we found no significant patient-related characteristic predictive of persistent hyperthyroidism. A trend toward persistent hyperthyroidism was noted in the younger patients, those with longer duration of goiter and longer antithyroid drug treatment, those receiving propylthiouracil before RAI, those with larger goiters, and those with a higher RAI uptake. Also similar to other studies, 54% of our study cohort were hypothyroid by 4 months after RAI therapy.

Conclusion: On the basis of our preliminary data, calculated-dose RAI therapy is effective in controlling hyperthyroidism, with 60% of our patients hypothyroid and 24% euthyroid by 6 months after such treatment. No baseline characteristics were significantly associated with persistent hyperthyroidism. By 4 months after RAI therapy, 54% of patients were hypothyroid.

Abstract #765

Oscillating Thyroid Function in Graves’ Disease: From Hyperthyroidism to Hypothyroidism and Back to Hyperthyroidism

Dina AbdelMannan, MD, and Harris C. Taylor, MD, FACE

Objective: To describe the fourth reported example of spontaneous alteration of hyperthyroidism to hypothyroidism and back to hyperthyroidism and to postulate the mechanism responsible as spontaneous change in the ratio of thyrotropin receptor stimulating antibodies (TSAb) to blocking antibodies.

Case Presentation: A previously healthy 53-year-old man was seen in consultation in August 1995 because of complaints of weight loss (13.6 kg) despite increased appetite, diarrhea, and itchiness. Physical examination revealed a pulse of 70 beats/min, a palpable but not enlarged thyroid gland, and shoulder girdle atrophy but no ophthalmopathy. Serum thyrotropin was <0.01 µIU/mL (normal range, 0.4 to 5.5), and the free thyroxine index was 8.2 (normal range, 1.7 to 3.9). The 24-hour radiiodine uptake was 19%. He refused treatment and was lost to follow-up. In April 1997, the patient was referred again with complaints of weight gain, fatigue, and dry hands. The thyrotropin level was 43 µIU/mL, and the free thyroxine index was 0.9. Treatment with levothyroxine was initiated at a dosage of 25 µg/day and gradually increased to 175 µg/day. The serum thyrotropin normalized to 0.9 µIU/mL, and he remained euthyroid for 2 years. In December 2001, however, the thyrotropin level was 0.004 µIU/mL, free triiodothyronine (FT$_3$) was 5.6 pg/mL (normal range, 1.5 to 3.5), and free thyroxine (FT$_4$) was 2.2 ng/dL (normal range, 0.7 to 1.8). Thyrotropin-binding inhibitory immunoglobulin (TBII) and TSAb were both elevated at 9.9 U/L and 364%, respectively (normal <5 U/L and 30 to 150%, respectively). Levothyroxine therapy was discontinued, and 5 months later, 24-hour radioiodine uptake was 14.5%. Serum thyrotropin was 0.005 µIU/mL, FT$_3$ was 11.1 pg/mL, and FT$_4$ was 2.2 ng/dL. 1 year after discontinuation of levothyroxine therapy. TBII and TSAb were still high at 21.7 U/L and 329%, respectively (normal <5 U/L and 30 to 150%, respectively). Treatment with methimazole (10 mg twice daily) was begun, and 2 months later, FT$_3$ was 1.1 pg/mL and FT$_4$ was 0.4 ng/dL, resulting in reduction of the methimazole dosage to 2.5 mg/day.

Discussion: Spontaneously resolving Graves’ disease with subsequent hypothyroidism reverting again to hyperthyroidism has been recognized since 1988 (1). To our knowledge, however, there have been only three such documented examples (1-4). We describe the fourth such case, characterized by hyperthyroidism spontaneously
evolving to hypothyroidism, in turn reverting to hyperthyroidism again. Studies in humans suggest that the mechanism may be a fluctuation in the thyrotropin receptor antibody from a stimulating (TSAb) to a blocking antibody and back again to TSAb (1-4). A similar oscillation has recently been described in a mouse model of Graves’ disease, wherein immunization with human thyrotropin receptor and subsequent sequential blood sampling demonstrated that 13% of the animals displayed a fluctuation between TSAb and blocking antibodies (5).

**Conclusion:** Spontaneously alternating hyperthyroidism, hypothyroidism, and hyperthyroidism in autoimmune thyroid disease, albeit rare, does occur and may depend on the balance between TSAb and blocking antibody activities.

**References**


**Abstract #766**

**Clinical Interpretation of Thyroid-Stimulating Hormone (Thyrotropin) Results**

Richard Allen Dickey, MD, FACP, FACE, Leonard Wartofsky, MD, and Stanley Feld, MD, MACE

**Objective:** To clarify the expression and interpretation of thyrotropin (thyroid-stimulating hormone or TSH) results.

**Methods:** We undertook a literature review of published TSH results, assessed the findings, and propose an adjustment in the normal range for TSH.

**Results:** The terminology for TSH results has been misunderstood, has promoted miscommunication between physicians and patients, and needs to be revised to facilitate more appropriate clinical decision making for patients with thyroid dysfunction. We propose to clarify and simplify the way TSH test results are presented in orders to improve physicians’ interpretation, response to, and explanation of TSH test results. On the basis of review and interpretation of key literature about clinical results and recent information on the relatively stable and narrow range of TSH values in patients without thyroid disease, an argument is marshaled in support of a narrower, optimal or true “normal range” for TSH of 0.4 to 2.5 µIU/mL (or mIU/L).

**Discussion:** The authors have clarified and proposed a simpler, clinically more appropriate way to interpret and express TSH results. This adjusted approach should facilitate clinical decision making for patients with thyroid dysfunction.

**Conclusion:** A new way of addressing TSH results is presented, and a new normal range for TSH is recommended. This approach to TSH results is also intended to stimulate thoughtful reconsideration of how TSH results have been seen in the past. The same issues that we have proposed to resolve the interpretation of the terminology for TSH results should apply to most other laboratory test results as well.

**Abstract #772**

**Prevalence of Thyroid Incidentalomas on Computed Tomographic Scanning and Magnetic Resonance Imaging**

Aleksandra Kraeher, MD, Mohsen Eleedrisi, MD, FACE, Rakesh Patel, DO, Eric Walser, MD, and Alfred Madamba, MD

**Objective:** To assess the frequency and clinical significance of thyroid nodules incidentally identified during the course of computed tomographic (CT) scanning and magnetic resonance imaging (MRI).

**Case Presentation:** We reviewed all the CT scans and MRI reports performed at our facility for reasons unrelated to thyroid pathologic conditions from 1992 to 2000. We examined the prevalence of incidentally discovered thyroid nodules as well as the fine-needle aspiration biopsy reports on the lesions that were chosen to be investigated further.

**Discussion:** On review of 33,289 CT scans and 10,630 MRI reports, we encountered 151 incidental thyroid nodules (0.45%) on CT and 50 (0.47%) on MRI (total of 201 [0.46%]). In these cases, solitary nodules were identified on CT scans in 132 patients (87.4%) and on MRI in 45 patients (90%). The diameter of these nodules varied from 2 mm to 4 cm. Of the lesions measured, 16% were <1 cm, 50% were 1 to 1.9 cm, 25% were 2 to 2.9 cm, and 9% were ≥3 cm. The prevalence of nodules was greater in women (71.5% on CT scans and 86% on MRI) than in men. Cytologic evaluation was performed in 18 subjects (10 lesions on CT and 8 on MRI) and revealed benign tumors, except in 4 patients who had equivocal results. Two of these patients underwent hemithyroidectomy.
my and one underwent total thyroidectomy; the final diagnoses were benign lesions, except for one case of follicular carcinoma.

**Conclusion:** These data indicate that the prevalence of incidental thyroid nodules on CT scans and MRI is low. The data also suggest a low risk of malignant involvement, a fact that supports a conservative approach when such lesions are found.

**Abstract #776**

**First Trimester Positive Thyroid Peroxidase Antibodies and Postpartum Thyroiditis Among Pregnant Filipino Women**

*Carolyn R. Narvacan-Montano, MD, and Augusto D. Litonjua, MD, FACE*

**Objective:** To determine the association between first trimester positive thyroid peroxidase antibodies (TPOAb) and postpartum thyroiditis (PPTD).

**Methods:** We performed a prospective cohort study in the outpatient department of the Makati Medical Center in Manila. Blood samples for TPOAb were obtained from 340 pregnant patients during their first trimester. Thyroid dysfunction was determined 1 month after delivery.

**Results:** The prevalence of PPTD in this study was 7.4%. The odds of developing PPTD, controlling for parity, history of miscarriage or abortion, presence of goiter, family history of thyroid disease, and smoking, were 23.84 times as much among those with positive TPOAb as among those with negative TPOAb (odds ratio, 23.84; 95% confidence interval, 5.87 to 96.88; *P* = 0.000).

**Discussion:** Postpartum thyroiditis is defined as a syndrome of transient or permanent thyroid dysfunction occurring during the first year after delivery and based on an autoimmune inflammation of the thyroid. Classically, a thyrotoxic phase is followed by a hypothyroid phase. The reported prevalence of this syndrome varies widely, from 1.1 to 21.1%. The discrepancies in prevalence may reflect differences in diagnostic criteria as well as variable predisposing genetic factors and iodine intake among screened populations. The prevalence of PPTD in this study, defined as thyroid dysfunction 1 month after delivery, was 7.4%

Postpartum thyroiditis is closely associated with the presence of TPOAb. Indeed, if a pregnant woman is positive for TPOAb early during pregnancy, her chances of developing postpartum thyroiditis are 30 to 52%. In this study, 88% of the pregnant women were positive for TPOAb and 12% were negative for TPOAb at the time of screening.

The clinical importance of postpartum thyroiditis was highlighted by Amino et al (1) in the 1980s. Stagnaro et al (2) found that existing thyroid autoimmunity increases the probability of spontaneous fetal loss. Moreover, some evidence indicates that thyroid failure due to autoimmune thyroiditis, often mild and clinical, leads to permanent substantial impairment in the neuropsychologic performance of the offspring.

**Conclusion:** The presence of TPOAb clearly confers a significant risk (odds ratio of 23.84) for the development of thyroid dysfunction. Furthermore, this study was able to elucidate the combination of genetic susceptibility and environmental factors that led to thyroid autoimmunity. Thus, in our view, determinations of thyroid-stimulating hormone (thyrotropin) should be done in young women with goiter, a family history of thyroid disease, or a personal history of goiter and among multiparous patients with a history of miscarriage or abortions. We likewise recommend that if the thyrotropin value is abnormal, free thyroxine and TPOAb should additionally be determined.

**References**

1. Amino N et al.
2. Stagnaro et al.

**Abstract #780**

**Disproportionately Chilly Hypothyroidism**

*Richard W. Pinsker, MD, FACE, Alkesh Patel, MD, Kartik Desai, MD, and Dhimant Dani, MD*

**Objective:** To discuss cases of hypothermia associated with less than severe hypothyroidism based on two almost concurrently encountered patients.

**Case Presentation:** In September 2004, a 93-year-old man with Alzheimer’s dementia was transferred from a nursing home with cough, altered mental status, and a body temperature of 33.9°C orally (34.6°C rectally). He was confused and not responding to verbal commands. The blood pressure was 140/74 mm Hg, and the pulse was 74 beats/min. An electrocardiogram showed normal findings. A work-up for sepsis was negative. No hypoglycemia was noted. The thyroid-stimulating hormone (thyrotropin) level was reported as 13.1 μIU/mL in conjunction with a normal free thyroxine value of 1.0 ng/dL. The endocrine consultant thought that an intravenous trial of levothyroxine was warranted; thus, intravenous administration of 50 µg/day was started, along with corticosteroids given intravenously. In 36 hours, his temperature normalized. The altered mental status improved and rapidly returned to baseline condition. The corticosteroid therapy was tapered and then discontinued.

A 59-year-old woman with Down syndrome was admitted to a local hospital in September 2004 because of presumed sepsis and hypothermia. Cultures were negative, and the patient was sent home. One week later, she was admitted to our hospital with chills and unrecordable
temperature. A work-up for sepsis was negative. Laboratory studies showed the following: thyrotropin 6.11 µIU/mL, free thyroxine 1.1 ng/dL, prolactin 59.3 ng/mL, and glucose 67 mg/dL. The patient was fully alert and responded well to verbal commands. Computed tomography of the head and pituitary region revealed no abnormalities. Before a cosyntropin stimulation test, the baseline plasma cortisol was 10.3 µg/dL, and the value increased to 17.9 µg/dL after the test. The patient was given hydrocortisone and levothyroxine (100 µg/day) intravenously. In 48 hours, her temperature was 37°C. Within a few days, she was discharged from the hospital with an oral regimen of levothyroxine (50 µg/day) and corticosteroids. A luteinizing hormone (LH) level of 0.0 mIU/mL and follicle-stimulating hormone (FSH) level of 0.7 mIU/mL were later reported.

**Discussion:** Severe hypothyroidism is often listed as a cause of hypothermia. In our two cases, however, the hypothyroidism appeared to be mild. In our first patient, a thyrotropin level of 13.1 µIU/mL was the only laboratory abnormality detected. He responded well to an intravenous thyroid regimen. Our second patient had an even more modest thyrotropin concentration of 6.11 µIU/mL and a normal free thyroxine value. Nearly deficient FSH and LH were troubling. No mass lesion was noted. Indeed, thyrotropin-releasing factor could have stimulated prolactin, which in turn could have inhibited gonadotropins. Biologically inactive thyrotropin in hypothalamic hypopituitarism was another possibility.

**Conclusion:** Even mild hypothyroidism can sometimes be seen in patients with hypothermia. Of course, other causes of hypothermia—especially sepsis—must always be considered. In our patients, the hypothermia responded well to levothyroxine therapy, even though their thyroid disease was “modest.”

**Abstract #784**

**Natural History of Graves’ Ophthalmopathy After Radioiodine Therapy**

Julie Hallanger Johnson, MD, Ross E. Bryan, Gregory D. Jenkins, Roanna L. Vine, RN, and Vahab Fatourechi, MD, FACE

**Background:** Graves’ ophthalmopathy affects the quality of life of many patients with Graves’ disease. Some investigators have suggested that radioiodine (RAI) therapy may adversely affect Graves’ ophthalmopathy.

**Objective:** To study the frequency of development of new ophthalmopathy after RAI therapy for Graves’ disease during a 10-year period and to determine the predictive factors for development of new ophthalmopathy after RAI therapy.

**Methods:** At our institution, Graves’ hyperthyroidism is treated predominantly with RAI ablation, with the goal of achieving hypothyroidism within 6 months. A calculated dose of 200 µCi per gram of estimated thyroid weight per 24-hour uptake is usually given. We analyzed the medical records of patients who received RAI therapy for Graves’ disease between January 1990 and December 1993 (N = 592; 77% female; mean age, 49 years).

**Results:** Graves’ ophthalmopathy was present before RAI therapy in 105 of the 592 patients (17.7%). In our sample, 21% of smokers had eye disease at the time of RAI therapy, in comparison with 14% of nonsmokers (P = 0.03). Of patients without ophthalmopathy at RAI therapy for Graves’ disease, 19.6% had ophthalmopathy by 10 years after such therapy, with only 5.1% developing new ophthalmopathy during the first year. The survival free of Graves’ ophthalmopathy was 94.9%, 86.3%, 85.8%, and 80.4% at 1, 3, 5, and 10 years, respectively. The development of new ophthalmopathy was not related to sex, smoking status, serum thyroxine value, thyroid weight, or age of the patient. Thyroid-stimulating immunoglobulin levels (N = 294) were marginally related to development of ophthalmopathy (P = 0.05). Requiring a second dose of RAI did not appear to be a risk factor for the development of new ophthalmopathy (P = 0.91).

**Discussion:** Only a small percentage of patients with Graves’ disease (5.1%) developed new ophthalmopathy during the first year after ablative RAI therapy for hyperthyroidism.

**Conclusion:** The data suggest that RAI therapy for Graves’ disease does not have a significant adverse effect on the eyes of patients without ophthalmopathy at the time of such therapy.

**Abstract #788**

A Case of Metastatic Calcitonin-Secreting Nonthyroidal Neuroendocrine Carcinoma

Shirin Haddady, MD, Alan Perry Farwell, MD, and Ashraf Khan, MD

**Objective:** To describe a case of an extrathyroidal calcitonin-producing neuroendocrine carcinoma manifesting with mediastinal and cervical lymphadenopathy.

**Case Presentation:** A 45-year-old African American woman, who had tested positive for the human immunodeficiency virus (HIV) in 1997 and had a history of substance abuse, was evaluated for cough, chest pain, shortness of breath, and a 9.1-kg weight loss during a period of 2 to 3 months. Chest radiography, which had shown normal findings 2 years previously, revealed a widened mediastinum, and chest computed tomographic (CT) scanning showed hilar adenopathy, a 4-cm subcarinal lymph node, and 2 nodules in the right middle lobe of the lung. A biopsy of the subcarinal node was consistent with medullary carcinoma of thyroid origin. The serum calcitonin level was elevated at 74.6 pg/mL (normal range, 0 to 4.6). An evaluation for pheochromocytoma was negative, as were liver function tests and an abdominal CT scan.
Neck CT revealed multiple enlarged jugular and submandibular lymph nodes as well as a 1.2-cm nodule in the thyroid.

The patient underwent a total thyroidectomy and a median sternotomy in conjunction with cervical and mediastinal lymph node dissection. Pathologic examination of the thyroid tissue revealed multiple colloid nodules and an incidental 0.2-cm papillary microcarcinoma, but no evidence of medullary carcinoma. Nonetheless, 6 of 12 perithyroidal lymph nodes and 2 mediastinal lymph nodes were positive for metastatic neuroendocrine carcinoma with morphologic features similar to those of the original biopsy specimen. The tumor showed positive staining for calcitonin, chromogranin, thyroid transcription factor, synaptophysin, S-100 protein, and cytokeratin. Immunostaining for thyroglobulin and Congo red was negative.

Postoperatively, the serum calcitonin level increased to 141.2 pg/mL. 111In-octreotide scanning demonstrated uptake in the 2 nodules in the postero medial right lung. Follow-up chest CT showed an increase in the right-sided hilar and subcarinal adenopathy and several new 1-cm lymph nodes. The patient is awaiting surgical exploration of the demonstrable disease.

Discussion: Calcitonin-secreting neuroendocrine tumors with a primary site outside the thyroid are very rare. Successful treatment of the disseminated disease is difficult, with a poor response to chemotherapeutic agents. Radical tumor resection is the only potentially curative approach. In this patient, somatostatin agonist therapy is also being considered because of reports of symptomatic improvement and tumor stabilization in some patients with high-dose continuous treatment.

Conclusion: Metastatic calcitonin-producing neuroendocrine tumors may not necessarily originate within the thyroid but may also arise from other sites, such as the lung.

Abstract #794

Thyrotoxic Hypokalemic Periodic Paralysis in a White Man: Case Report and Review of the Literature

Oluymesi Modinat Durodoye, MD, and Alan Perry Farwell, MD

Objective: To report a case of thyrotoxic hypokalemic periodic paralysis (THPP) in a white male patient with previously undiagnosed hyperthyroidism.

Case Presentation: A 40-year-old white man was seen in an outlying emergency department (ED) with a history of episodic muscle weakness, tingling, and numbness, occurring mostly in both lower extremities and progressing to daily episodes. On presentation to the ED, the patient had a serum potassium level that was mildly low; after potassium replacement, he was transferred to our ED for a neurologic evaluation, which was unremarkable. Despite a suppressed level of thyroid-stimulating hormone (thyrotropin), the association between the neurologic symptoms and thyrotoxicosis was missed. The patient returned to the outlying ED 10 days later with recurrent symptoms and was found to have severe hypokalemia (serum potassium 1.8 mEq/L). In addition, thyroid function tests revealed an elevated free thyroxine level (3.8 ng/dL) and free thyroxine index (9.44), and thyroid peroxidase antibodies were found to be present. The patient was admitted, the potassium was replaced, and propranolol and propylthiouracil therapy was begun.

Discussion: Hypokalemic periodic paralysis is a condition characterized by potentially fatal episodes of muscle weakness or paralysis. Attacks are sudden in onset, intermittent, and usually associated with transient hypokalemia. The condition can be familial, sporadic, or associated with thyrotoxicosis (THPP), predominantly due to Graves’ disease. Weakness usually begins in the proximal muscles of the legs and can become generalized, as in the case presented. Review of the literature revealed that THPP is a condition most commonly seen in Asian male populations, but it does occur in other races and can be easily misdiagnosed.

Conclusion: THPP should be among the entities in the differential diagnosis in the evaluation of young men who present with symptoms of acute paresthesia and weakness of no other apparent cause.

Abstract #806

Hyperthyroidism and Hypokalemic Periodic Paralysis in a Middle Eastern Man

Cynthia C. Abacan, MD, and Charles Faiman, MD, MACE

Objective: To present a case of a young man in whom acute, severe, and generalized muscle weakness developed in association with hypokalemia in the setting of Graves’ disease.

Case Presentation: A 25-year-old healthy man of Middle Eastern extraction presented with the sudden onset of inability to move his extremities after awakening. He denied having shortness of breath, numbness, or pain. Physical examination revealed diminished strength and reflexes in all extremities. The findings on the rest of the examination were normal. Laboratory tests showed a serum potassium concentration of 1.5 mEq/L (reference range, 3.5 to 5.0) and a serum magnesium level of 1.6 mg/dL (1.7 to 2.4). Other serum chemistry determinations were normal. The results of the complete blood cell count, urinalysis, and urine toxicology screen were all unremarkable. Intravenous administration of potassium and magnesium normalized the serum levels of these analytes. He was able to regain motor strength after 2 to 3 hours without further therapy. Two days later, he was seen in the emergency department because of shortness of breath,
pallpitations, and diaphoresis. His blood pressure was 148/64 mm Hg and heart rate was 122 beats/min. The thyroid gland was diffusely enlarged (estimated weight, 35 g), nontender, and with a noted bruit. The rest of the examination was unremarkable. Results of laboratory tests (reference ranges shown parenthetically) confirmed the hyperthyroid state: serum thyrotropin 0.011 µIU/mL (0.4 to 5.0), free thyroxine >7.8 ng/dL (0.7 to 1.8), and free triiodothyronine 30 pg/mL (0.8 to 4.6). Thyroid-stimulating immunoglobulin was elevated at 960% (70 to 150%). Treatment was initiated with propylthiouracil (150 mg every 6 hours) and propranolol (40 mg every 8 hours), with a plan to perform radioiodine ablation once the patient was biochemically euthyroid.

Discussion: This patient has Graves’ disease associated with hypokalemic paralysis. Although thyrotoxic hypokalemic periodic paralysis (THPP) is most commonly seen in Asian persons, it can involve all racial groups. It is often sporadic. There is a male preponderance. The paralysis often occurs at rest after consumption of a high-carbohydrate meal. Mental function and sensation are intact. Frequently, the typical features of thyrotoxicosis are subtle. Associated metabolic abnormalities such as hypophosphatemia and hypomagnesemia have been described. Administration of potassium is the standard therapy; however, after potassium replacement, rebound hyperkalemia may occur. Propranolol has been reported to normalize plasma potassium levels within 2 to 3 hours. Treatment of the thyrotoxicosis leads to the resolution of THPP.

Conclusion: THPP is seen in persons of all races. To the best of our knowledge, this is the second case of THPP reported in a patient of Middle Eastern extraction. THPP needs to be sought as a possible cause for hypokalemic paralysis. The episodes of paralysis cease to occur once the euthyroid state is achieved.

Abstract #821

Painful Thyroiditis in a Patient With Graves’ Disease

Sujata M. Wagh, MD

Objective: To report the rare occurrence of painful thyroiditis and subsequent hypothyroidism in a patient with a history of Graves’ disease.

Case Presentation: A 33-year-old woman with an unremarkable medical history was referred to the Endocrine Clinic for evaluation of a low serum level of thyrotropin (thyroid-stimulating hormone or TSH) of 0.05 µIU/mL (normal range, 0.28 to 3.89), agitation, mood swings, heat intolerance, and palpitations. Physical examination revealed mild left conjunctival erythema, a 30-g diffusely enlarged goiter, and brisk reflexes. Laboratory studies (normal ranges indicated parenthetically) showed the free thyroxine (T4) index was 10.4 (3.6 to 14), and the total serum triiodothyronine (T3) level was high at 198 ng/dL (90 to 182). The T3 resin uptake was 30% (24 to 35%). Tests for serum anti-thyroid peroxidase and antithyroglobulin antibodies were strongly positive at >1,000 IU/mL (<35) and >3,000 IU/mL (<40), respectively. A thyroid scan showed a diffuse pattern of uptake, with a mildly increased 6-hour 123I uptake of 26.4% (8 to 20%). Treatment was initiated with methimazole (10 mg/day).

Eleven months later, while still taking methimazole, the patient experienced abrupt painful enlargement of the thyroid, which was tender to palpation. At this time, the serum TSH level was 3.95 µIU/mL, the free T4 was 0.59 ng/dL (0.58 to 1.64), and total serum T3 was 108 ng/dL.

The erythrocyte sedimentation rate was elevated to 76 mm in 1 hour (0 to 15). The patient could not be contacted after the results of these thyroid tests were available. She returned 2 months later with an enlarging goiter, fatigue, weight gain, hoarseness, and a depressed mood. Her thyroid was now diffusely enlarged to about twice the normal size, her pulse was 58 beats/min, and the relaxation phase of the deep tendon reflexes was delayed. The serum TSH was substantially increased to 94 µIU/mL, and the serum T4 level was undetectable at <1 µg/dL. Methimazole therapy was discontinued, and patient was given levothyroxine, 100 µg/day and with the dosage gradually increased to 137 µg/day. Eight months after levothyroxine therapy had been instituted, the serum TSH level was still mildly elevated at 4.94 µIU/mL.

Discussion: A patient with apparent Graves’ disease, as judged on the basis of the presence of thyrotoxicosis, positive antibodies, and elevated 123I uptake, subsequently exhibited features of subacute thyroiditis and had sustained hypothyroidism. Several cases of painful goiter followed by rapidly progressive thyroid failure in patients with hyperthyroid Graves’ disease have been reported in the literature. Most of these patients were treated with glucocorticoids or anti-inflammatory drugs and experienced relief of pain. In a few cases, these painful episodes have reportedly been recurrent, even during the hypothyroid phase, and have necessitated subtotal thyroidectomy for prevention of further episodes. In contrast to most cases of subacute thyroiditis, patients with Graves’ disease in whom subacute thyroiditis develops usually have sustained thyroid failure.

Conclusion: The combination of Graves’ disease and subacute thyroiditis in the same patient is a rare clinical entity. Nevertheless, this scenario does occur and probably confers an increased risk of permanent hypothyroidism.
Abstract #828

Thrombocytopenia in Autoimmune Thyroid Disease: Case Presentations and Review of the Literature

Adriana Gabriela Ioachimescu, MD, Antoine Makkissi, MD, and Robert S. Zimmerman, MD

Background and Objective: Idiopathic thrombocytopenic purpura (ITP) in patients with thyroid disease is a rare condition with an unclear pathogenesis. We report 3 cases of autoimmune thyroid disease (ATD) and thrombocytopenia and review the literature on this topic.

Case Presentation: The following 3 patients underwent follow-up for 2 years, 4 years, and 1 year, respectively. In all cases, hematologic evaluation including peripheral blood smear and bone marrow biopsy supported the diagnosis of ITP.

Case 1: A 49-year-old woman with cold intolerance, dry skin, easy bruising, and menorrhagia was diagnosed with hypothyroidism and ITP. Results of laboratory studies were as follows (normal ranges shown in parentheses): platelet count 36 × 10^3/µL (150 to 400), microsomal antibody titer 1,934 IU/mL (<5), thyrotropin (thyroid-stimulating hormone or TSH) 6 µIU/mL (0.4 to 5.5), and free thyroxine index (FTI) 5.1 (6 to 11). Despite restoration of a euthyroid state and treatment with prednisone, the platelet count remained within 15 and 56 × 10^3/µL.

Case 2: A 40-year-old man with ITP and a stable platelet count from 119 to 146 × 10^3/µL was diagnosed as having hypothyroidism. His microsomal antibody titer was 445 IU/mL, TSH level was 12.3 µIU/mL, and FTI was 7.3. After initiation of thyroid hormone replacement therapy, the platelet count increased to 180 × 10^3/µL, with a concomitant TSH value of 0.004 µIU/mL. During follow-up, he became euthyroid, but the platelet count declined to 121 to 141 × 10^3/µL.

Case 3: A 47-year-old woman with weight loss, heat intolerance, goiter, epistaxis, and menorrhagia was diagnosed as having Graves’ disease and thrombocytopenia. Her platelet count was 48 × 10^3/µL. Thyroid-stimulating immunoglobulins were 1,124% (70 to 150%), the microsomal antibody titer was 7.9 IU/mL, the serum TSH level was 0.008 µIU/mL, and FTI was 22.4. Intravenous administration of immunoglobulin transiently improved the platelet count up to 100 × 10^3/µL. Subsequently, she became euthyroid with use of methimazole and radioiodine therapy, but the platelet count remained in the range of 40 to 90 × 10^3/µL.

Discussion: Two mechanisms have been proposed for ITP in patients with ATD. First, the presence of platelet antibodies in patients with ATD and thrombocytopenia suggests an autoimmune mechanism. Second, increased platelet turnover was demonstrated in hyperthyroidism, and many case reports have shown resolution of thrombocytopenia after a euthyroid state was restored.

Two of our patients had no response to normalization of thyroid function; this result suggests an autoimmune cause for the thrombocytopenia. One of our patients (case 2) had transient improvement but subsequent recurrence of thrombocytopenia; thus, two mechanisms may have been present—an immune-related one and a hormone-related one. The use of methimazole in this patient did not lower the platelet count.

Conclusion: The course of thrombocytopenia in patients with ATD is variable, as documented in our cases. Longitudinal studies of a larger number of patients are needed for further clarification of mechanisms and identification of the role of platelets, thyroid autoantibodies, and thyroid hormonal status in the differential diagnosis and prognosis of patients with thrombocytopenia.

Abstract #831

The Changing Face of Myxedema Coma

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Objective: To review the current diagnostic criteria and treatment options for myxedema coma.

Case Presentation: A 94-year-old woman experienced progressive decline at home during the course of 1 month. She was diagnosed as having hypercapnic respiratory failure (pH = 7.28; Paco_2 = 61 torr), with no history of structural or functional lung disease. The patient required intubation and ventilatory support. A diagnostic bronchoscopy was performed, after which she had severe changes in mental status (Glasgow Coma Scale 8 of 15). A respiratory microbiologic study revealed many neutrophils and 3+ Staphylococcus aureus. She remained afebrile despite the infection. Because of a history of hypothyroidism, thyroid function tests were performed, which revealed the following results (normal ranges included parenthetically): thyroid-stimulating hormone (TSH) 74 µIU/mL (0.3 to 5.0), free thyroxine (T_4) 0.5 ng/dL (0.8 to 1.8), and total triiodothyronine (T_3) 49 ng/dL (80 to 180).

Discussion: Early myxedema coma was diagnosed, and the patient was treated with levothyroxine (100 µg daily) and T_3 (10 µg twice daily) intravenously. Antibiotics and corticosteroids were administered empirically, pending the results of a cosyntropin stimulation test, which were normal. Within 48 hours after intravenous administration of levothyroxine and T_3, the patient’s condition improved (Glasgow Coma Scale 10 and less ventilator dependence). She was extubated on day 4 of treatment and was ambulatory on day 7, with full return of consciousness. By the time of dismissal, the free T_4 was 0.8 ng/dL and free T_3 was 2.8 pg/mL.
**Conclusion:** In contrast to William Ord’s original 1879 report and subsequent series throughout the next century, reports during the past 3 decades have required neither coma nor myxedema for the diagnosis of myxedema coma. Instead, altered mental status, defective thermoregulation, and a precipitating event have become the defining triad, in the setting of biochemical hypothyroidism. Early treatment with thyroid hormone can be effective, and the combination of T3 and T4, although without proven results, may bypass impaired peripheral conversion of T4 to T3. Low doses of T3 seem to be safe, and the intravenous route of administration is preferred. The diagnosis of myxedema coma should be considered in patients with hypothyroidism who experience changes in mental status and altered thermoregulation during intercurrent illness, and consideration should be given to intravenous replacement of thyroid hormone. It may also be useful to consider renaming the condition, to provide a more accurate reflection of its initial manifestations.

**Abstract #845**

**Troponin Levels in Hypothyroidism**

*James R. Mulinda, MD, FACE, and Sudeshna Kundu, MD*

**Objective:** To investigate the association among elevated serum thyrotropin, creatine kinase, and troponin I levels in patients with hypothyroidism.

**Methods:** We investigated the cardiac enzyme status in 14 consecutive patients with primary hypothyroidism and elevated serum thyrotropin levels but without cardiac symptoms. All serum samples were sent to a commercial laboratory (Quest Diagnostics, Philadelphia, PA) for analysis.

**Results:** Of the 14 patients, 2 were men and 12 were women; their ages ranged from 21 to 98 years. The serum creatine kinase level was elevated in 5 of the 14 patients (36%). Two patients (14%) had detectable serum troponin I levels in the lower reference range. No patient had elevated serum troponin I levels.

**Discussion:** Hypothyroidism is an established cause of elevated levels of serum creatine kinase, but the association with serum troponin I has not been widely reported. Nevertheless, serum troponin has become increasingly important in the diagnosis of myocardial injury. In this study, although some patients with primary hypothyroidism had elevated levels of creatine kinase, no patient had an elevated level of serum troponin and only 2 patients had low detectable levels. Because both primary hypothyroidism and cardiac disease are prevalent conditions, identifying reliable and cost-effective testing may affect patient care and the cost of health care.

**Conclusion:** This study suggests that measurement of the serum troponin level may be a reliable method for identifying patients with primary hypothyroidism but without symptoms of myocardial injury, regardless of whether the serum creatine kinase level is elevated. Because primary hypothyroidism and cardiac disease are prevalent conditions, further studies to confirm this finding are warranted.

**Abstract #847**

**Maternal and Fetal Outcomes of Pregnancies Complicated by Hyperthyroidism**

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**Objective:** To describe and classify the clinical profile of pregnant patients with hyperthyroidism, to determine the maternal and fetal outcomes, and to compare the outcomes when the mothers were classified in reference to their thyroid status.

**Methods:** The study cohort consisted of 44 pregnant patients with diffuse toxic goiter. We undertook a paired medical record review to determine outcomes of pregnancy, and we compared the specific outcomes of the neonates by performing an independent groups test.

**Results:** The ages of the pregnant patients ranged from 18 to 44 years, the number of deliveries for each patient ranged from 0 to 6, the age of gestation (AOG) ranged from 32 to 42 weeks, and the duration of thyroid disease ranged from 0.2 to 14 years. Of the 44 pregnant patients, 36% had active thyroid disease and were divided into clinically and biochemically euthyroid or hyperthyroid, 59% were in suspected remission of their thyroid disease, and 5% were newly diagnosed as having hyperthyroidism. Maternal complications were as follows: pregnancy-induced hypertension (PIH), preterm labor, thyroid storm, abruptio placentae, ectopic pregnancy, congestive heart failure (CHF), and abortion.

Seventeen percent of infants were born to mothers in a euthyroid state, 22% to mothers with hyperthyroidism, 56% to mothers in suspected remission of their thyroid disease, and 5% to mothers with newly diagnosed hyperthyroidism. Fetal complications associated with uncontrolled hyperthyroidism were preterm delivery, small for gestational age, and congenital defects. Neonates of mothers with uncontrolled hyperthyroidism had the following mean data: birth length 46.61 ± 3.97 cm, birth weight 2.49 ± 0.79 kg, AOG 37.72 ± 1.92 weeks, and Apgar score 8.43 ± 0.77. Among infants of mothers with newly diagnosed hyperthyroidism, the corresponding mean data were found: birth length 50.0 ± 1.41 cm, birth weight 2.95 ± 0.07 kg, AOG 37.25 ± 4.59 weeks, and Apgar score 6.6 ± 2.88. Among infants of euthyroid mothers, the following mean data were compiled: birth length 47.85 ± 0.69 cm, birth weight 2.76 ± 0.39 kg, AOG 37.93 ± 1.71 weeks, and Apgar score 8.56 ± 0.18. Finally, among infants of mothers in suspected remission of their thyroid disease, the
following mean data were recorded: birth length 47.23 ± 4.55 cm, birth weight 2.75 ± 0.63 kg, AOG 38.04 ± 2.93 weeks, and Apgar score 8.43 ± 0.77. The mean birth weight of infants of hyperthyroid mothers was lower than the weight for infants of euthyroid mothers, but the difference was not statistically significant. Birth length, Apgar scores, and weight for gestational age did not vary among the four thyroid groups.

Discussion: An increased incidence of maternal and fetal complications of pregnancy has been associated with uncontrolled hyperthyroidism. Occurrence of PIH is high among mothers with hyperthyroidism, as found in this study. Fetal outcomes noted among our study population were small for gestational age, congenital defects, and preterm delivery. These findings were similar to those in other studies.

Conclusion: Pregnanies of patients with hyperthyroidism are complicated by PIH, CHF, preterm labor, and thyroid storm. Small for gestational age, preterm delivery, and congenital defects are common problems among infants of mothers with uncontrolled hyperthyroidism; however, the neonatal outcomes did not vary significantly when classified on the basis of the maternal thyroid status.

Abstract #870
Persistently Increased Levels of Thyroglobulin Despite Treatment of Papillary Thyroid Carcinoma: A Manifestation of Struma Ovarii
Anne M. Rosenberg, MD, Clive S. Grant, MD, William F. Young, MD, and John C. Morris III, MD

Objective: To discuss a case of benign struma ovarii causing persistently elevated serum thyroglobulin levels in a patient with a history of papillary thyroid carcinoma (PTC) but no evidence of recurrent or metastatic disease and to compare the presentation in the current patient with initial manifestations in published cases of struma ovarii in the literature.

Case Presentation: A 70-year-old woman underwent subtotal thyroidectomy in 1992 for grade 1 PTC and received 100 mCi of 131I postoperatively. Her first lymph node recurrence in 1994 was treated with surgical excision and 300 mCi of 131I. A second recurrence of PTC in the thyroid bed and surrounding lymph nodes was treated surgically in 2001. She had persistent elevation of her thyroglobulin level postoperatively. Despite serial imaging with neck ultrasonography, total-body 131I scans, and computed tomographic (CT) scans of her neck and chest, no source for her persistently elevated thyroglobulin level was detected.

The patient presented to her local physician with nephrolithiasis in 2003. An abdominal CT scan disclosed the presence of bilateral ovarian teratomas. Surgical excision and pathologic examination revealed mature cystic teratomas containing benign thyroid tissue. Postoperatively, her serum thyroglobulin level normalized.

Discussion: Struma ovarii is a specialized ovarian teratoma consisting primarily of thyroid tissue. Whether benign or malignant, struma ovarii is a rare occurrence. Women with struma ovarii may present with a pelvic mass, hyperthyroidism, ascites, or pseudo-Meigs’ syndrome. Struma ovarii may also contain foci of PTC. The coexistence of struma ovarii and thyroid conditions such as Graves’ disease or thyroid cancer may impose diagnostic challenges.

Conclusion: In a patient who presented with persistently elevated thyroglobulin levels after complete treatment of her PTC, the cause of the abnormal thyroglobulin values presented a diagnostic challenge. Ultimately, benign struma ovarii was found to be the source of her high serum thyroglobulin level, with normalization of thyroglobulin levels after bilateral oophorectomy.

Abstract #899
Cardiac Tamponade During Treatment of Myxedema Coma, With Findings of Lymphomatous Pericardial Effusion
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Objective: To describe a patient who presented with myxedema coma and had a pericardial effusion with tamponade and lymphoma.

Case Presentation: A 74-year-old woman with a known history of untreated hypothyroidism presented with shortness of breath, decreased level of consciousness, and weight loss. She was found to have hypotension, hypoxia, and hypothermia. The thyrotropin (thyroid-stimulating hormone or TSH) level was 103 µIU/mL (normal range, 0.27 to 4.2) and total thyroxine (T₄) was 0.4 µg/dL (normal range, 5.1 to 14.1). A test for thyroid antibodies was positive. An echocardiogram showed a large pericardial effusion without evidence of right atrial or right ventricular diastolic collapse, an indication of no tamponade. The patient was treated with intravenously administered levothyroxine, which yielded clinical improvement. A repeated TSH determination on hospital day 9 was 49 µIU/mL, total T₄ was 2.7 µg/dL, and free T₄ was 0.35 ng/dL (normal range, 0.93 to 1.70). On hospital day 10, the patient was found to be hypotensive, with a decreased level of consciousness and increased jugular venous distention. She had hypercapnia and required ventilatory assistance and dopamine. Repeated echocardiography showed a large pericardial effusion with evidence of right ventricular diastolic and systolic collapse, indicative of tamponade. The patient underwent a pericardial window procedure. She was again administered an intravenous
bolus of levothyroxine, and supplemental doses were given aggressively during the next several days until the free T₄ level was maintained in the normal range. The patient’s condition improved during the next 2 weeks. Results of analysis of the pericardial and pleural fluid showed a monoclonal population of B cells, and bone marrow biopsy findings were consistent with low-grade non-Hodgkin’s lymphoma.

**Discussion:** We describe a patient with autoimmune thyroiditis who presented with myxedema coma and pericardial effusion. During treatment with levothyroxine, cardiac tamponade developed, and the pericardial fluid was found positive for lymphoma. Pericardial effusions are not uncommon, although cardiac tamponade is uncommon in patients with myxedema. Whether the lymphoma contributed to the tamponade is unknown. Autoimmune thyroiditis is associated with thyroid lymphoma, primarily of B-cell origin. Only a few cases of extrathyroidal lymphomas associated with autoimmune thyroiditis have been reported.

**Conclusion:** Despite levothyroxine treatment, cardiac tamponade may develop during clinical improvement of patients with myxedema. In addition, patients with autoimmune thyroiditis may have undiagnosed lymphoma, which may contribute to the development of pericardial effusion and tamponade.

**Abstract #900**

**Use of Multiple Imaging Modalities for Detection of Recurrent and Metastatic Thyroid Cancer**

**Puneet S. Arora, MBBS**

**Objective:** To illustrate the utility of available imaging modalities in detecting thyroid cancer recurrence and metastatic lesions in a 41-year-old woman.

**Case Presentation:** A 41-year-old woman had a thyroid mass diagnosed as papillary thyroid cancer with lymph node metastatic involvement in 1994. Total thyroidectomy followed by radioiodine (RAI) ¹³¹I treatment was done. In January 2000, she had a stimulated thyroglobulin (Tg) level of 63 ng/mL, and ¹³¹I was administered. Whole-body scanning (WBS) both before and after RAI therapy was negative. In June 2001, she had a stimulated Tg of 23.9 ng/mL, and negative WBS results. The patient was again given 142 mCi of ¹³¹I, and WBS was negative after therapy. She transferred care in September 2003, when her endocrinologist retired. Ultrasonography (US) of the neck revealed a mass in the thyroid bed, which was confirmed on magnetic resonance imaging. Intraoperative US showed 2 more masses, all of which proved to be papillary cancer on final pathologic examination. She was then lost to follow-up until November 2004. Thyrogen-stimulated Tg was then 12.1 ng/mL, and US of the neck was negative. A positron emission tomographic (PET) scan showed a hypermetabolic small anterior triangle lymph node, suggestive of metastatic cancer. Further imaging and excision are pending.

**Discussion:** Six years after initial therapy for papillary thyroid cancer with lymph node metastatic lesions, this patient had lymphadenopathy positive for recurrent metastatic papillary cancer detected by elevated Tg levels. Iodine scans never detected the masses, and ¹³¹I treatment did not help in such a situation despite 2 administrations. A neck mass was detected on US. During surgical excision, intraoperative US showed 2 more masses, emphasizing the utility of this modality for detection of neck recurrences. One year later, however, the Tg level was still elevated (albeit less than before), and a PET scan proved to be extremely sensitive under this circumstance, when WBS and US showed no abnormalities. Several investigators have recommended PET scans in all patients with normal findings on WBS and elevated Tg levels. US, however, has proved to be sensitive for neck recurrences and should be considered first. Continuing surveillance of stimulated Tg levels is critical despite normal WBS findings and US studies of the neck in patients with known lymph node involvement.

**Conclusion:** Numerous imaging modalities available for surveillance of thyroid cancer serve important roles in detection of recurrent or metastatic lesions.

1. With normal findings on WBS, ¹³¹I treatment is unlikely to be effective.
2. US of the neck should be considered before PET scans for detection of locoregional recurrences in cases with normal WBS findings.
3. PET scans are a valuable tool for finding thyroid cancer recurrences or metastatic lesions when other imaging modalities fail to detect the source of a high Tg level.
4. No single imaging modality is adequately sensitive independently. Appropriate use of multiple imaging modalities is recommended.

**Abstract #911**

**Incidence Rate and Related Risk Factors of Hypothyroidism After Thyroidectomy**

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**Background:** The issue of hypothyroidism after thyroidectomy is still under debate. Currently, all patients receive thyroid hormones postoperatively, whereas most of them may not actually need such treatment. This study examines the incidence of hypothyroidism and its possible risk factors among patients who underwent thyroidectomy at a major referral hospital.

**Methods:** The thyroid function profile of 102 patients who underwent thyroidectomy at Shariati Hospital was investigated on the following occasions: immediately...
Thirty men and 72 women were included in this study. The mean age of participants was 39 ± 13.6 years (40.5 ± 14.2 years for men and 38.4 ± 5.1 years for women). Hypothyroidism developed in 36 of the 102 patients (35.3%), occurring a mean of 5.0 ± 3.2 months after the surgical procedure. Increased age, type of operation, histopathological type (Graves’ disease and adenomatous goiter), underlying disease (Graves’ disease and toxic multinodular goiter) and its duration, lymphocytic infiltration, and use of levothyroxine preoperatively were found to have an association with the incidence of hypothyroidism. In contrast, no association was found between the occurrence of hypothyroidism and sex of the patients, grade of thyromegaly, postsurgical complications, or immediate presurgical level of thyroid-stimulating hormone (thyrotropin).

Discussion: Age, histopathologic type, type of operation, and underlying disease were important factors predicting the occurrence of hypothyroidism after thyroidectomy in this study.

Conclusion: This can serve as a pilot study for more extensive investigations of predictive factors in the future. Use of indicators such as Graves’ disease and lymphocytic infiltration in pathologic specimens may ultimately be helpful in projecting the potential occurrence of hypothyroidism in patients undergoing thyroidectomy, and the absence of such factors may obviate the administration of thyroid hormones.

Abstract #915

Positive Positron Emission Tomographic Scan in a Patient With Papillary Thyroid Cancer and Cervical Lymphadenopathy: An Unusual Diagnosis of Scrofula

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Objective: To describe a patient with a history of papillary thyroid cancer and cervical lymphadenopathy, a negative whole-body scan, and a positive positron emission tomographic (PET) scan, who was found to have an infectious cause for her PET-positive adenopathy.

Case Presentation: A 40-year-old woman originally from Vietnam underwent total thyroidectomy for papillary thyroid cancer in 1999. Pathologic examination revealed a 1-cm by 1-cm papillary cancer in the left thyroid lobe and a 0.5-cm papillary cancer in the right lobe. After total thyroidectomy, she was treated with radioiodine ablation and was prescribed levothyroxine therapy. She was noncompliant with her therapy, and in October 2004, she presented with cervical lymphadenopathy. She had no weight loss, cough, fever, neck pain, dysphagia, or dyspnea. The serum thyroglobulin level was <0.3 ng/mL in conjunction with negative antithyroid antibodies, the thyrotropin value was 8.3 µIU/mL, and free thyroxine was 2.41 ng/dL. Other laboratory tests included a normal complete blood cell count, electrolytes, blood urea nitrogen, creatinine, calcium, and liver enzymes. Pertinent history included a positive tuberculin skin test (purified protein derivative) attributed to a bacille Calmette-Guérin vaccination during childhood. Chest radiography showed normal findings. Magnetic resonance imaging revealed extensive left cervical adenopathy along the jugular vein, posterior triangle, and left supraclavicular lymph nodes. The size of the lymph nodes ranged from 2.2 to 2.5 cm by 1.3 to 1.5 cm. A radioiodine scan after levothyroxine withdrawal was negative. Fine-needle aspiration of a lymph node revealed polymorphic neutrophils and lymphocytes. With this history, a PET scan was performed, which showed positive uptake involving both sides of the neck and the mediastinal area. Lymph node biopsy disclosed caseating granulomatous inflammation. No organisms were identified on acid-fast bacilli (AFB) stain. While awaiting the results of AFB culture, the patient was treated with pyrazinamide, ethambutol, rifampin, and isoniazid.

Discussion: Papillary carcinoma of the thyroid constitutes approximately 60 to 80% of thyroid cancers. It most often recurs in the thyroid bed or in regional cervical and mediastinal lymph nodes as metastatic lesions. Recurrences are generally detected through monitoring of serum thyroglobulin levels and periodic radioiodine scanning under thyrotropin stimulation. As thyroid cancer dedifferentiates, it metabolizes iodine less efficiently, and a radioiodine scan may be negative in the presence of recurrent disease. A fluorodeoxyglucose-PET scan has been helpful in the diagnosis of non-iodine-avid metastatic thyroid cancer. A positive PET scan in a patient with a history of papillary thyroid cancer is highly suggestive of the presence of metastatic lesions. In the current patient, although the PET scan was positive, the cervical adenopathy was related to a separate granulomatous inflammatory process.

Conclusion: A positive PET scan may occur in patients with cervical lymphadenopathy due to granulomatous lesions. It is important to be aware of this fact, especially in patients from countries with a very high incidence of tuberculosis.
Abstract #920

Reversible Hyperthyroxinemia in a Patient With Secondary Adrenal Insufficiency

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Objective: To describe an unusual presentation of hyperthyroxinemia in a patient who had secondary adrenal failure that resolved after treatment of adrenal insufficiency.

Methods: We present clinical findings and laboratory data in a 42-year-old African American man and review the literature on the association of secondary adrenal insufficiency and hyperthyroxinemia.

Case Presentation: A 42-year-old African American man presented with an episode of syncope. In the hospital, the patient was noted to have episodes of hypotension and hypoglycemia, with blood glucose concentrations in the range of 23 to 57 mg/dL. Physical examination revealed temporal wasting, a normal male hair pattern, no tremors, no proptosis, and absence of a goiter. Secondary adrenal insufficiency was diagnosed with a morning plasma cortisol value of 0.09 µg/dL and adrenocorticotropic hormone (corticotropin) level of 12 pg/mL. Laboratory studies showed the following: serum creatinine 3.3 mg/dL, blood urea nitrogen 20 mg/dL, creatine kinase 707 U/L, total calcium 8.9 mg/dL (normal, 8.5 to 10.6), albumin 3.2 g/dL, and normal results of liver function tests. The results of kidney function tests normalized with hydration. His thyroid function tests revealed the following (normal ranges shown parenthetically): thyrotropin (thyroid-stimulating hormone or TSH) 9.65 µIU/mL (0.4 to 4.0), thyroxine (T4) 11.37 µg/dL (4.5 to 12.5), triiodothyronine (T3) 194 ng/dL (82 to 179), and T3 resin uptake 40.5% (24 to 35%). Other pertinent laboratory data (and normal ranges) included prolactin 16.7 ng/mL (2.5 to 17), alpha-subunit 0.7 ng/mL (<1.0), insulin-like growth factor-I 19 ng/mL (90 to 360), follicle-stimulating hormone 6.3 mIU/mL (1.5 to 14), luteinizing hormone 4.9 mIU/mL (0.4 to 5.7), total testosterone 416 ng/dL (286 to 1,511), thyroid-stimulating immunoglobulin <75 µIU (<130), thyroid peroxidase antibody 25.1 IU/mL (0 to 2.0), sex hormone-binding globulin 28 nmol/L (8 to 49), and negative adrenal antibodies. Treatment was begun with prednisone, 5 mg daily. Magnetic resonance imaging of the sella showed no tumor. Thyroid uptake with 123I revealed an uptake of 31.5% (10 to 30%) when the TSH level was 3.3 µIU/mL. After 2 months of corticosteroid replacement, his serum TSH level decreased from 9.65 µIU/mL to 1.72 µIU/mL, T4 decreased from 11.37 µg/dL to 8.45 µg/dL, and T3 declined from 194 ng/dL to 125 ng/dL.

Discussion: This is a case of an unusual presentation of secondary adrenal failure and hyperthyroxinemia that was reversed with corticosteroid replacement. Samuels (1) demonstrated the elevation of TSH levels after hydrocortisone withdrawal in patients with adrenal insufficiency; the exact mechanism for this response is unknown. We postulate that, because of long-standing adrenal insufficiency and a temporary defect in the feedback regulation, our patient had elevated levels of T3 and T4 in association with a high TSH concentration. A similar case report (2) described a patient with primary adrenal insufficiency and elevated levels of TSH, T4, T3, and prolactin. Our case is unique inasmuch as we describe a patient with secondary adrenal failure, a normal level of serum prolactin, and elevated levels of TSH, T4, and T3.

Conclusion: This is an unusual presentation of hyperthyroxinemia in a patient who had secondary adrenal failure that resolved after treatment of adrenal insufficiency.

References


OTHER

Abstract #830

Thyroiditis, Hypophysitis, and Diabetes Insipidus in a Patient Presenting With Hypercalcemia

Khalidoun Mohammad Al-Rayess, MD, and Alan L. Burshell, MD

Objective: To describe a patient presenting with hypercalcemia and thyroiditis, who also had development of diabetes insipidus and panhypopituitarism, presumed to be due to lymphocytic hypophysitis.

Case Presentation: A 59-year-old white man presented to the hospital with a 3-month history of nausea, vomiting, weight loss, decreased oral intake, and confusion. Laboratory studies showed hypercalcemia, low levels of parathyroid hormone and vitamin D metabolites, and an undetectable level of parathyroid hormone-related protein. The patient was found to have hyperthyroidism with 0% iodine uptake at 24 hours, consistent with thyroiditis. Further testing showed panhypopituitarism in association with adrenal insufficiency, diabetes insipidus, and hypogonadism. Subsequently, central hypothyroidism developed, after the thyroiditis resolved. The insulin-like growth factor-I level was in the low-normal range. Magnetic resonance imaging of the pituitary showed normal findings except for a slightly prominent gland.

Discussion: In this patient, panhypopituitarism was likely due to lymphocytic hypophysitis, which has been reported previously in conjunction with autoimmune thyroiditis. This is the first case, however, in which a patient with thyroiditis and lymphocytic hypophysitis has presented with hypercalcemia and also has had development of central diabetes insipidus and central hypothyroidism.

Conclusion: To the best of our knowledge, this is the first case description of a patient having hypercalcemia, autoimmune thyroiditis, panhypopituitarism including central hypothyroidism, and diabetes insipidus.

Abstract #901

The “Well-Connected” Endocrinologist: A Case Study of the Implementation and Integration of Multiple Software Technologies

Timothy Silleck Bailey, MD, FACE, and Chandrasekhar P. Varma, MD, FACE

Objective: To review the benefits and pitfalls of implementation and integration of key technologies essential to today’s practicing endocrinologist.

Case Presentation: In March 2003, our 2-physician endocrinology practice with 2 offices purchased an electronic medical record (EMR) system integrated with an office management system (Alteer Office). Over a period of 6 months, paper medical records were eliminated. This step allowed us to add a nurse-practitioner without hiring additional staff or leasing more space. Both photocopy and standard fax machines have been replaced by scanners and electronic fax, which route all documents to patients’ records. Consultation notes are always sent to referring physicians the same day the patient is seen.

A Telehealth device (which transmits blood glucose data from patients’ homes to our office) coupled with a diabetes registry (iMetrikus MediCompass) was implemented to enable us to reduce both the office time needed for uploading of blood glucose data and the resources required to manage patient telephone calls between visits. A side benefit is that the registry helps us to recruit for clinical trials and will help us to document our quality of care to qualify for economic incentives for the upcoming “Pay for Performance” initiatives.

Information for patient care is obtained from MEDLINE (PubMed). Drug information is available on a handheld device (Epocrates on Palm). Patient information is printed from the American Association of Clinical Endocrinologists, the Endocrine Society, and other sources and is indexed by links on our website (both staff personnel and patients have the same view). Document imaging software (ScanSoft PaperPort) allows us to eliminate paper for diverse nonclinical functions, such as study protocols, insurance explanation of benefits, contracts, and vendor bills. We have even replaced our answering service with an on-line alternative (PerfectServe).

Instant messaging (Yahoo) for nonconfidential logistical queries (for example, “Could you have the hospital send the new patient’s laboratory results?”) has dramatically accelerated work flow (confidential messaging is part of the EMR). Patients can send us secure messages via our website (Medem). These different technologies are all used in concert with standard e-mail.

Discussion: The introduction of new technology imposes an initial stress on an organization. No one vendor provides everything necessary for the practice of endocrinology. Therefore, careful thought about how different software can be used together is critical.

A careful, deliberate, and scheduled installation is essential. Implementation of too few or too many features at one time can create unnecessary stress. In our setting, training was nontrivial but was a key factor to success. Our staff would not be willing to return to standard technology.

Conclusion: The practice of endocrinology has been dramatically enhanced over the past few years by
advances in computer technology. Endocrinologists who adopt technology appropriately will realize many tangible benefits.

Abstract #914

Polyglandular Autoimmune Syndrome in a Patient With Sickle Cell Anemia and Iron Overload

Allison Elise Kerr, MBBS, Wolali Odonkor, MD, Gail Nunlee-Bland, MD, Juanita Archer, MD, Anitha Kolukula, MD, and Onyinye Onyekwere, MD

Objective: To report a case of polyglandular autoimmune syndrome (PAS) in a patient who had sickle cell anemia (HbSS), pernicious anemia, and type 1 diabetes mellitus.

Case Presentation: A 33-year-old Jamaican woman, who had HbSS and an undefined family history of thyroid disease, presented with newly diagnosed diabetes mellitus. At the time of initial assessment, she had diabetic ketoacidosis. Further work-up revealed type 3 PAS. The pertinent laboratory findings were as follows (normal values shown in parentheses): serum GAD65 antibodies, 509 U/mL (≤1.0 U/ml); islet cell antibody titers, >1:8 (<1:2); ovarian antibodies, positive; thyroid peroxidase antibodies, 29.5 IU/mL (<2.0 IU/ml); adrenal antibodies, negative; parietal cell antibodies, 76.5 U (>24.9 units is positive); hemoglobin A1c, 7.8% (<6.0%); fructosamine, 397 µmol/L (174 to 286); antiendothelial antibodies, negative; anti-tissue transglutaminase antibodies, negative; and HLA-DR4. Results of thyroid function tests, follicle-stimulating hormone, luteinizing hormone, and estradiol were within normal limits. She responded appropriately to a 250-µg cosyntropin test with an increase from a baseline cortisol level of 8.23 µg/dL to 23 µg/dL at 60 minutes. Insulin therapy was initiated, and the patient continued to receive her regularly scheduled dosing of vitamin B12.

Discussion: In this unusual case, a Jamaican woman had HbSS, iron overload with alloantibodies against erythrocyte antigens, and type 3 PAS (based on the Neufield and Blizzard classification). The pertinent literature relative to type 1 diabetes mellitus occurring in patients with HbSS and iron overload, and the incidence of type 3 PAS in patients with HbSS, was reviewed. We found no reports on the incidence or the occurrence of sickle cell disease and PAS. Some studies, however, have reported on the presence of autoantibodies to rheumatologic organs with increasing number of transfusions in patients with sickle cell disease.

Diabetes mellitus in the presence of iron overload is not an unusual finding in patients with sickle cell disease. The exact mechanism by which diabetes develops in the presence of iron overload has not been fully explained, and no published reports have suggested that there is induction of antibody formation to mediate this effect of iron.

Conclusion: We postulate that in the presence of numerous blood transfusions as well as genetic and environmental factors, patients may be at increased risk of developing autoimmune polyendocrinopathies and endocrine organ dysfunction, unrelated to iron overload.

ADDITIONAL 2004 ABSTRACTS

The following abstracts were inadvertently omitted from the published compilation of abstracts for the 2004 American Association of Clinical Endocrinologists Annual Meeting and Clinical Congress (April 28-May 2, 2004, in Boston, Massachusetts).

Abstract #1a

Feasibility of a Basal-Bolus Insulin Program in a Community Hospital

Michael S. Balkin, MD, FACE, Robert Courgi, MD, FACE, Anna Dushenkov PharmD, and Annie Kazandjian, RN, MSN

Objective: To describe the experience of a 390-bed community hospital in instituting a basal-bolus insulin regimen for control of hyperglycemia.

Methods: During a 2-year period, an intense education program for the physician and nursing staffs was commenced to teach the concepts and application of basal-bolus insulin. New insulin order sheets, medication administration records, glucose monitoring sheets, and nursing protocols were developed. A monitoring program was instituted to determine the effect of the program on blood glucose control and to assess the degree of physician compliance with the new program.

Results: On the latest assessment, 93% of all insulin orders were written on the new order sheets, and 67% of all insulin orders included basal insulin. After initiation of the basal-bolus insulin program, adverse drug events involving insulin increased significantly from a previous maximum of 5 per month to 13 per month but then declined to 0.75 per month during the first quarter of the year; none involved permanent harm. When the last 3-month period before the introduction of our program was compared with the latest quarter, the mean glucose level had decreased from 175 mg/dL to 168 mg/dL, with only 0.1% more glucose values in our target range of 80 to 180 mg/dL.

Conclusion: Basal-bolus insulin regimens are feasible in a community hospital. Whether significant improvements in glucose control and patient outcome can be achieved remains to be determined. With use of this program, however, adverse drug events related to insulin have been decreased.
Abstract #2a

Cardiovascular Effects in Patients With Mild Heart Failure Receiving Pioglitazone or Glyburide

Alfonso Perez, MD, Mehmood Khan, MD, FACE, Patrick Gallagher, BS, and Yinzhong Chen, PhD

Objective: To evaluate the cardiovascular effects of pioglitazone versus glyburide in patients with type 2 diabetes and mild cardiac disease.

Methods: We enrolled 300 subjects in a 52-week randomized, multicenter, double-blind, comparator-controlled study, in which patients received pioglitazone (N = 151; 15 to 45 mg daily) or glyburide (N = 149; 2.5 to 15 mg daily). At baseline and 52 weeks, a 6-minute walking distance was measured in the study participants.

Results: Mean changes from baseline in 6-minute walking distances were 2.4 ± 8.3 meters and 8.7 ± 8.4 meters for patients receiving pioglitazone and glyburide, respectively (P = 0.573). There were 13 hospitalizations due to cardiovascular events in the pioglitazone group and 13 in the glyburide group (P = 0.972).

Conclusion: No significant differences were found between the pioglitazone study group and the glyburide study group in cardiovascular effects, as measured by 6-minute walking tests and mortality and morbidity.
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*The index is arranged alphabetically by subject section, and the authors’ last names are alphabetized within each section.

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