Comparison of bone mineral density and body proportions between women with complete androgen insensitivity syndrome and women with gonadal dysgenesis

T S Han, D Goswami, S Trikudanathan, S M Creighton and G S Conway
Department of Endocrinology, University College London Hospitals, 250 Euston Road, London NW1 2PQ, UK
(Correspondence should be addressed to G S Conway; Email: g.conway@ucl.ac.uk)

Abstract

Objectives: To compare bone mineral density (BMD) and body proportions between women with complete androgen insensitivity syndrome (CAIS) and with gonadal dysgenesis (GD).

Setting: Adult Disorders of Sexual Development and Ovarian Failure Clinics at University College London Hospitals.

Design: Retrospective cross-sectional study of three groups of women aged 17–58 years with varying degrees of exposure to sex hormones and different combinations of sex chromosomes. Forty-six subjects had CAIS, 18 had GD and 46,XY (GD(XY)), and 25 had GD and 46,XX (GD(XX)). In addition, body proportions of subgroups of these women were analysed.

Outcome measures: Oestrogen therapy, karyotype, anthropometry and BMD.

Results: Height differed between groups ($F$ ratio 5.2, $P = 0.007$), with GD(XX) women being the shortest (mean ± S.D.: 1.66 ± 0.10 m), GD(XY) women the tallest (1.74 ± 0.09 m) and CAIS women were in-between (1.70 ± 0.07 m). Delayed gonadectomy resulted in taller stature in CAIS women ($P = 0.011$). The ratio of lower to upper body length in GD(XY) women was significantly ($P = 0.001$) greater than that of CAIS women. Multivariate logistic regression analysis (adjusted for age and height) showed that among women with XY karyotype, GD(XY) women were 5.2 times (95% confidence interval (CI): 1.3–20.1, $P = 0.018$) more likely than CAIS women to have a low hip BMD. This difference was not evident among women with GD of different karyotypes ($P = 0.938$). Spinal BMD did not differ between subject groups. Further adjustment for oestrogen replacement did not alter these relationships.

Conclusions: Taller stature in late gonadectomised CAIS women suggests an oestrogen deficiency in these women prior to gonadectomy. Increased lower to upper body ratio in GD(XY) women compared with the other groups implies that these subjects have the greatest degree of oestrogen deficiency in puberty. Androgen rather than sex chromosomes may play an important role in cortical bone mineralisation in CAIS women, probably via estrogen receptor-α either directly or via aromatisation during critical periods of growth prior to gonadectomy.

Introduction

Complete androgen insensitivity syndrome (CAIS) is caused by loss of function mutations of the androgen receptor (AR) (1, 2) and affects 1 in 20 000–90 000 births (3, 4). Individuals with CAIS (46,XY karyotype) are phenotypically female with normal pubertal development but lack Müllerian duct structures and androgen-dependent body hair. They typically present with inguinal hernia during infancy or with primary amenorrhea during adolescence (5).

In comparison, women with gonadal dysgenesis (GD) and 46,XY karyotype (GD(XY)) (also known as Swyer’s syndrome) also present with primary amenorrhea and are characterised by streak gonads with normal uterine development after exposure to oestrogen. Women with GD(XY) lack a gonadal source of androgen and oestrogen but retain an adrenal androgen production and have intact AR function. Women with CAIS and GD(XY) are taller than women with 46,XX karyotype (6, 7). Tall stature in these conditions may be contributed to by both a Y chromosome effect and oestrogen deficiency in puberty delaying closure of epiphysis (8, 9). An ‘oestrogen effect’ can be explored by comparing exposure to exogenous oestrogens with final height and by comparing upper and lower body proportions. For most individuals with CAIS and GD(XY), administration of oestrogens occurs soon after gonadectomy in those who are at the age of puberty (11 years) or older.

Several studies have reported osteopaenia in women with CAIS (10, 11) even after adjusting for bone size using volumetric density (12). Oestrogen replacement
has been shown to improve bone mineral density (BMD) in women with CAIS (13, 14). Bone density in GD(XY) has not been studied.

It is not clear whether low BMD in CAIS is influenced by inadequate oestrogen replacement or lack of androgen action on bone (10). This question cannot be explored by comparing a CAIS group with normal controls from whom they differ in three ways: the presence of a Y chromosome, oestrogen deficiency and androgen resistance. To address the effect of androgen on bone, we have compared women with CAIS with women with GD(XY) who share the Y chromosome and oestrogen deficiency but who have normal sensitivity to androgens. In addition, women with GD and 46,XX karyotype (GD(XX)) were also included to determine the effects of sex chromosomes on BMD by comparing them with GD(XY) women. The present study also evaluated hormonal effects on stature and body proportions in these three groups of women.

Methods

Subjects and study design

This retrospective cross-sectional study of Caucasian women who attended the Adult Disorders of Sexual Development and Ovarian Failure Clinics at University College Hospital, London, comprised 46 women with CAIS, 18 women with GD(XY) and 25 with GD(XX). The varying degrees of exposure to sex hormones and various combinations of sex chromosomes in these women enabled the present study to match them for XY karyotype and status of GD. Body proportions of subgroups of 14 CAIS, 7 GD(XY) and 9 GD(XX) women were also assessed. The study was approved by the Ethics Committee of University College London Hospitals Trust.

Diagnosis

The clinical diagnosis of women with CAIS was based on unambiguous female phenotype, scant androgen-dependent body hair, karyotype, testicular histology and absent uterus (15). In adults who have been exposed to high circulating testosterone concentrations, usually for some years, we consider this clinical diagnosis to be secure. We have, wherever possible, sought congruity between classical endocrine and gonad histology features of CAIS before accepting the diagnostic label, although in a tertiary adult setting every detail of previous workup is not uniform, and so this data are not presented here, but this topic has been described previously (16). After gonadectomy, the main competing diagnoses that can be reliably excluded are 5-α reductase deficiency (SRD5A2) and forms of congenital adrenal hyperplasia (e.g. P450 oxidoreductase deficiency) that can be detected using urinary steroid profiling – this test has been completed in all cases. 17β-hydroxysteroid dehydrogenase deficiency was the only other competing diagnosis that has not been formally excluded. Subjects with GD were diagnosed as unambiguous female phenotype with streak gonads and intact Müllerian structures and were divided into those with 46,XY or 46,XX karyotype.

Hormone replacement therapy (HRT)

Age of gonadectomy, age at starting oestrogen and cumulative oestrogen deficiency years were recorded. Cumulative oestrogen deficiency years were estimated from non-compliance after initiation of oestrogen replacement therapy adding, in the case of GD(XY) and GD(XX), the number of years after age 11 that the diagnosis was delayed. Oestrogen replacement in this group was based on patient choice and the vast majority received standard adult doses of oestradiol valerate 2 mg, conjugated equine oestrogens 0.625 mg, transdermal oestradiol 50 µg daily or oestradiol implant 50 mg every 6 months. Those with a uterus and on the combined oral contraceptive pill had a ‘pill-free’ week every month. Most of CAIS women used unopposed oestrogens and two of them chose to use testosterone replacement using mixed testosterone esters (Sustanon) 250 mg every 4 weeks. The compliance for oestrogen was overall good in our cohort of patients, being more than 80% in most cases.

Parameters that describe oestrogen usage over time are problematic as some are influenced by age (e.g. the oestrogen index = years of HRT/age) and all are based on recall in this age group. In addition, adult clinics receive cases from a variety of paediatric centres in which the method and pace of induction of puberty vary. In previous studies of oestrogen-deficient young women, we have found that ‘oestrogen start age’ is a reliable parameter and ‘cumulative years of oestrogen deficiency after the age of 11’ (i.e. no HRT) is also reproducible.

Anthropometry and BMD

Subjects’ weight, height and sitting height (upper body length) were measured by standard balance and stadiometer. Body mass index was calculated as weight divided by height squared (kg/m²). Lower body length was calculated from the difference between height and sitting height. From these parameters, ratios of lower body to height or to upper body length were computed. Bone density measurements in all subjects were made using a dual energy X-ray absorptiometer (DEXA; Hologic QDR 4500 fan beam, Hologic Inc., Waltham, MA, USA). Methods of BMD measurements using the current DEXA have been essentially unchanged compared with the previous DEXA (Hologic QDR 1000 fan beam) used at the same department described by Han et al. (17). Total spinal BMD was obtained between lumbar levels 1–4 (L1–L4) and total hip BMD...
at femoral neck, trochanteric and intertrochanteric regions. The results of BMD were provided in g/cm² and \( T \)-scores that expressed BMD statistically in terms of number of standard deviations by which a result differed from the mean young women (17).

**Statistical analysis**

The present study used statistical package (SPSS v14, Chicago, IL, USA) for analyses. ANOVA was used for assessing differences between groups and generalised linear model for calculating adjusted means. Multivariate logistic regression analysis was employed using BMD \( T \)-score as dependent variable and subject groups as independent variables. The relationships were analysed with adjustments for potential confounding factors including age, height, and oestrogen therapy.

For the purpose of logistic regression analysis, continuous variables were converted to binary variables. BMD at the hip and spine was categorised into high and low groups using cut-offs corresponding to \( T \)-score of \(-1\) (reference groups had BMD above these \( T \)-scores). Height, age and oestrogen therapy were dichotomised at the group mean values to create binary variables for analysis. Independent \( t \)-tests were used to compare the differences in body proportions between groups.

**Results**

Subjects were between 18 and 58 years old with the mean age being higher in the CAIS group (Table 1). Women with CAIS had gonadectomy and oestrogen replacement at an earlier age than GD(XX) women and they also had the lowest duration of oestrogen deficiency. There were no significant differences (\( \chi^2 = 0.245, P = 0.855 \)) in the proportions of women who did not take HRT (15.9% of CAIS women, 16.7% of GD(XX) women). CAIS women had gonadectomy and oestrogen replacement at an earlier age than GD(XX) women and also had the lowest duration of oestrogen deficiency. There were no significant differences (\( \chi^2 = 0.245, P = 0.855 \)) in the proportions of women who did not take HRT (15.9% of CAIS women, 16.7% of GD(XX) women).

Height differed between groups (\( F \) ratio 5.2, \( P = 0.007 \)), with GD(XX) group being the shortest (mean 1.66 m ± s.d. 0.10), GD(XX) the tallest (1.74 m ± 0.09) and CAIS intermediate in stature (1.70 m ± 0.07). Sixteen women had AR mutations identified as part of their previous workup. These 16 women did not differ by any measured parameter from the 30 women with no genetic workup (Table 2).

Table 1 shows body proportions in different subject groups. GD(XX) women were significantly taller than CAIS women and GD(XX) women. CAIS women and GD(XX) women had almost identical mid-parental height. CAIS women achieved their expected adult height based on mid-parental height whereas GD(XX) women had adult height exceeding their expected height by 7 cm. There were significant correlations between adult height and mid-parental height both in CAIS women (\( r = 0.63, P = 0.022 \)) and GD(XX) women (\( r = 0.77, P = 0.041 \)). All groups had similar upper body length, but GD(XX) women had greater ratio of lower body length to height as well as ratio of lower to upper body length than CAIS women and GD(XX) women. Figure 2 shows a comparison of the lower to upper body

**Table 1 Characteristics of women with CAIS and women with gonadal dysgenesis.**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>CAIS (n = 46)</th>
<th>GD(XX) (n = 18)</th>
<th>GD(XX) (n = 25)</th>
<th>ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>32.2 (10.7)</td>
<td>29.3 (8.5)</td>
<td>25.4 (7.3)</td>
<td>4.3</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>67.7 (12.3)</td>
<td>71.4 (14.0)</td>
<td>65.8 (21.3)</td>
<td>0.7</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.70 (0.07)</td>
<td>1.74 (0.09)</td>
<td>1.66 (0.10)</td>
<td>5.2</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.5 (4.2)</td>
<td>23.5 (4.1)</td>
<td>23.8 (6.1)</td>
<td>0.0</td>
</tr>
<tr>
<td>Hip BMD (( T )-score)</td>
<td>-0.58 (0.99)</td>
<td>-0.66 (1.24)</td>
<td>-1.14 (1.15)</td>
<td>3.7</td>
</tr>
<tr>
<td>Adjusted hip BMD (( T )-score)</td>
<td>-0.55 (1.07)</td>
<td>-0.67 (1.04)</td>
<td>-1.58 (1.26)</td>
<td>4.9</td>
</tr>
<tr>
<td>Spine BMD (( T )-score)</td>
<td>-1.28 (1.19)</td>
<td>-0.88 (1.58)</td>
<td>-1.59 (1.15)</td>
<td>3.0</td>
</tr>
<tr>
<td>Adjusted spine BMD (( T )-score)</td>
<td>-1.29 (1.22)</td>
<td>-0.88 (1.10)</td>
<td>-1.78 (1.10)</td>
<td>2.2</td>
</tr>
<tr>
<td>Gonadectomy age (years)</td>
<td>15.9 (7.3)</td>
<td>20.3 (6.0)</td>
<td>–</td>
<td>5.0</td>
</tr>
<tr>
<td>Age at start of oestrogen (years)</td>
<td>17.5 (5.3)</td>
<td>18.7 (4.2)</td>
<td>20.6 (4.3)</td>
<td>2.6</td>
</tr>
<tr>
<td>Oestrogen deficiency (years)</td>
<td>3.1 (5.2)</td>
<td>8.2 (4.6)</td>
<td>8.9 (4.8)</td>
<td>11.8</td>
</tr>
</tbody>
</table>

CAIS, complete androgen insensitive syndrome; GD, gonadal dysgenesis; ANOVA, analysis of variance.

*Adjusted means for age and height using general linear model.
length ratios of women in the present study to those from a reference population of normal 21-year-old Dutch men and women (18).

In all groups, the mean BMD T-score at the hip was higher than that at the spine (Table 3). Both hip and spinal BMD differed between the three groups. In particular, the CAIS group had the highest values of BMD at the hip. Figure 3 shows that, as expected, there were a substantial number of women with BMD in the range of osteopaenia and osteoporosis. Only 24% of women with CAIS had low hip BMD (T-score below −1.0) compared with 50% of women with GD(XY) and 55% of GD(XX) women (P < 0.05). Low spinal BMD was more prevalent in all subject groups but little difference between CAIS and GD(XY) groups was observed.

Multivariate logistic regression analyses (Fig. 4a and b) of the risk of low BMD with adjustments for age and height showed that when women with 46,XY chromosomes were compared, using women with CAIS as reference group, women with GD(XY) were 5.2 (95% confidence interval (CI): 1.3–20.1, P = 0.018) times more likely to have low BMD at the hip. When women with GD were compared, using women with GD(XX) as reference group, women with GD(XY) did not have significantly different BMD at the hip (odds ratio (OR) 1.06, 95% CI: 0.3–4.4, P = 0.938). BMD at the spine did not differ between subject groups. Controlling for each other’s group did not change these relationships substantially. Further adjustments for the duration of oestrogen deficiency and HRT status in

Table 2 Characteristics of complete androgen insensitive syndrome (CAIS) women without or with available androgen receptor (AR) mutation information.

| AR mutation information | Not available (n=30) | Available (n=16) | Difference | p  
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Height (m)</td>
<td>1.70 (0.07)</td>
<td>1.70 (0.8)</td>
<td>0.00</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>66.5 (10.0)</td>
<td>70.0 (15.9)</td>
<td>−3.5</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.1 (3.3)</td>
<td>24.2 (5.6)</td>
<td>−1.2</td>
</tr>
<tr>
<td>Hip BMD (T-score)</td>
<td>−0.62 (1.09)</td>
<td>−0.51 (0.79)</td>
<td>−0.11</td>
</tr>
<tr>
<td>Spinal BMD (T-score)</td>
<td>−1.24 (1.27)</td>
<td>−1.34 (1.09)</td>
<td>0.10</td>
</tr>
<tr>
<td>Gonadectomy age (years)</td>
<td>16.2 (7.9)</td>
<td>15.6 (6.5)</td>
<td>0.6</td>
</tr>
<tr>
<td>Age at start of oestrogen deficiency (years)</td>
<td>17.1 (5.1)</td>
<td>18.3 (5.8)</td>
<td>−1.2</td>
</tr>
<tr>
<td>Proportions not on HRT (%)</td>
<td>23.3</td>
<td>12.5</td>
<td>10.8</td>
</tr>
</tbody>
</table>

Table 3 Body dimensions in subgroups of women.

<table>
<thead>
<tr>
<th></th>
<th>CAIS (n=14)</th>
<th>GD(XY) (n=7)</th>
<th>GD(XX) (n=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>42.1 (10.5)</td>
<td>36.7 (10.5)</td>
<td>27.9 (7.3)</td>
</tr>
<tr>
<td>Gonadectomy age (years)</td>
<td>21.3 (9.5)</td>
<td>22.1 (2.3)</td>
<td>−</td>
</tr>
<tr>
<td>Oestrogen deficiency (years)</td>
<td>8.2 (10.0)</td>
<td>7.8 (5.4)</td>
<td>5.7 (2.7)</td>
</tr>
<tr>
<td>Mid-parental height (m)</td>
<td>1.69 (0.04)</td>
<td>1.69 (0.06)</td>
<td>−</td>
</tr>
<tr>
<td>UB length (m)</td>
<td>0.88 (0.04)</td>
<td>0.87 (0.02)</td>
<td>0.87 (0.03)</td>
</tr>
<tr>
<td>LB length (m)</td>
<td>0.81 (0.05)</td>
<td>0.89 (0.06)</td>
<td>0.82 (0.08)</td>
</tr>
<tr>
<td>LB:height ratio</td>
<td>0.48 (0.01)</td>
<td>0.51 (0.02)</td>
<td>0.48 (0.03)</td>
</tr>
<tr>
<td>LB:UB ratio</td>
<td>0.92 (0.06)</td>
<td>1.02 (0.07)</td>
<td>0.94 (0.10)</td>
</tr>
</tbody>
</table>

CAIS, complete androgen insensitivity syndrome; GD, gonadal dysgenesis; UB, upper body; LB, lower body. *P<0.01, †P<0.05 compared with GD(XY) group.

Figure 1 Quadratic regression analysis to determine the relationship between height and age of gonadectomy with r² = 20% and P=0.011 in CAIS women, r² = 11% and P=0.421 in GD(XY) women and r² = 18% and P=0.002 overall.

Figure 2 Comparing lower to upper body length (LB:UB) ratios in different groups of women. Differences (95% CI) between GD(XY) minus CAIS women = 0.10 (0.05–0.15), P=0.001 and between GD(XY) minus GD(XX) women = 0.08 (−0.01 to 0.17), P=0.076. Lower to upper body ratios of normal 21-year-old Dutch males (solid horizontal line) and 21-year-old Dutch females (dashed horizontal line) are shown for comparison (18).
multivariate logistic analyses did not alter the differences in BMD between subject groups (data not shown).

Discussion

The present study examined three groups of women with varying degrees of exposure to sex hormones and various combinations of sex chromosomes, providing a unique free-living human model for the evaluation of relative contribution of these factors on the development of body proportions and bone. There was a significant increase in the risk of low BMD in GD(XY) compared with CAIS, while these differences were not observed between the two GD groups of women of different karyotypes, suggesting that androgens rather than sex chromosomes may have a role in protecting BMD in CAIS women.

In the present study, taller stature in CAIS women appeared to be determined by later age of gonadectomy and introduction of oestrogen replacement, but not by the duration of oestrogen deficiency. It has been shown previously that in comparison with normal males, CAIS women with intact gonads have increased serum levels of luteinising hormone, similar levels of testosterone and follicle stimulating hormone (15). Before gonadectomy, women with CAIS have been shown to have reduced circulating concentrations of oestradiol, which originated from both direct glandular secretion and peripheral aromatisation of androgen precursors (19). The present study provides evidence for this oestrogen-deficient state based on the association between gonadectomy age and height, suggesting that oestrogen levels sufficient to close the epiphyses are achieved only with the exogenous source post-gonadectomy. These findings are consistent with data observed in CAIS women from previous studies – adult stature of CAIS women was shown to approach their target male adult height (20), whereas a CAIS woman who underwent gonadectomy and had oestrogen replacement had reduced adult height (9). The oestrogen levels are, however, sufficient for development of a normal external female phenotype to a greater degree than that seen in the GD group.

Figure 3 Distribution of (a) hip BMD and (b) spine BMD in women with CAIS and gonadal dysgenesis.

Figure 4 Age and height-adjusted odds ratios and 95% CI to estimate the risk of (a) low BMD GD(XY) women with reference to AIS(XY) women and (b) GD(XX) women with reference to GD(XY) women.
The present study has shown that GD(XY) women had adult height exceeding their mid-parental height by 7 cm whereas this difference was not observed in CAIS women. GD(XY) women also had significantly greater ratios of lower body to height or lower body to upper body compared with CAIS women indicating that GD(XY) women are probably less oestrogenised than CAIS women during periods prior to gonadectomy since these two groups were well matched for oestrogen deficiency and age of gonadectomy in the subgroup analysis. The difference in lower to upper body ratios between CAIS and GD(XY) women reflects hormonal influences on long bone whereas the difference between GD(XY) and GD(XX) women reflects the influences from Y chromosome. The latter observation is consistent with previous observations (18, 21). It is of interest that body proportions of women with GD(XX) distinctly followed eunuchoid patterns with their ratios of lower to upper body being greater than 1.0, and they also had greater arm span than height by 5 cm (data not presented). Their exceptionally high ratio could potentially be used as a screening tool for GD(XY) in women who first present with primary amenorrhoea. More subjects are required for assessing its value in clinical practice.

The findings of greater BMD at the hip than at the spine in CAIS women in the present study are consistent with those observed by Danilovic et al. in a study of complete and partial AIS women (22). The long-term effects of androgens on BMD in free-living subjects have not been demonstrated. Results in the present study, using groups of matched women who differed only in AR sensitivity, indicated that androgens might have some direct action on cortical bone mineralisation based on two accounts: first, women with CAIS are completely resistant to androgen at AR levels; secondly, these women appeared to be oestrogen deficient as indicated by the inhibitory effects on statural growth in those receiving early oestrogen replacement (Fig. 3). Androgens have been shown to have a direct stimulatory effect on estrogen receptor (ER) of osteoblasts (23–25) and may also act on the bone via AR as well as ER (particularly ER-α) – either directly by testosterone per se or through aromatisation of androgen to oestrogen (26). The lack of relationship between the age of gonadectomy or age of introducing oestrogen replacement and BMD in CAIS (data not presented) suggests that androgens probably exert their greatest effects on bone mineralisation in early periods of life (prior to gonadectomy).

**Study limitations**

We have not been able to control for differences in the regimens for the induction of puberty. In adult clinics, we inherit cases from a wide area (throughout the South of England) and accept that every referring centre will have managed puberty differently. Previously, we tried to collect a parameter that reflects the ‘ramping up’ of oestrogen dose after introduction but there is no easy way of accurately representing this concept. It may be that women with 46,XYGD had slower introduction of low doses of HRT and women with CAIS will go straight on to average adult doses and this would contribute to their greater oestrogen deficiency. Secondly, we have focussed on the interplay between oestrogen and androgens but we could not control for the difference in the administration of progesterone. Women with CAIS do not receive progesterone while the other two groups do have exposure that may account for some of the group differences. When oestrogen replacement therapy is considered, the trade-off between the prevention of long-term bone loss and achieving an ‘ideal’ adult height is crucial but there is no established consensus on the optimal age of oestrogen replacement.

**Conclusions**

Taller stature in late gonadectomised CAIS women suggests oestrogen deficiency in these women prior to gonadectomy. As well as Y chromosome, oestrogen deficiency contributes considerably to tall stature in GD(XY) women. Increased lower to upper body ratio in women with GD(XY) compared with the other groups implies that these subjects have the greatest degree of oestrogen deficiency in puberty. Androgen rather than sex chromosomes may play an important role in cortical bone mineralisation in women with CAIS, probably via ER-α either directly or via aromatisation during critical periods of growth prior to gonadectomy. Based on our observations, late gonadectomy may benefit BMD and the resulting tall stature may be limited by introducing oestrogen replacement prior to gonadectomy as soon as the diagnosis is made.

**Disclosure**

Fundings: Deepti Goswami was in receipt of Commonwealth Scholarship from the Commonwealth Scholarship Commission, Association of Commonwealth Universities, London, UK. We declare that there is no conflict of interest that would prejudice its impartiality.

**References**


Han TS, Cadge B & Conway GS. Hearing impairment and low bone mineral density increase the risk of bone fractures in women with Turner’s syndrome. *Clinical Endocrinology* 2006 **65** 643–647.


Received 19 April 2008
Accepted 28 April 2008

www.eje-online.org