

## Case Report

## Insights into Therapy with Denosumab or Zoledronic Acid

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### Introduction

Currently, bisphosphonates are considered the first-line therapy for the management of postmenopausal osteoporosis (Bilezikian, 2009). However, oral formulations have been associated with poor absorption and potential irritation of the upper gastrointestinal tract (Cosman, 2009), which may undermine adherence and thus, patient outcomes (Jonsson et al., 2011) in everyday clinical practice. Intravenous bisphosphonates, such as zoledronic acid, have been suggested as a reasonable choice in those patients unable to tolerate oral bisphosphonates (Cosman, 2009). The antiresorptive agent denosumab, a receptor activator of nuclear factor- $\kappa$ B ligand (RANKL) inhibitor, is another therapeutic option in postmenopausal osteoporosis (Lewiecki, 2010). Hence, the question is raised whether denosumab or zoledronic acid should be considered first in those patients with an increased risk of fracture who are not candidates for oral bisphosphonate therapy.

To answer the aforementioned question, denosumab and zoledronic acid were “compared” in terms of efficacy, safety and cost-effectiveness. Data on the effect on bone-quality properties were regarded as “proxy” outcomes (compared to fracture data) and were not considered.

### Comparative effectiveness

Apart from the two large randomized, controlled clinical trials (RCTs) in oncology patients (Fizazi et al., 2011; Henry et al., 2011), no head-to-head data from RCTs is available for direct comparison of denosumab versus zoledronic acid. Since there is no primary fracture data regarding the comparative effectiveness of denosumab versus zoledronic acid in osteoporosis, an adjusted indirect comparison was undertaken using Bucher methodology (Bucher et al., 1997). Using the assumption of similarity and phase 3 RCT fracture data (Black et al., 2007; Cummings et al., 2009) as inputs, the relative risks of site-specific fracture were computed and are presented in Table 1 (unpublished data). In general, no sta-

tistical significance in terms of site-specific fracture relative risk reduction was detected. Thus, denosumab and zoledronic cannot be considered as different from each other in terms of efficacy.

### Safety

The safety profile of denosumab has focused upon the possibility of increased serious skin infections and, in those with renal compromise, hypocalcemia (Amgen Inc, 2010). With regard to the serious infection risk in osteoporosis patients, it has been suggested that denosumab is associated with a borderline increased risk of serious infections [Risk Ratio (RR): 1.25, 95% CI: 1.00-1.54] when intention-to-treat analysis was used (Toulis and Anastasilakis, 2010) and with a non-significant RR of 2.1, when per-protocol analysis was used (von Keyserlingk et al., 2011). Weighing over the evidently small attributable risk and the weak evidence in one hand, and the biological plausibility (lymph nodes, activated T and B lymphocytes express RANKL) on the other hand, it seems that denosumab is a safe choice for patients with postmenopausal osteoporosis. Even in advanced renal failure, denosumab is not contraindicated, but due precautions should be taken with regard to hypocalcemia.

The safety profile of zoledronic acid can largely be summarized in terms of the renal system, hypocalcemia and post-infusion flu-like symptoms (John Camm, 2010). Use of zoledronic acid is not recommended in patients with severe renal dysfunction, as defined by creatinine clearance rates of  $< 35$  mL/min. An increased risk of serious atrial fibrillation (Black et al., 2007) was not confirmed in the Recurrent Fracture Trial (Lyles et al., 2007).

Both denosumab and zoledronic acid have been associated with osteonecrosis of the jaw (Kyrgidis and Toulis, 2011; Pazianas, 2011), an association which appears to be clinically noteworthy primarily in the oncology setting (Bilezikian and Grbic, 2011). It is an exceedingly rare event when these drugs are used for the treatment of osteoporosis.

### Remarks on efficacy and safety:

Two useful points with direct implication to clinical practice are notable with regard to a denosumab and zoledronic acid comparative profile: the safety and efficacy in patients with renal impairment and resolution of effect. Denosumab was found safe and effective in the subset of FREEDOM patients with renal function by creatinine clearance compromised to a level of 15 mL/min (Jamal et al., 2011). This is a distinctive feature of denosumab as compared to zoledronic acid, which is contraindicated in this subset of patients. Another differentiating point between these two effective treatments is in terms of resolution of effect. Denosumab's effects in terms of bone turnover markers and bone mineral density are rapidly reversible within months after the drug is stopped. (Bone et al., 2011). Zoledronic acid is not readily reversible. The advantage here might be with zoledronic because effects after discontinuation of zoledronic acid are likely to be more long-lasting than denosumab. (Watts et al., 2010). This very advantage might be a disadvantage because of the accumulation of bisphosphonate over the long term in bone.

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## LETTER FROM THE PRESIDENT



Summer is rapidly disappearing and many of you are still settling into the first one hundred days of your fellowship, a challenging time both for taking on new clinical responsibilities, as well as for the daunting task of learning research techniques for those of you new to the laboratory. This is not often an easy or comfortable time for young investigators and clinicians, but these new demands of fellowship quickly become second nature and success soon follows.

EFF has a new web-based homepage called EFF Connections. This website, with its ability to create social networking and develop common interests amongst you and your peers, could be a helpful support tool for you in navigating the early challenges of a fellowship. I encourage all of you to register online at <http://eff.memberfuse.com> to take advantage of the educational and networking opportunities available on this site. Your login is your e-mail address (at which you received this journal) and your password is "Fellows" (cap sensitive). We hope to initiate case-based discussion groups online before the end of the year.

Our online publication, *EndoTrends*, is always in need of case reports. The process of writing for this reviewed publication provides great experience in learning how to prepare materials for publication. Successful authors are remunerated for publication and ultimately for leading future discussion groups. I heartily encourage all of you to consider a submission.

Finally, I'd like to thank all of the research grant awardees who participated in the EFF/ADA research forum held in San Diego this June. The quality of research presented and the challenging discussions that ensued are proof that as rigorous and exhausting the first part of a fellowship may seem, the end results as you finish your training careers are indeed quite remarkable. Best wishes for a successful autumn.

Sincerely,

Mark Stolar, M.D.  
President

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## Insights into Therapy with Denosumab or Zoledronic Acid

### Cost-effectiveness

Several cost-effectiveness analyses of denosumab compared to other osteoporosis treatments have recently been published (Hiligsmann and Reginster, 2010; Hiligsmann and Reginster, 2011; Jonsson et al., 2011), and submitted by the manufacturer to the National Institute for Clinical Excellence (NICE). Unfortunately, none of them used zoledronic acid as a primary comparator.

To explore this comparison, a Markov cohort model was used to investigate the cost-effectiveness of denosumab administered for five years to a typical, otherwise healthy, Greek postmenopausal population (Age 67 years with a T-score: - 2.7) (unpublished data). Analysis was undertaken from a healthcare perspective using a ten-year horizon. The base-case incremental cost-effectiveness ratio for denosumab versus no treatment was 5436.43 €/Quality-Adjusted Life Years (QALY), whereas denosumab was dominated by zoledronic acid (discount rate 0%). The latter finding was not robust in one-way sensitivity analyses, using the adjusted relative risks for hip and spine fractures, corresponding to the lower CIs (Table 1). In two-way sensitivity analyses exploring the effect of the starting age of the cohort and cohort T-score, denosumab outperformed no treatment by the age of 73 years in virtually all range of osteoporotic T-scores in terms of both net health and monetary benefits (Figure 1). In summary, no clear-cut conclusions could be drawn regarding the comparative cost-effectiveness of denosumab and zoledronic acid. It should be underscored that the above cost-effectiveness data cannot be generalized and is not applicable in the American setting.

### Conclusion

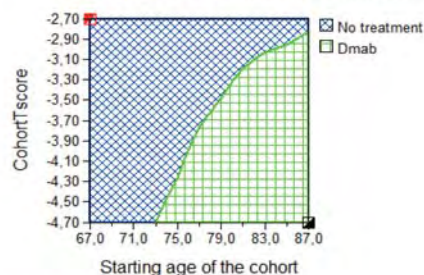
Taking comparative efficacy, safety and cost-effectiveness data into consideration, it appears that both denosumab and zoledronic acid could be considered as treatment alternatives to those patients with postmenopausal osteoporosis, unable or intolerant of oral bisphosphonates, with the exception of the subset of patients with significant renal impairment. This latter group of patients should not be treated with zoledronic acid.

**Table 1.** Adjusted indirect comparison between denosumab and zoledronic acid in terms of relative risk (site-specific fracture data).

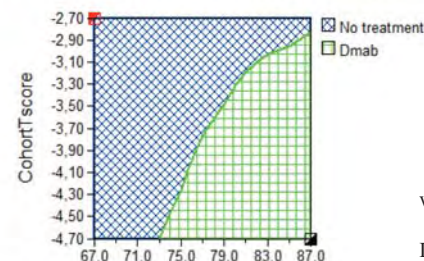
Denosumab versus Zoledronic acid	
<b>Hip fx</b>	1.017
(95% CI)	0.564 – 1.835
<b>Clinical Vertebral fx</b>	1.348
(95% CI)	0.706 - 2.574
<b>Wrist fx</b>	1.067
(95% CI)	0.845-1.346

Fx: fracture, CI: Confidence Interval

**Figure 1.** Two-way sensitivity analysis  
 Net Health Benefit (wtp=20000,) Sensitivity Analysis on  
 Starting age of the cohort and CohortTscore



**Net Monetary Benefit (wtp=20000,) Sensitivity Analysis on  
 Starting age of the cohort and CohortTscore**



wtp: Willingness to pay

Disclosure: Author states no conflict of interest.

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## Successful Inpatient Medical Management of Extreme Obesity in a 16-Year-Old Adolescent Boy

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### Abstract

Coinciding with the increasing worldwide prevalence of obesity [1] and its co-morbidities, including increased risk of cardiovascular events [2], occurrence of obesity in the adolescent population is a growing concern since it remains one of the most difficult diseases to treat and treatment choices are limited. These include lifestyle modification, medications and surgery in selected cases. Bariatric surgery has been a successful intervention in curing obesity and either preventing or curing diabetes; consequently it has been advocated for severely obese adolescents. However, it is questionable whether benefits outweigh potential drawbacks in this population and whether certain at-risk cases may have an indication for medical management.

Such a treatment dilemma presented to us when a 16-year-old boy was hospitalized for morbid obesity with a weight approximating 800 pounds. During his admission to the hospital, he successfully lost over 400 pounds over approximately three months and maintained the weight loss after discharge. To our knowledge, there have been no reported cases of this magnitude in the medical literature. This case provides a unique example of successful medical treatment of morbid obesity using an intensified inpatient treatment plan, and warrants a discussion of our treatment strategy and the merits of medical versus surgical options for the treatment of morbid obesity.

### Case Presentation

A 16-year-old Caucasian boy presented for evaluation and treatment of morbid obesity prompted by child welfare services, who had received referrals for possible medical neglect. The admission weight was 787 pounds and was attributed to excessive dietary intake. He was unable to walk for more than a few steps. A visit to the home determined that it was unsafe for him to be at home, and he was placed under protective custody of The Department of Health and Human Services and was subsequently admitted to the University of Oklahoma Children's Hospital for evaluation and treatment. He had difficulty breathing when lying down and required oxygen. He also had difficulty urinating due to a retracted penis related to abundant pubic fat, and he had developed testicular and scrotal cellulitis. Other problems included hypertension, glucose intolerance and obstructive sleep apnea. The past medical history was otherwise benign. He was born full-term by caesarian section. He was 24 inches tall and 9 pounds in weight.

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He was identified as having a language disorder in kindergarten and received speech therapy. He displayed delays in the attainment of basic academic skills. The social history revealed that he lived at home with his mother, who was unemployed. There had been increased stress due to domestic violence prior to the death of his father due to lung cancer. His father was an alcoholic and was verbally and physically abusive towards him and his mother. Patient had started gaining weight after his father's death at age ten and he had become aggressive in demanding food to the extent that his mother became afraid of him. He was reported to have been loud and abusive towards his mother. He attended a public school until 9th grade but started homeschooling in 10th grade. He had not seen a physician for over a year despite several medical problems, and this was attributed to his mother not being able to take him to his appointments due to his morbid obesity, since he could not fit into a car. The family history revealed that his mother and several aunts had type 2 diabetes and his father had lung cancer as stated above.

Diet history revealed that the total daily calories calculated out to be > 6000 Kc/day. He ate scrambled eggs, pieces of toast, 4-5 slices of bacon and orange juice for breakfast. He ate some sausage and then two cups of ramen noodles after breakfast. At lunch, he ate a sandwich or salad, fruits and cottage cheese, followed by more ramen noodles. His mother made dinner mostly consisting of meat and vegetables. He sometimes ate Kentucky Fried Chicken. After dinner, he ate ice cream, more noodles and fruit.

He was taking Hydrochlorothiazide 25mg orally twice daily and Enalapril 10mg orally every 12 hours.

On physical exam his height was 186 centimeters and he weighed 326 kilograms. His BMI was 94.2 kg/m<sup>2</sup>. He had minimal acanthosis nigricans around the neck and elbows, and there were no cutaneous striae. Heart was regular and chest was clear without wheezing or rales. The abdomen was obese without masses. Deep tendon reflexes could not be elicited. The extremities had normal strength.

A multidisciplinary approach was applied to management of his morbid obesity during the hospitalization. Specialty consultations included dietetics, physical therapy, psychiatry, pediatric endocrinology, pulmonology and orthopedics. The HbA1c was 6.2% and treatment with exenatide (Byetta)[3] 10mcg subcutaneous was given twice daily, metformin 500mg oral twice daily and sibutramine 10mg daily was initiated. He did not tolerate metformin due to diarrhea and later switched to pioglitazone 45mg oral once daily, but this was discontinued since exenatide alone provided good glucose control. His diet was initially restricted to less than 3000 calories included in three meals and three snacks per day, and he was provided dietary education on making healthy food choices. Daily physical therapy was also implemented. The regimen resulted in gradual weight loss.

It was felt that his previous social environment had made a large contribution to his overall health. Behavioral and cognitive therapy, and subsequently a structured residential or group home placement with supervision, were recommended by a pediatric psychiatrist and implemented. He was found to have severe obstructive sleep apnea requiring continuous positive airway pressure (CPAP) at night, but this resolved after a few weeks.

During three months of hospitalization, he successfully lost approximately 400 pounds. After discharge to his home under the care of his mother, he relapsed and started gaining back his weight. Consequently he was placed in a group home where he currently resides, and he has successfully maintained his weight at approximately 325 pounds since then. He followed up with Pediatric Endocrinology once every 3-6 months with continued dietary and nursing support until recently, when he was referred to Adult Endocrinology.

## Discussion

In addition to chronic co-morbidities associated with obesity such as glucose intolerance, hypertension and dyslipidemia, cases with extreme morbid obesity may have more immediate risk associated with compromised pulmonary function [4], justifying hospitalization. Our case presented with evidence of impaired glucose tolerance and hypertension

manageable by pharmacological means, however compromise in pulmonary function and limitation in mobility developed and demanded urgent attention. At the time of presentation, it was clear that a multidisciplinary approach to his problem could be better served as an inpatient with prioritized treatment of his impaired pulmonary function, a potential cause of death. This was managed with supplemental oxygen and apnea monitoring while providing optimal semi-recumbent positioning for sleep. After he was stable, we approached his long-term care utilizing physical therapy, medical nutrition therapy and medications to attain weight loss. We attribute successful restoration of pulmonary function and mobility followed by long-term weight reduction to the inpatient team approach with daily supervision by house-staff and attending physicians in a traditional university setting, however replication elsewhere is also feasible.

We identified two main etiological factors. One was exposure to gestational diabetes known to be associated with childhood obesity and subsequent type 2 diabetes [5]. The second factor was an emotional drive to eat apparently originating while his abusive father was alive, and exacerbated after his death triggering conflicting emotional deprivation leading to increasing desire to compensate by eating [6]. A third possible component is an underlying genetic predisposition, such as leptin deficiency or leptin resistance. The latter was suggested by his extremely high leptin level, which has been reported previously in association with obesity and is also thought to be a reflection of fat cell size [7-8]. Interestingly, we observed a remarkable reduction in leptin after weight loss, suggesting association with the remarkable decrease in body fat but possibly preservation of fat cell numbers. MC4R, the gene containing the most common mutation associated with morbid obesity, was normal, although 5% of individuals with severe obesity, hyperphagia and hyperinsulinemia may have this mutation [9].

Weight loss management began with a gradual increase in mobility aided by physical therapists, and was continued during a maintenance program with constant motivation and psychological support, which was maintained after placement in a group home. Pharmacological therapy was superimposed on the intensified lifestyle management. We based our pharmacological choices of sibutramine and metformin on the clinical presentation and evidence for efficacy in adolescence [10-11], with the exception, of exenatide which is known to promote weight loss in adults with diabetes [12], although blood glucose control was the treatment goal. Metformin was discontinued because of gastro-intestinal side-effects, but exenatide was continued over a three-year period.

Our long-term multidisciplinary medical approach can be contrasted with bariatric surgery. Although not a viable option at the onset, it might have been considered if long-term weight loss management had failed. In general, bariatric surgery has been restricted for youths who have reached a BMI of 40 kg/m<sup>2</sup> in the presence of co-morbidities such as diabetes, hypertension or dyslipidemia according to the National Institute of Health (NIH) guidelines. The number of adolescents undergoing bariatric surgery has increased in recent years. As compared to adults, adolescent patients had a shorter hospital stay and lower mortality rates. Out of 771 bariatric surgeries in adolescents in 2003, no deaths were reported, but long-term effects and complications of bariatric surgery in adolescents are not yet known [13].

Our case presented as an extreme example of the effects of severe obesity on basic survival functions such as pulmonary function and mobility, although presentation of the metabolic syndrome criteria were mild and treatable, such as transient hypertension and mild dyslipidemia characterized by a low HDL-C and mild and reversible glucose intolerance treatable with exenatide. He represents the extreme end of the spectrum of cases, with severe obesity at a young age with serious implications since cases with early onset obesity are at higher risk of developing long-term cardiovascular complications as compared with people who develop obesity as adults. We present treatment options for successful short-term and partial long-term success including lifestyle, pharmacological therapy and psychotherapy to address severe emotional issues which appeared to override intrinsic predisposing factors, such as gestational exposure to diabetes and hyperphagia.

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Of note, there was no specific program in the Children's Hospital at the University of Oklahoma for the management of extreme obesity. All involved subspecialists such as the endocrinologist, pulmonologist, dietitians, physical therapists and psychiatry played important roles. It was the teamwork that resulted in his remarkable improvement.

This case report encourages hospitals to establish formal teams and programs to combat morbid obesity, which is now affecting many children. Our choice of treatment modalities did not have the risks of bariatric surgery and proved successful in the long-term.

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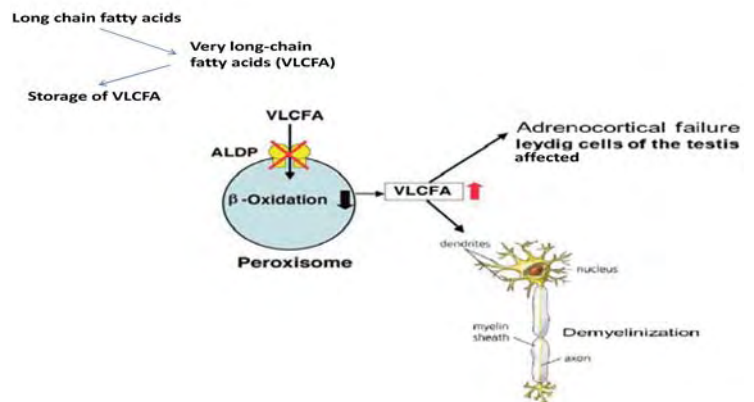
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## Adrenoleukodystrophy

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### Introduction

ALD is an x-linked disorder due to a mutation of the ABCD1 gene located on chromosome Xq28. As a peroxisomal storage disease, ALD results in excessive accumulation of very long chain fatty acids (VLCFA), especially in the adrenal gland, leydig cells and the CNS [1] (Figure 1). Affected males have one of three main phenotypes: 1) a childhood cerebral form, 2) adrenomyeloneuropathy or 3) primary adrenal insufficiency (10 AI) [2, 3]. The disorder occurs in approximately 1:21,000 males, with an onset of 4 - 10 years of age [4]. Measurement of VLCFA (C26:0; C26:0/C24:0 and C26:0/C22:0) in the blood is a good screening tool [5]. Molecular gene testing of the ABCD1 gene locus is confirmatory [6]. Treatments include reduction/alteration in dietary fats, use of Lorenzo's oil [7] and, in selective cases, hematopoietic stem cell transplantation (HSCT) in early stages of cerebral involvement [8]. Because of the adrenal involvement, replacement of adrenal hormones (glucocorticoid and mineralocorticoid) is imperative for the majority of affected individuals [9]. We report a 16-yr-old male who presented with 10 AI and was found to have ALD.



**Figure 1.** VLCFAs are normally degraded by intracellular peroxisomes. In ALD, however, the VLCFA is unable to enter the peroxisomes due to a defect in ALDP that transports VLCFA from to cytosol into the peroxisome.

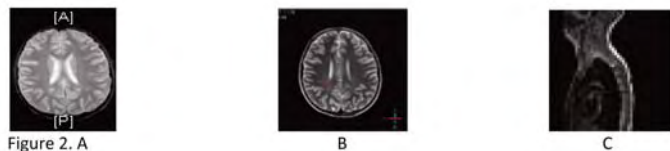
### Case Report

A 16 y/o male presented with a three-year history of progressive symptoms, including behavioral changes characterized by a flat affect and social withdrawal, poor school performance and limited personal interactions. For several months prior to his diagnosis, he had experienced several unexplained episodes of intermittent nausea and vomiting unaccompanied by diarrhea or fever. He reported a craving for salty foods and a progressive darkening of the skin. Pertinent findings on physical examination included the following: Wt: 44.2 kg (<5%) Ht.161.3 cm (<10%) BP 83/48 mmHg. He was alert and appeared to understand directions, but rarely respond to verbal questions and was noticeably withdrawn. There was diffuse hyper-pigmentation of the skin, including sun exposed and non-exposed areas. The genitalia were Tanner Stage 2. There were no vocal neurological deficits.

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His work-up revealed the following:

- A random serum cortisol was 1.1 ug/dl.
- An ACTH stimulation test (250 mcg IV bolus) demonstrated a cortisol of <0.1 ug/dl for both the baseline and the 60 minimal response.
- Adrenal autoantibodies were negative.
- Levels of blood VLCFA (C26:0,C24:22,C26:22) were elevated.
- Changes in the posterior white matter were noted on an MRI of the brain, while the spine was grossly normal.



**Figures 2 A & B Brain MRI.** Symmetric increased signal intensity bilaterally within the splenium and posterior periventricular white matter. Signal intensity within the posterior limb of the internal capsule with extension inferiorly into cerebral peduncle of the midbrain. **Figure C.** Normal spine.

## Discussion

Twenty percent of patients with a clinical presentation of Addison's disease are found to have ALD as a 1<sup>o</sup> etiology [9]. ALD is frequently characterized by signs and symptoms of 1<sup>o</sup> AI - unexplained vomiting, weakness or coma. The elevated blood levels of VLCFA may directly alter adrenal function by inhibiting the effects of ACTH on adrenocortical cells or by initiating an autoimmune response. Adrenocortical failure occurs in combination with irreversible degenerative neurological defects. ALD also affects the leydig cells, resulting in delayed puberty [4] as illustrated in this patient. Early diagnosis of ALD is essential to prevent the occurrence of adrenal crisis, which can be life threatening. Although adrenal steroid replacement may avoid an adrenal crisis, it does not reduce the progressive damage to the nervous system characteristics of ALD. Restriction of dietary VLCFA does not seem to decrease intracellular VLCFA concentration, since endogenous synthesis continues [7].

Experimental treatments include Lorenzo's oil (a mixture of oleic and erucic acid), which decreases the endogenous biosynthesis of VLCFA via competitive inhibition [7]. In males with neurological manifestations and early MRI evidence of CNS involvement, HSCT has been suggested as the treatment of choice [8]. All members of the family should be screened for ALD, since manifestations in some affected males and all affected females may occur at a later age. The utility of including ALD testing in newborn screening is currently being investigated.

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## Long-Term Effects of Cross-Sex Hormonal Treatment on Bone Health in Adult Gender Identity Disorder

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## Introduction

Though the exact prevalence of gender identity disorder (GID) in the United States remains undefined, over the past few decades, GID (or transsexualism) has become increasingly recognized and accepted as a medical entity. In September of 2009, the Endocrine Society issued clinical practice guidelines on the endocrine treatment of transsexual persons [1]. GID even gained media attention when Oprah Winfrey featured Chaz Bono, the female-to-male (FTM) daughter of the well-known musical duo Sonny and Cher, and Lea T, a famous male-to-female (MTF) Brazilian supermodel, on separate episodes during her final season.

Patients with GID identify or desire to live and be accepted as a member of the gender opposite to that assigned to them at birth [2]. Patients are classified as either MTF, a biological male who identifies as or desires to be female, or FTM, a biological female who identifies as or desires to be male [1]. While the etiology of GID remains unknown, recent research suggests that it may in part be a disorder of sexual differentiation based on studies examining the bed nucleus of the stria terminalis [2, 3]. After careful evaluation by a mental health professional and real-life experience where patients live in their desired gender role, they often progress to hormone therapy, possibly followed by gonadectomy [1]. Post-operatively, it is recommended that hormone therapy be continued, often at reduced doses, to maintain both secondary sexual characteristics and bone health [1].

Despite the increasing acknowledgement of GID as a clinical entity, it is a consistently neglected subject area in traditional medical training [4]. Nevertheless, patients suffering from GID seek out both hormonal and surgical therapies in order to alleviate their gender dysphoria. Thus, to optimally care for this unique patient population, it is pivotal that physicians, and particularly endocrinologists, be aware of the comprehensive process of sex reassignment, the various treatment options, and perhaps most importantly, the side effects of such treatments. The following case evaluates the long-term effects of cross-sex hormonal treatment on bone health in GID.

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## Case

A 26-year-old female with GID was referred to the endocrinology clinic to initiate cross-sex hormone therapy. She had suffered persistent discomfort with her biological sex since her early teenage years and desired to start testosterone therapy immediately. She had been living as a man for the past 11 months and was carefully evaluated by a mental health professional who believed that she met the eligibility and readiness criteria for testosterone therapy. Her past medical history was unremarkable. The patient inquired about any adverse consequences that testosterone could have on her bones because she has a 58-year-old mother with a recent hip fracture secondary to osteoporosis.

## Discussion

It is well-established that sex steroids are pivotal to skeletal integrity. They assist in general bone metabolism, the attainment of pubertal peak bone mass, and the maintenance of adult bone mass as is evidenced by the increased fracture risk observed in postmenopausal women and hypogonadal men [5,6]. In particular, estrogen, rather than testosterone, has been found to be the dominant hormone responsible for bone mineral density [7]. Testosterone has its predominant effect on cortical rather than trabecular bone, which some believe is related to a greater number of androgen receptors on cortical bone cells [8].

Patients undergoing cross-sex hormone for the treatment of GID therapy provide researchers with a unique opportunity to further evaluate the roles of estrogen and testosterone on bone when the hormonal milieu is reversed. However, this is a difficult group to study as it is an uncommon and extremely heterogeneous patient population. Importantly, the appropriateness of dual-emission X-ray absorptiometry (DXA) evaluation and which reference population to utilize when interpreting DXA results with blurred gender lines is unclear. At present, the reference gender is typically that of the biological sex. Such ambiguity raises questions about the validity of DXA evaluations for these patients. Additionally, cross-sex hormone therapy regimens for MTF and FTM patients are not universally standardized and patients undergo sexual reassignment surgeries at various stages in their lives further complicating any comparisons [9].

Despite these limitations, researchers have tried to evaluate whether cross-sex hormone therapy in patients with GID can sufficiently compensate for the role of genotypic hormones on bone health. Though the literature in this area is methodologically flawed and conflicting, commonly cited studies have not found significant decreases in bone mass in either MTF or FTM patients in the short-term [5, 10, 11]. The effects of long-term cross-sex hormone therapy on bone health have been evaluated via markers of bone metabolism and DXA measurements at L2-L4 for an average of 28 to 63 months. While bone mineral density (BMD) was largely unchanged in the MTF cohort, results were less assuring for the FTM cohort, where bone mass significantly decreased over time. Using serum LH as a marker of adequate hormonal substitution, the authors concluded that higher doses of androgens were likely needed by this patient group [5]. In contrast, a later study evaluated BMD in FTM patients during a two-year prospective observational case series. They found that supra-physiologic testosterone therapy increased BMD at the hip, possibly explained by the larger percentage of cortical bone, and maintained BMD at the spine [7]. More recently, BMD values were found to be generally preserved in MTF transsexuals, and either preserved or increased at sites rich in cortical bone in FTM transsexuals [6]. Though definitive conclusions about cross-sex hormone therapy on bone health remain elusive, it appears that bone density is generally preserved in both MTF and FTM transsexuals.

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# FOUNDATION NEWS

## EFF Welcomes Michael Berelowitz, MBChB, FCP(SA), FACP, Back to the Board of Directors



Dr. Michael Berelowitz is a founding member of the Endocrine Fellows Foundation and helped guide the organization at its inception as the Chief Financial Officer. Recently retired from Pfizer Inc. as a Senior Vice President, Dr. Berelowitz is returning to the Board to help guide EFF's continuing development.

Dr. Berelowitz has enjoyed a medical career combining extensive senior leadership experience in academia and the pharmaceutical industry. He is now in a position to share this

unusual skill set and apply those insights he has gained over a 40-year career, where they might bring the most value.

After growing up in Zimbabwe, Dr. Berelowitz attended the University of Cape Town, where he completed his medical degree in 1968. He did his residency training in Pathology, Nuclear Medicine and Internal Medicine in 1972, and fellowship training in Endocrinology and Metabolism in 1975. He moved from South Africa to the United States in 1977 where he has held appointments at the University of Chicago, University of Cincinnati College of Medicine, SUNY at Stony Brook, and most recently, Mount Sinai School of Medicine.

As a medical academic and specialist in Endocrinology, Dr. Berelowitz divided his efforts between laboratory and clinical research, teaching and clinical practice, and in administrative and faculty appointments of increasing responsibility. He left full-time academics in 1996 as Professor of Medicine at SUNY Stony Brook, after 11 years as the Head of the Division of Endocrinology and Metabolism, for a new set of challenges at Pfizer Inc.

At Pfizer, Dr. Berelowitz had medical responsibilities that included leading a diabetes team, the cardiovascular group (including Lipitor and Norvasc), the Global Medical Organization, and finally, as Senior Vice President, the Head of Clinical Development and Medical Affairs for all Specialty Care medicines. During his 15-year career with Pfizer, he had extensive experience with, and understanding of, all aspects of pharmaceutical medicine ranging from the changing global medical environment, strategic, clinical operating and tactical planning, program and budget oversight, and people management and mentoring.

This wide-ranging background provides Dr. Berelowitz with a unique perspective from which to pursue his passion – applying cutting-edge science to bringing important new medicines to people that need them, physicians who would prescribe them and societies that will value them.

## Endocrine Fellows Foundation Preceptorship in Metabolic Bone Diseases

Columbia University, College of Physicians and Surgeons  
New York, New York

John P. Bilezikian, M.D.

Chief, Division of Endocrinology

May 16 – May 27, 2011

The Preceptorial in Metabolic Bone Diseases, sponsored by the Endocrine Fellows Foundation, was held at Columbia University Medical Center, Division of Endocrinology, for a two-week period from May 16-May 27, 2011. The faculty of the Metabolic Bone Diseases Unit, comprised of Drs. John P. Bilezikian, Ethel S. Siris, Elizabeth Shane, Shonni J. Silverberg, Mishaela Rubin, Emily Stein, Aubrey Stoch, Marcella Walker, Adi Cohen, Donald McMahon, Stavroula Kousteni, Emily Stein, Serge Cremers, David Dempster, Robert Lindsay, Felicia Cosman, and Jeri Nieves, as well as other participating Columbia faculty (Patricia Ducy, Gerard Karsenty, Thomas Nickolas, Alison Pack, Wylie Hembree, Ronald Staron and Michael Yin) all taught in this comprehensive

introduction to basic and clinical aspects of metabolic bone diseases. Professor Clifford Rosen (The Maine Center for Osteoporosis Research and Education, Senior Staff Scientist, The Jackson Laboratory) served as our outstanding guest faculty. The Fellows gained comprehensive exposure to all the important metabolic bone diseases, as well as engaged in discussions related to mechanisms, pathophysiology, evaluation and therapeutics.

The Fellows who were selected (see photograph) learned in an environment that was workshop-oriented. There was ample time not only for formal presentation of material that covered fundamental principles of basic and clinical bone physiology and pathophysiology, but also for active dialogue between the instructors and the Fellows. The Fellows were also introduced to key areas of research such as protocol design, acquisition, interpretation of data and statistical testing. Additionally, the Fellows attended conferences, clinical case discussions, the Metropolitan New York Bone Club and research seminars. The Fellows had the opportunity to investigate a topic of particular interest to them and to present their work to the Faculty at the end of the preceptorial period.

The Preceptorship in Metabolic Bone Diseases has been held at Columbia for over ten years. As has been the case without exception in the past, this most recent program was met with great enthusiasm by the Fellows who were fortunate to be selected to attend this highly popular program of the Endocrine Fellows Foundation. The Preceptorship was supported by unrestricted educational grants from Amgen, Merck, Eli Lilly, and Warner-Chilcott.



Back row (left to right): Monica Grover (Baylor College of Medicine), Aarthi Arasu (University of California, San Francisco), Melissa Price (Montefiore Medical Center, Albert Einstein College of Medicine), Bianca Alfonso (Beth Israel Medical Center), Konstantinos Toulis (Aristotle University), Noga Minsky Chlamtac (Mount Sinai School of Medicine), Naga Yalla (University of Kentucky).

Front row (left to right): Nalruporn Chokrungraranon (Banner Good Samaritan Hospital/VA Health Care System, Phoenix, Arizona), Dr. Bilezikian, Marisa Censani (Columbia University Medical Center, College of Physicians & Surgeons), Sofiya Milman (Montefiore Medical Center, Albert Einstein College of Medicine).

## Grant Award Recipients for the 2011 Spring Cycle Fellows Development Research Grant Program in Diabetes, Obesity, and Fat Cell Biology

— This research grant is supported by an unconditional educational grant from Amylin Pharmaceuticals, Inc. and provides for clinical grants in the area of cardiometabolic disorders in obesity and diabetes. Four grants have been awarded for the 2011 Spring Cycle in the amount of \$15,000 each.

Jonathan Howell, M.D., Ph.D. – Cincinnati Children's Hospital Center  
*Incretin Expression and Regional Patterning in Human Pluripotent Stem Cell Derived Intestine*

Program Director: Philippe Backeljauw, M.D.

Ania Jastreboff, M.D. – Yale University  
*GLP-1 Analogue Effect on Neural Food Reward-Motivation Pathways*  
Program Director: Silvio Inzucchi, M.D.

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Shana McCormack, M.D. – Massachusetts General Hospital  
*Cardiovascular Fitness in Overweight Children and Adolescents Before and After an Intensive In-Home Exercise Training Intervention*  
Program Director: Joseph A. Majzoub, M.D.

Tracy Tylee, M.D. – University of Washington  
*A Role for Leptin in the Regulation of Voluntary Activity in Mice*  
Program Director: Dace Trence, M.D.

**Marilyn Fishman Grant for Diabetes Research** — This research grant, named in honor of EFF's long-time Executive Director, is funded through an unconditional education grant from the partnership of Bristol-Myers Squibb and AstraZeneca International. This grant is limited to studies involving metabolism, obesity and Type 2 diabetes (both clinical and basic research). Four grants have been awarded for the 2011 Spring Cycle in the amount of \$15,000 each.

Erin Dunnigan, M.D., MBA – University of Texas Southwestern Medical Center  
*QR-Bromocriptine as an Adjunct to Insulin and Metformin in the Treatment of Type 2 Diabetes*  
Program Director: Ildiko Lingvay, M.D., MPH, MSCS

Daniel Hsia, M.D. – Baylor College of Medicine  
*Differences in Glucose Metabolism in Adolescent Patients Before and After Bariatric Surgery*  
Program Director: Katherine Hwu, M.D.

Paula Newton, M.D. – Washington University School of Medicine  
*The Impact of Acute Moderate Intensity Exercise on Blood Glucose in Children and Young Adults with Type 2 Diabetes Mellitus*  
Program Director: Paul Hruz, M.D., Ph.D.

Cynthia Yazbeck, M.D. – University of Pittsburgh  
*Contribution of Adipocyte-Specific ATGL-Medicated Triacylglycerol Hydrolysis to Adipocyte Function, Insulin Responsiveness and Inflammation In Vivo*  
Program Director: Andrew F. Stewart, M.D.

**The EFF Endocrine Research Grant** — This grant is for general endocrine topics, including but not limited to, thyroid, bone, adrenal, pituitary, growth and reproductive disorders. Two grants have been awarded for the 2011 Spring Cycle in the amount of \$7,500 each.

Bethany Freedman, M.D., Ph.D. – Children's Hospital Boston  
*Adrenal Lineage Development: The Role of the Zona Glomerulosa*  
Program Director: Joseph Majzoub, M.D.

Joelle Taylor, M.D. – Eastern Virginia Medical School  
*A Novel In Vitro Human Trophoblast-3D Endometrial Culture to Study Invasion and the Role of BMP2*  
Program Director: David Archer, M.D.

**Cycle 2, Fall 2011 Research Grant Applications**  
The online research grant application process is open for Cycle 2, Fall 2011 grant applications. Grant applications are due by September 9, 2011. Please see the EFF website, [www.endocrinefellows.org](http://www.endocrinefellows.org), for more information.

# Calendar of Events

## September 2011

September 14-15  
EFF/ASBMR Fifth Fellows Forum on  
Metabolic Bone Diseases  
EFF and ASBMR  
San Diego, CA  
[www.endocrinefellows.org](http://www.endocrinefellows.org)

September 16-20  
ASBMR 2011 Annual Meeting  
American Society for Bone and  
Mineral Research  
San Diego, CA  
[www.asbmr.org](http://www.asbmr.org)

## October 2011

October 1-5  
29th Annual Scientific Meeting  
The Obesity Society  
Orlando, FL  
[www.obesity.org](http://www.obesity.org)

October 26-30  
ATA 81st Annual Meeting  
American Thyroid Association  
Indian Wells, CA  
[www.thyroid.org](http://www.thyroid.org)

## November 2011

November 3-5  
9th Annual World Congress on Insulin  
Resistance, Diabetes & Cardiovascular  
Disease  
Metabolic Institute of America  
Hollywood, CA  
[www.insulinresistance.us](http://www.insulinresistance.us)

## December 2011

December 4-6  
World Diabetes Congress  
International Diabetes Federation  
Dubai  
[www.idf.org](http://www.idf.org)

## March 2012

March 7-10  
ISCD 18th Annual Meeting  
International Society for Clinical  
Densitometry  
Los Angeles, CA  
[www.iscd.org](http://www.iscd.org)

## April 2012

April 29-May 1  
AAES 2012 Annual Meeting  
American Association of Endocrine  
Surgeons  
Iowa City, IA  
[www.endocrinesurgery.org](http://www.endocrinesurgery.org)

## May 2012

May 23-27  
21st Annual Meeting and Clinical  
Congress  
American Association of Clinical  
Endocrinologists  
Philadelphia, PA  
[www.aace.com](http://www.aace.com)

## June 2012

June 8-12  
72nd Scientific Sessions  
American Diabetes Association  
Philadelphia, PA  
[www.scientificsessions.diabetes.org](http://www.scientificsessions.diabetes.org)

June 23-26  
94th Annual Meeting and Expo  
The Endocrine Society  
Houston, TX  
[www.endo-society.org](http://www.endo-society.org)