Effects of Estrogen Replacement Therapy on Bone and Glucose Metabolism in a Male with Congenital Aromatase Deficiency

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Abstract

Little is known about the impact of estrogen replacement therapy for bone formation, glucose metabolism and hormonal parameters on males with aromatase deficiency. Transdermal estrogen (TE) replacement was initiated at 100 µg/week in months 0 – 3, 50 µg/week in months 3 – 6, 25 µg/week in months 6 – 12, 75 µg/week in months 12 – 24, and 25 µg/week in months 24 – 36 to substitute for the deficiency in a 27-year-old homozygous male with a mutation on the *CYP19* gene. Estradiol levels increased from < 10 at baseline to 45, 12, 27 and 17 pg/ml (normal range 10 – 50) after 6, 12, 24 and 36 months, and inversely correlated to LH and FSH levels. Testosterone levels changed from 31.2 nmol/l at baseline to 3.8, 22.1, 7.1 and 22.0 nmol/l (9.5 – 30) after 6, 12, 24 and 36 months, respectively, and correlated closely to basal and stimulated LH and FSH levels at 100 µg GnRH. Bone maturation progressed, and metacarpal and phalangeal epiphysis closed after 12 months. Spongiosa-hydroxyapatite of the radius assessed by quantitative computed tomography changed from 52 to 83, 51, 69 and 71 mg/cm^3 (120 – 160); bone mineral density of the lumbar spine assessed by dual energy X-ray-absorptiometry (normal value > 1.150) increased from 0.971 (T-Score –2.24) to 1.043 (–1.64), 1.065 (–1.46), 1.128 (–0.93) g/cm^2 and 1.021 (–1.82) after 6, 12, 24 and 36 months of TE, respectively. Osteocalcin as a bone formation parameter and aminoterminal collagen type I telopeptide as a bone resorption parameter increased during high-dose estrogen supplementation, and then decreased during the lower doses. Lipoprotein (a) increased from 20 mg/dl at baseline to 60 and 62 mg/dl after 6 and 12 months, and then decreased to 24 and 25 mg/dl after 24 and 36 months, respectively, while total cholesterol, HDL, LDL and triglycerides did not change. AUC glucose decreased continuously after oral glucose load, and HOMA IR reached its lowest value the 75 µg weekly estradiol dose. This study confirms the role of estrogens in achieving bone mineralization and maturation in human males. Additionally, estradiol has dual negative feedback sites that on the hypothalamus to decrease GnRH pulse frequency, and on the pituitary to decrease responsiveness to GnRH. The improvement in glucose metabolism after estrogen replacement therapy suggests a probable role of sex steroids in insulin sensitivity. The optimal weekly dose of transdermal estrogen replacement for normalizing estrogen levels and maintain bone mass in adult males with aromatase deficiency may be 50 – 75 µg spread over two doses.

Key words
Estrogen in males · Bone and glucose metabolism

Introduction

A recent report described a 29-year-old male affected by aromatase deficiency resulting from a novel homozygous inactivating mutation of the *CYP19* ($P450_{arom}$) gene in the fourth case of this type [1]. All four males suffered undetectable estrogen levels due to aromatase deficiency, were diagnosed between 24 and 39 years, and had osteoporosis and open metacarpal and phalan-

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Bibliography
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geal epiphyses [1–4]. These studies have demonstrated that estrogen is necessary for achieving epiphyseal closure and peak bone mass in males [5–9]. Conjugated or transdermal estradiol supplementations promote skeletal mineralization after complete epiphyseal closure and increase bone mineral density [5,6,10,11]. The increase in bone mass from declining androgen concentrations after estrogen supplementation strengthens the essential role for the establishment of bone mineralization and peak bone mass in growing boys, as well as the maintenance of bone mass in adults [12,13]. To maintain bone mass in a male with aromatase deficiency, Rochira et al., suggested 25 µg twice weekly as an adequate substitutive dose of transdermal estradiol [6].

In a male with aromatase deficiency due to an inactivating mutation of the *CYP19* gene, fasting insulin levels were elevated and declined after treatment with conjugated estrogen [10]. In 2002, we have reported elevated insulin concentrations in a male with an aromatase deficiency, but less is known about the development of glucose metabolism after long-term estrogen replacement therapy [4]. The present study was designed to analyze bone maturation, bone mineralization, glucose metabolism and hormonal parameters to determine the optimal dosage of estrogen replacement therapy for aromatase deficiency management in adult males.

Subjects and Methods

Case report

The present study was performed on a 27-year-old male with aromatase deficiency resulting from a homozygous inactivating mutation of the *CYP19* ($P450_{arom}$) gene (A to C substitution in intron A), which has been previously reported [4]. The propositus was the only child of consanguineous parents. At initial presentation, the patient weighed 120 kg with eunuchoid proportions, was 197 cm tall, had an arm span of 204 cm, and a shoe size of 15. Physical examination was unremarkable except for bilateral genu valgum, kyphoscoliosis, abdominal striae and pectus carniatus. The patient's childhood and pubertal development were unremarkable. At 14 years of age, he was 170 cm tall (97^{th} percentile), and continued to grow until the age of 24. Pubic and axillary hair was normal, as were the size (13 and 14 ml) and consistency of the testis. His sexual identity and psychosexual orientation as assessed by questionnaire were heterosexual, and his libido was normal. He had spontaneous erections sufficient for intercourse. He lived with his parents and his behavior was very friendly. The patient was single, had no offspring and was employed as a civil servant. His intellectual and physical capacities were normal. His blood pressure was normal (125/80 mmHg). His waist circumference was 124 cm and waist-hip ratio was 1.02. Before and 6 months after estrogen replacement, semen analysis revealed oligoazoospermia. The patient refused further semen analysis.

Study protocol

We started estrogen replacement therapy at 50 µg twice weekly (Estraderm, patch system) over 3 months and 25 µg twice weekly from months 3 to 6 to achieve epiphyseal closure. From month 6 to 12, we intended to treat the patient with 25 µg twice weekly, but he was administered 25 µg only once weekly. The dose then increased to 50 and 25 µg weekly for 12 months (months 12–24) and reduced to 12.5 µg twice weekly for further 12 months (months 24–36). 1,000 IU vitamin D and 1,000 mg calcium were administrated daily in months 6 to 36.

Measurement of the Bone Mineral Density

Bone mineral density was assessed by dual energy X-ray absorptiometry (DEXA) (model DPX-L, Lunar Corporation, Madison, WI, USA). Analysis was performed using software version 1.31. The T-score was defined as the deviation from mean bone density in healthy young adults of similar gender and ethnicity. The Z-score was derived from the mean bone density of adults of similar age and gender. Forearm measurement at the distal radius (left) was performed by QCT (model: Stractec XCT-900, pQCT, Stratec Medizintechnik GmbH Pforzheim, Germany).

Biochemical Measurements

Blood samples were obtained by venipuncture after an overnight fast. Estradiol was determined by competitive immunoassay (DPC Biermann GmbH Bad Nauheim, Germany), estrone and androstenedione by RIA (Diagnostic Systems Laboratories GmbH, Sinsheim, Germany), 17-OH-progesterone by RIA (BioSource GmbH, Solingen, Germany), and DHEAS by electroluminescence (DPC Biermann GmbH Bad Nauheim, Germany). Cortisol, prolactin, testosterone, LH and FSH were measured by chemiluminescence assay (Bayer Vital GmbH, Fernwald, Germany).

GH was determined by chemiluminescent immunometric assay (Nichols Institute Diagnostics GmbH, Bad Nauheim, Germany) with intraassay and interassay coefficients of variation (CVs) for a low point on the standard curve at 5.4% and 7.9%, respectively. IGF-I concentrations were measured by immunoradiometric assay (Nichols Institute Diagnostics GmbH, Bad Nauheim, Germany) with an intraassay and interassay CVs for low IGF-I concentrations at 2.4% and 5.2%, respectively.

PTH was determined by chemiluminescent immunometric assay (DPC Biermeann GmbH Bad Nauheim, Germany), 25-hydroxy vitamin D by RIA (Byk-Sangtec Diagnostica GmbH, Dietzenbach, Germany), osteocalcin by RIA (Brahms Diagnostica GmbH, Berlin, Germany), bone-specific AP by enzymatic luminescence (Metra Biosystems GmbH, Osnabrueck, Germany) and aminoterminal collagen type I telopeptide by enzyme-linked immunosorbent assay (Ortho-Clinical Diagnostics GmbH, Neckargemuend, Germany).

HOMA IR (homeostasis model assessment of insulin resistance – (fasting insulin µU/ml x fasting plasma glucose mmol/l)/22.5 – a well-accepted parameter for insulin resistance determination) was applied before and after estrogen treatment [14–16].

Results

Bone age as assessed by roentgenographic standards for bone development by Gruelich and Pyle was 16.5 years before treatment. After estrogen replacement, bone maturation progressed and phalangeal epiphysis closed after 12 months (Fig. **1**).

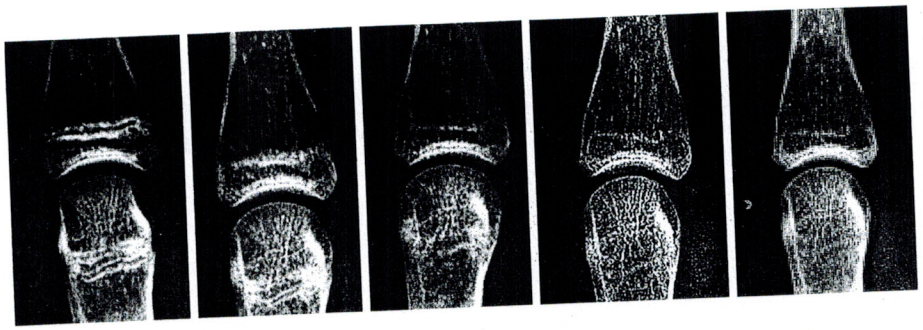

Fig. 1 X-ray images of the development of the epiphyseal closure (base of the left digitus IV) before and during estradiol replacement therapy in the propositus.

Spongiosa-hydroxyapatite of the radius assessed by quantitative computed tomography changed from 52 to 83, 51, 69 and 71 mg/cm³ (120–160), while bone mineral density of the lumbar spine assessed by dual energy X-ray-absorptiometry (normal value > 1.150) increased from 0.971 (T-Score -2.24) to 1.128 (–0.93) g/cm² after 24 months during estrogen replacement therapy at 25–50 µg twice weekly. Bone mineral density decreased to 1.021 (–1.82) g/cm² at 12.5 µg estradiol twice weekly over 12 months (Fig. **2**, Table **1**).

Osteocalcin and aminoterminal collagen type I telopeptide – as a bone formation and bone resorption parameters, respectively – did not increase until high-dose estrogen replacement, and then decreased after 12, 24 and 36 months (Table **1**).

Estradiol levels first increased to a high normal value during treatment with 50 µg estradiol twice weekly, and declined later on at lower doses. Estradiol serum levels were inversely related to LH and FSH levels. Testosterone levels changed from 31.2 nmol/l at baseline to 3.8, 22.1, 7.1 and 22.0 nmol/l (9.5–30) after 6, 12, 24 and 36 months, and were closely related to basal and stimulated LH and FSH levels at 100 µg GnRH (Table **2**).

Lipoprotein (a) increased from 20 mg/dl at baseline to 60 and 62 mg/dl after 6 and 12 months during 50 µg estradiol twice weekly, and then decreased to 24 and 25 mg/dl after 24 and 36 months at lower dosages, whereas total cholesterol, HDL, LDL and triglycerides did not change. AUC glucose after an oral glucose load (100 g) decreased continuously, while AUC insulin remained stable after 6 months (Fig. **3**). HOMA IR decreased during treatment with 75 µg estrogen weekly and increased afterwards at 25 µg weekly (Table **3**).

No loss of libido or notable gynecomastia was reported by the patient. Interestingly, the patient was very attached to his mother, and developed a progredient compulsion neurosis (such as closing bottles and windows) after 24 months of treatment.

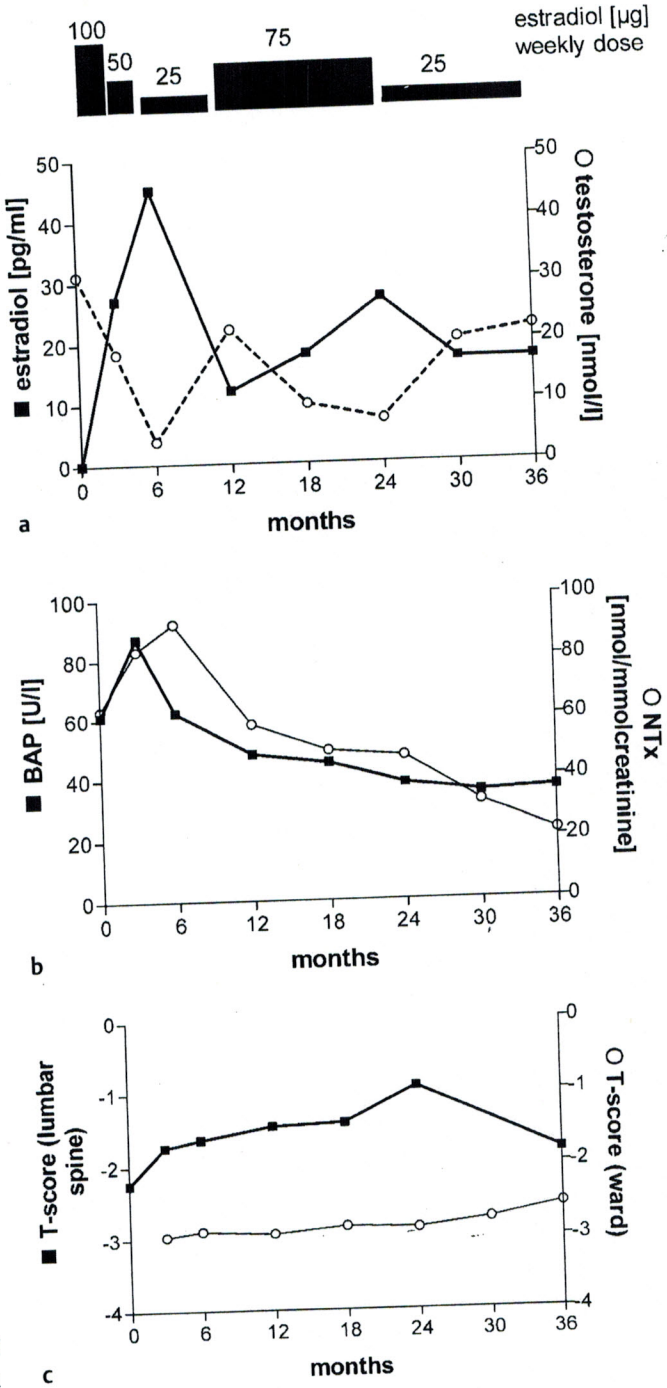

Fig. 2 Estradiol, testosterone levels (**a**); bone specific phosphatase (BAP), aminoterminal collagen type I telopeptide (NTx) (**b**); T-score of the lumbar spine and of the ward triangle (**c**) before and during estradiol replacement therapy in the propositus.

Discussion

The present case illustrates the essential role of estrogens in bone mineralization and maturation in males. Three other men affected with congenital aromatase deficiency have been reported so far [1,2,10]. Bilezikian et al. have described skeletal development in a 24-year-old male with conjugated estrogens over 3 years [10], and Rochira et al. have reported on the effects of transdermal estrogen treatment at varying doses on bone mineral density and hormonal parameters [6]. We present the results

Table 1 Changes in bone metabolism during estradiol replacement therapy in the propositus

	Baseline	3 m.	6 m.	12 m.	18 m.	24 m.	30 m.	36 m.	Normal
BMD, distal radius, QCT	52	66	83	51	n.d.	69	74	71	120–160 mg/cm³
Lumbar Spine, DEXA									
BMD	0.971	0.996	1.043	1.065	1.071	1.128	n.d.	1.021	>1.150 g/cm²
T-Score	−2.24	−1.74	−1.64	−1.46	−1.42	−0.93	n.d.	−1.82	<−1.0
Ward triangle, DEXA									
BMD	n.d.	0.575	0.584	0.579	0.590	0.587	0.602	0.628	>1.020 g/cm²
T-Score	n.d.	−2.96	−2.89	−2.93	−2.84	−2.87	−2.75	−2.56	<−1.0
Calcium	2.35	2.35	2.35	2.29	2.60	2.34	2.51	2.42	2.12–2.62mmol/l
Phosphorous	3.5	3.4	3.5	3.7	3.3	2.9	2.9	3.3	2.5–4.5 mg/dl
PTH intact	32	48	46	16	18	20	23	45	12–72 pg/ml
25-hydroxy vitamin D	7	7	15	17	10	19	12	14	12–120 ng/ml
Osteocalcin	13	n.d.	52	51	52	35	35	27	24–70 µg/l
Alkaline Phosphatase (AP)	217	285	195	162	152	103	101	63	60–180 U/l
Bone-specific AP	61	87	65	48	45	38	35	36	10–26 U/l
NT_X	63	83	92	58	49	47	32	22	5–54 nmol/mmol creat.

QCT, quantitative computed tomography (radius); DEXA, dual energy X-ray-absorptiometry; BMD, bone mineral density; NTX, aminoterminal collagen type I telopeptide; n.d., not done

Table 2 Changes in plasma hormone levels during estradiol replacement therapy in the propositus

	Baseline	3 m.	6 m.	12 m.	18 m.	24 m.	30 m.	36 m.	Normal
Weekly dosage of Estradiol (µg)		100	50	25	75	75	25	25	
Estradiol	<10	27	45	12	18	27	17	17	10–50 pg/ml
Estrone	17	31	34	12	n.d.	26	39	30	30–85 ng/ml
17-OH-Progesterone	1.9	0.27	0.15	0.85	1.0	0.51	0.97	1.20	0.3–2.0 µg/l
Testosterone	31.2	18.1	3.8	22.1	9.7	7.1	20.1	22.0	9.5–30nmol/l
Androstenedione	3.5	1.7	1.5	4.0	2.2	3.0	3.1	3.4	1.3–3.1 µg/l
SHBG	12	17	18	23	18	13	13	13	15–70 nmol/l
LH basal	6.0	2.1	1.9	2.8	3.2	1.3	4.6	3.6	2–10 mIU/ml
LH (30 min after GnRH)	39.0	20.1	12.8	32.2	33.2	22.2	10.7	21.9	(3-fold of basal value)
FSH	11.0	1.8	1.2	7.8	2.9	1.6	3.3	6.5	1–7 mIU/ml
FSH (30 min after GnRH)	18.5	4.8	2.4	15.2	7.6	4.6	34.2	10.1	(2-fold of basal value)
IGF-I	156	160	144	126	148	158	105	123	122–400 µg/l

Table 3 Changes in glucose metabolism and lipid parameter during estradiol replacement therapy in the propositus

	Baseline	3 m.	6 m.	12 m.	18 m.	24 m.	30 m.	36 m.	SI (normal range)
Weight	120	120	120	124	127	127	130	130	kg
Height	197	197	197	197	197	197	197	197	cm
AUC Glucose	17,316	13,770	12,780	14,220	12,840	12,990	11,520	10,920	mg/dl/min
AUC Insulin	277	209	139	n.d.	96	116	119	109	U/ml/h
HOMAIR	3.6	3.5	3.5	3.7	1.7	2.7	3.9	3.8	
Triglycerides	268	195	261	278	308	252	339	341	mg/dl
Total Cholesterol	176	167	198	185	174	172	170	194	mg/dl
LDL-Cholesterol	112	120	110	108	97	98	91	128	mg/dl
HDL-Cholesterol	21	26	31	27	27	27	24	44	mg/dl
LDL/HDL	5.37	4.66	3.56	4.00	3.59	3.63	3.79	2.91	
Lipoprotein a	20	39	60	62	35	24	18	25	<30 mg/dl
Apolipoprotein A1	82	98	127	120	133	120	104	105	115–190 mg/dl
Apolipoprotein B	101	102	112.3	128	126	85	101	87	60–160 mg/dl

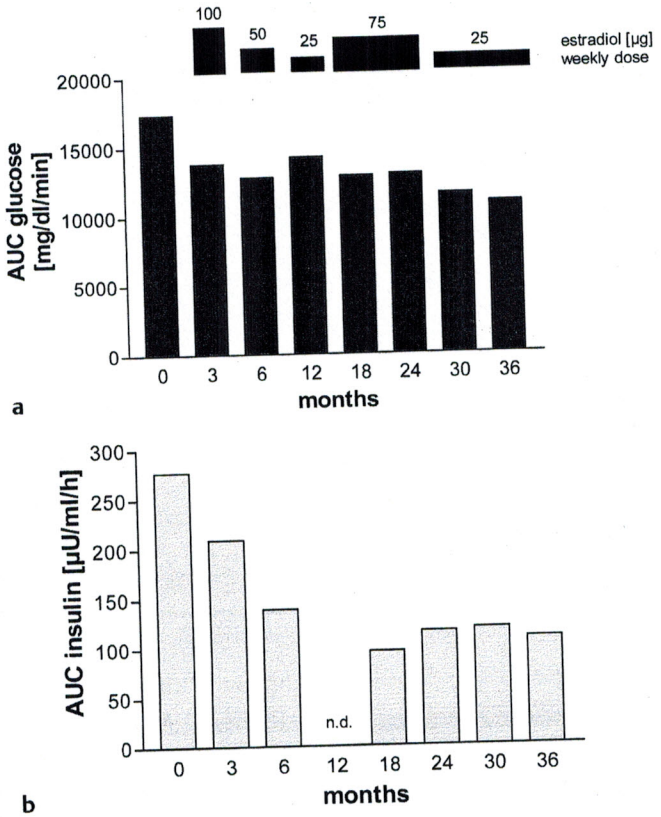

Fig. 3 Area under the curve (AUC) for glucose (**a**) and insulin (**b**) after an oral glucose load (100 g) before and during estradiol replacement therapy in the propositus.

of treatment with transdermal estradiol over 3 years on skeletal development, hormonal parameters, and glucose metabolism in males with congenital aromatase deficiency resulting from a novel homozygous inactivating mutation of the *CYP19* ($P450_{arom}$) gene [4].

The results of the present study provide evidence that both androgens and estrogens are important determinants of peak bone mass in the male skeleton. Metacarpal and phalangeal epiphysis closed after 12 months. Interestingly, bone mineral density in the lumbar spine rapidly increased with declining androgen levels and rising estrogen concentrations. The highest peak bone mass of the lumbar spine was calculated at 75 µg weekly, divided into two doses. In this phase of treatment, testosterone concentrations were at the lower end of the reference range. The observation of the inverse correlation of estrogens to LH and FSH levels clarifies that estrogens, in addition to testosterone and inhibin, regulate the secretion of gonadotropins in males [3,12,17–21]. Bone mineral density decreased after tapering the estradiol dose to 12.5 µg twice weekly. Spongiosa architecture and density profile analysis measured by quantitative computer tomography on the distal radius revealed a decelerated increase of the hydroxyapatite during estrogen replacement. Bone formation and resorption parameters declined simultaneously during estrogen replacement therapy.

In the last few years, an association has been demonstrated between impaired glucose tolerance with insulin resistance and lack of estrogens with elevated testosterone concentrations in aromatase-knockout and estrogen receptor-knockout male mice [22–24]. Recently, Maffei et al. reported on the occurrence of insulin resistance and diabetes mellitus type 2 in a male with an aromatase deficiency during high-dose testosterone treatment [1]. However, supraphysiological doses of testosterone administration do not affect insulin sensitivity in normal men, indicating that severe impairment of estrogen to testosterone ratio is responsible for the development of impaired glucose tolerance and insulin resistance. Confirming suggestions from previous findings [12], we also saw an improvement in glucose tolerance and insulin sensitivity after oral glucose load during estrogen replacement therapy, which was verified by glucose and insulin concentrations AUC analysis over 36 months. After 6 months, changes in HOMA IR as a parameter for insulin resistance were closely related to testosterone concentrations and varying doses of estrogen replacement. From these observations, we can conclude that measurements of insulin resistance and bone mineral density by DEXA reveal a close relationship to the optimal dose of estrogen administration in males with aromatase deficiency.

Interestingly, improvement in glucose metabolism was accompanied by weight gain. The observations on weight gain and nearly unchanged lipid levels during estrogen administration in the present study indicate that estrogen might have a direct affect on insulin sensitivity, and emphasizes high-serum testosterone as a possible influence on insulin sensitivity where estrogen activity is absent [1,12]. Lipoprotein a, as an independent risk factor for cardiovascular diseases, was related to changes from varying doses of transdermal estrogen and to testosterone concentration. The influence of estrogens and androgens on lipoprotein a are consistent with the observations of Zmuda et al., who have shown that testosterone plus testolactone, an aromatase inhibitor, reduce lipoprotein a levels in males [25,26].

In conclusion, this study clearly demonstrates the role of estrogens in achieving bone mineralization and maturation in human males. Improved glucose metabolism after estrogen replacement therapy suggests a probable role of sex steroids in insulin sensitivity. To normalize estrogen levels and maintain bone mass in adult males with aromatase deficiency, the optimal dose of transdermal estrogen replacement may be 50–75 µg weekly, divided into two doses.

References

[1] Maffei L, Murata Y, Rochira V, Tubert G, Aranda C, Vazquez M, Clyne CD, Davis S, Simpson ER, Carani C. Dysmetabolic syndrome in a man with a novel mutation of the aromatase gene: effects of testosterone, alendronate, and estradiol treatment. J Clin Endocrinol Metab 2004; 89: 61–70

[2] Morishima A, Grumbach MM, Simpson ER, Fisher C, Qin K. Aromatase deficiency in male and female siblings caused by a novel mutation and the physiological role of estrogens. J Clin Endocrinol Metab 1995; 80: 3689–3698

[3] Deladoey J, Fluck C, Bex M, Yoshimura N, Harada N, Mullis PE. Aromatase deficiency caused by a novel P450arom gene mutation: impact of absent estrogen production on serum gonadotropin concentration in a boy. J Clin Endocrinol Metab 1999; 84: 4050–4054

[4] Herrmann BL, Saller B, Janssen OE, Gocke P, Bockisch A, Sperling H, Mann K, Broecker M. Impact of estrogen replacement therapy in a male with congenital aromatase deficiency caused by a novel mutation in the *CYP19* gene. J Clin Endocrinol Metab 2002; 87: 5476–5484

[5] Carani C, Qin K, Simoni M, Faustini-Fustini M, Serpente S, Boyd J, Korach KS, Simpson ER. Effect of testosterone and estradiol in a man with aromatase deficiency. N Engl J Med 1997; 337: 91 – 95
[6] Rochira V, Faustini-Fustini M, Balestrieri A, Carani C. Estrogen replacement therapy in a man with congenital aromatase deficiency: effects of different doses of transdermal estradiol on bone mineral density and hormonal parameters. J Clin Endocrinol Metab 2000; 85: 1841 – 1845
[7] Simpson ER, Mahendroo MS, Means GD, Kilgore MW, Hinshelwood MM, Graham-Lorence S, Amarneh B, Ito Y, Fisher CR, Michael MD et al. Aromatase cytochrome P450, the enzyme responsible for estrogen biosynthesis. Endocr Rev 1994; 15: 342 – 355
[8] Simpson ER. Genetic mutations resulting in estrogen insufficiency in the male. Mol Cell Endocrinol 1998; 145: 55 – 59
[9] Simpson ER, Michael MD, Agarwal VR, Hinshelwood MM, Bulun SE, Zhao Y. Cytochromes P450 11: expression of the *CYP19* (aromatase) gene: an unusual case of alternative promoter usage. Faseb J 1997; 11: 29 – 36
[10] Bilezikian JP, Morishima A, Bell J, Grumbach MM. Increased bone mass as a result of estrogen therapy in a man with aromatase deficiency. N Engl J Med 1998; 339: 599 – 603
[11] Rochira V, Balestrieri A, Faustini-Fustini M, Carani C. Role of estrogen on bone in the human male: insights from the natural models of congenital estrogen deficiency. Mol Cell Endocrinol 2001; 178: 215 – 220
[12] Grumbach MM, Auchus RJ. Estrogen: consequences and implications of human mutations in synthesis and action. J Clin Endocrinol Metab 1999; 84: 4677 – 4694
[13] Grumbach MM. Estrogen, bone, growth and sex: a sea change in conventional wisdom. J Pediatr Endocrinol Metab 2000; 13: 1439 – 1455
[14] Radziuk J. Insulin sensitivity and its measurement: structural commonalities among the methods. J Clin Endocrinol Metab 2000; 85: 4426 – 4433
[15] Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985; 28: 412 – 419
[16] Haffner SM, Miettinen H, Stern MP. The homeostasis model in the San Antonio Heart Study. Diabetes Care 1997; 20: 1087 – 1092
[17] Rochira V, Balestrieri A, Faustini-Fustini M, Borgato S, Beck-Peccoz P, Carani C. Pituitary function in a man with congenital aromatase deficiency: effect of different doses of transdermal E2 on basal and stimulated pituitary hormones. J Clin Endocrinol Metab 2002; 87: 2857 – 2862
[18] Finkelstein JS, Whitcomb RW, O'Dea LS, Longcope C, Schoenfeld DA, Crowley WF Jr. Sex steroid control of gonadotropin secretion in the human male. I. Effects of testosterone administration in normal and gonadotropin-releasing hormone-deficient men. J Clin Endocrinol Metab 1991; 73: 609 – 620
[19] Veldhuis JD, Dufau ML. Estradiol modulates the pulsatile secretion of biologically active luteinizing hormone in man. J Clin Invest 1987; 80: 631 – 638
[20] Veldhuis JD, Rogol AD, Samojlik E, Ertel NH. Role of endogenous opiates in the expression of negative feedback actions of androgen and estrogen on pulsatile properties of luteinizing hormone secretion in man. J Clin Invest 1984; 74: 47 – 55
[21] Vanderschueren D, Bouillon R. Estrogen deficiency in men is a challenge for both the hypothalamus and pituitary. J Clin Endocrinol Metab 2000; 85: 3024 – 3026
[22] Couse JF, Korach KS. Estrogen receptor null mice: what have we learned and where will they lead us? Endocr Rev 1999; 20: 358 – 417
[23] Takeda K, Toda K, Saibara T, Nakagawa M, Saika K, Onishi T, Sugiura T, Shizuta Y. Progressive development of insulin resistance phenotype in male mice with complete aromatase (*CYP19*) deficiency. J Endocrinol 2003; 176: 237 – 246
[24] Jones ME, Thorburn AW, Britt KL, Hewitt KN, Wreford NG, Proietto J, Oz OK, Leury BJ, Robertson KM, Yao S, Simpson ER. Aromatase-deficient (ArKO) mice have a phenotype of increased adiposity. Proc Natl Acad Sci U S A 2000; 97: 12735 – 12740
[25] Zmunda JM, Thompson PD, Dickenson R, Bausserman LL. Testosterone decreases lipoprotein(a) in men. Am J Cardiol 1996; 77: 1244 – 1247
[26] Zmuda JM, Fahrenbach MC, Younkin BT, Bausserman LL, Terry RB, Catlin DH, Thompson PD. The effect of testosterone aromatization on high-density lipoprotein cholesterol level and postheparin lipolytic activity. Metabolism 1993; 42: 446 – 450