Bone mineral density in Prader-Willi females during the transition phase

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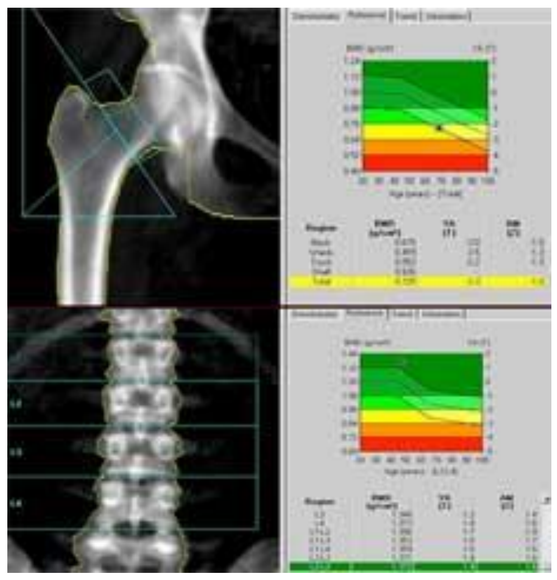
Background



Adult subjects with PWS have low Bone Mineral Density (BMD) and are at risk of osteoporosis. The relevance of altered BMD in PWS is related to the high risk of fracture in these patients. Whether the decreased BMD in PWS is mainly related to impaired GH secretion, reduced gonadal steroid levels, low neuromuscular activity, or deficient intakes of both calcium and vitamin D, however, is currently unknown. Previous data seem to support the view that the low BMD in PWS adults is not mainly due to GH insufficiency. Several observations suggest that peak bone mass is usually achieved by late adolescence, in the presence of adequate gonadal hormone concentrations. Consequently, the altered bone characteristics of PWS patients may be related to inadequate sex steroid levels during pubertal development.

Aim

The objective of this study was to investigate BMD in PWS females during the transition phase.

Patients and Methods

The patients' group consisted of 33 females with typical PWS clinical phenotype, aged 22.1±2.4 yr (range 17.9-25.0 yr). Cytogenetic analysis was performed in all subjects and 25 of them had a deletion of the paternally derived chromosome 15, while maternal uniparental disomy of chromosome 15 was found in 8 individuals. Nine patients had spontaneous menarche, and 2 of them showed regular menstruations. The remaining subjects suffered from secondary amenorrhea (n. 7) or primary amenorrhea (n. 24). Eleven subjects were undergoing sex steroids therapy (Group A), while the remaining 21 individuals were naïve to substitutive treatment (Group B). Twenty subjects had undergone GH treatment during childhood. In all patients dual-energy X-ray absorptiometry (DXA) (GE-Lunar, Madison, WI, USA) was used to measure BMD in the lumbar spine L1-L4 (gr/cm2), BMD T-score, and BMD Z-score. Data were expressed as mean ± SE. Differences in BMD between subgroups of PWS patients were evaluated by the Student's t-test and analysis of variance, as requested. Pearson's and Spearman's univariate analysis was performed to evaluate the possible correlation between BMD and different parameters considered (age, genotype, BMI SDS, sex steroids treatment, GH therapy). Then variables significantly associated were inserted and stepwise multiple linear regression analysis to evaluate the independent influence of different parameters on BMD (dependent variable). Statistical significance was set at $P<0.05$.

Results

Altogether, 4 PWS had osteoporosis (T-score <-2.5: 12.50%), 14 had osteopenia (T-score from -1.0 to -2.5: 43.75%) and 14 had normal BMD (43.75%). Three subjects out of 11 of Group A had osteopenia (27.3%), while the remaining 8/11 showed normal BMD (72.7%). Four PWS out of 21 of Group B had osteoporosis (19%), 11/21 had osteopenia (52.4%), and 6/21 had normal BMD (28.6%). Mean lumbar BMD, BMD T-score and BMD Z-score were higher in Group A in comparison to Group B (Table 1). Moreover, previously GH-treated patients had higher BMD T-score and BMD Z-score in respect to subjects naïve to GH treatment (Table 2). At univariate analysis we found a positive correlation between BMD and sex steroids therapy ($p<0.001$) and GH treatment ($p<0.001$). Stepwise multivariate regression analysis, confirmed that only substitutive therapy (beta=0.230; $p<0.005$) and GH treatment (beta=0.230; $p<0.003$) were significant predictors of BMD.

Patients	Age (yrs)	BMD (gr/cm2)	BMD T-score	BMD Z-score
Group A	21.2±0.4	1.108±0.02	-0.69±0.17	-0.66±0.24
Group B	22.5±0.4	0.947±0.03	-1.51±0.26	-1.30±0.28
P value		*0.006*	*0.04*	*0.12*

Table 1

Patients	Age (yrs)	BMD (gr/cm2)	BMD T-score	BMD Z-score
GH+	20.9±0.5	1.037±0.04	-0.91±0.22	-0.71±0.25
GH-	23.9±0.9	0.944±0.04	-1.72±0.32	-1.69±0.32
P value		*0.08*	*0.04*	*0.02*

Table 2

Conclusions

Altogether we found that the majority of PWS females during the transition phase (56%) had reduced BMD. Our data support the view that the altered bone characteristics of PWS patients may be related to inadequate sex steroid levels during pubertal development. Moreover, we have demonstrated a positive effect of GH treatment on BMD, differently from those observed in previous studies. Apart from GH and sex steroids, however, other hormonal factors may be involved in the regulation of BMD, including adipokines and ghrelin. Adiponectin appears to exert a negative effect on bone mass, while leptin seems to be positively associated to BMD. Concerning ghrelin, a positive correlation with trabecular BMD has been reported in elderly women, but data from clinical studies on humans are still contradictory. In this context, patients with PWS are known to have: (a) higher levels of both total adiponectin and high-molecular-weight adiponectin, compared with BMI-matched controls (b) hyperleptinemia, similarly to what observed in weight-matched controls, and (c) a progressive deterioration through life of the regulation of ghrelin secretion, with inappropriate high levels in older children and adults. Consequently, it may be hypothesized that low BMD in PWS adults reflects a complex interaction of different endocrine abnormalities, rather than the deficiency of a single hormonal axis, and therefore this point deserves further study. Furthermore, other elements are able play a role in determining or maintaining low bone mass, such as lifestyle factors. Based on our data, we may conclude that (1) delayed timing of sex steroids therapy should be avoided in PWS females, and (2) GH therapy during childhood seems to exert positive effects on BMD during the transition phase.

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ESPE 2015 661-P3

Bone

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DOI: 10.3252/pso.eu.54espe.2015

Poster presented at: 54th Annual Meeting 1-3 October ESPE 2015 BARCELONA European Society for Paediatric Endocrinology

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