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LETTER TO THE EDITOR

Bone mineral density in older patients with never-treated congenital hypogonadotropic hypogonadism

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Sex steroids are major regulators of skeletal development and bone mineral content, and sex steroid deficiency can thus lead to osteoporosis and fractures in later life [1]. Hypogonadism in both genders is associated with bone loss and frailty. Its deleterious effects on bone mineral density (BMD) are epitomized by women with ovarian failure and by aging men undergoing surgical or pharmacological castration for prostate cancer [1].

Congenital hypogonadotropic hypogonadism (CHH) and Kallmann syndrome (KS) are rare diseases that represent a paradigm of severe and lifelong sex-steroid deficiency, which starts in the antenatal period and which would account for the subnormal BMD seen in young CHH/KS patients [1, 2].

From a series of 472 CHH/KS patients referred to our department, we studied BMD in a subgroup of six male patients (2 KS and 4 normosmic CHH) diagnosed >40 years (43–76 years) and who denied ever receiving steroid replacement therapy. The lack of treatment was supported further by the absence of spontaneous pubertal development and complete hypogonadal status at diagnosis (hypogonadal habitus associated with hypogenitalism and testicular hypotrophy), with very low circulating gonadotropin and sex steroid levels (Suppl. Table 1).

In these individuals, BMD was evaluated by means of dual X-ray absorptiometry and compared to values observed in 25 age-matched and BMI-matched CHH/KS men, also evaluated >40 yrs-old but diagnosed and treated <25 (median age at treatment 18, range 16–24 years).

BMD at the lumbar spine (L1-L4) was low for age in both the never-treated (1.00 ± 0.19 g/cm^2) and treated patients (1.04 ± 0.19 g/cm^2, Fig. 1a). BMD at the femoral neck was also low in the never-treated (0.86 ± 0.13 g/cm^2) and in the treated patients (0.89 ± 1.16 g/cm^2), although less markedly than at the lumbar spine (Fig. 1b). Mean BMD was not significantly different between the never-treated and treated patients. Indeed, the *z*-score did not differ between the untreated and treated CHH/KS men either at the lumbar spine ($p = 0.77$, Fig. 1c) or at the femoral neck ($p = 0.56$, Fig. 1d). Further, *z*-score was normal in three never-treated patients, indicating that their BMD was similar to that of healthy individuals of similar age. It is noteworthy that no pathological fractures had occurred in either the treated or the never-treated patients. Interestingly, the oldest patient in the never-treated group, diagnosed at 76, had a typical KS and carried the recurrent truncating *KAL1/ANOS1* mutation R257X. His BMD was 0.99 g/cm^2 at the lumbar spine and 0.75 g/cm^2 at the femoral neck.

Total testosterone and estradiol levels were similarly low at diagnosis in the never-treated and treated patients (Suppl. Table 1), indicating severe gonadotropin deficiency in both groups. At last evaluation, the very low sex-steroid levels ruled out the existence of reversible forms [2]. Serum calcium and thyrotropin levels were normal in all the CHH/KS patients. Low 25-hydroxy vitamin D levels (<50 nmol/L)

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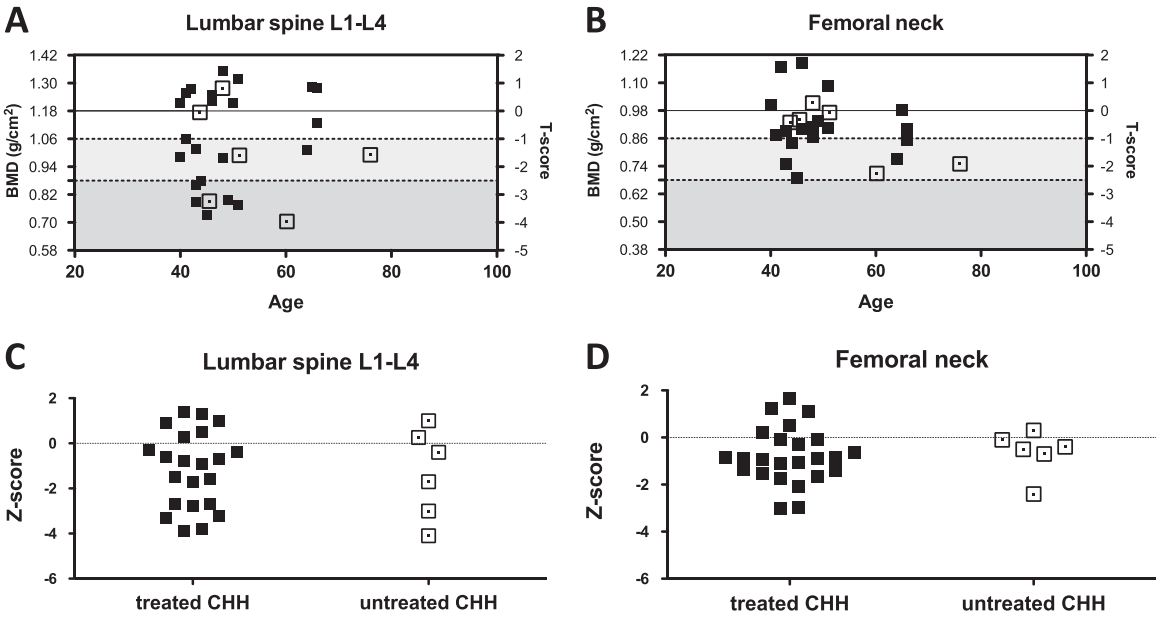

Fig. 1 Bone mineral density (BMD) in 6 untreated and 25-treated-elder men with congenital hypogonadotropic hypogonadism/Kallmann syndrome (CHH/KS). The data in all panels are reported as individual values. *Open squares* indicate never-treated CHH/KS men and *closed squares* indicate treated (median age at treatment initiation: 18 years, range 16–25) CHH/KS men. **a** BMD plot at the lumbar spine (L1-L4); **b** BMD plot at the femoral neck; **c** *z*-score at the lumbar spine (L1-L4) in untreated (-1.28 ± 1.80) vs. treated CHH/KS (1.14 ± 1.67), $p = 0.77$; **d** *z*-score at the femoral neck in untreated (-0.81 ± 0.98) vs. treated CHH/KS (-0.98 ± 1.22), $p = 0.56$. All BMD measurements were performed by dual energy X-ray absorptiometry with a Lunar Prodigy Advance device (GE Healthcare Lunar iDXA, Buckinghamshire, UK) with a maximal exposure assessed at 1.75 uSv

were found in 4 never-treated and in 21-treated patients (Suppl. Table 1).

To our knowledge, this is the first report of BMD values in never-treated older patients born with CHH/KS. The lack of difference in average BMD between the treated and never-treated CHH/KS patients was wholly unexpected. Several mutually compatible hypotheses might contribute to explain these findings. First, although the patient interviews and clinical and hormonal investigations strongly supported the absence of any previous or ongoing hormone treatment, we could not completely rule out the possibility of occasional hormone treatment in the past. Similarly, we could not exclude the possibility of suboptimal adherence to chronic hormone therapy in the treated patients [3]. Furthermore, it is not excluded that, despite a proper hormone replacement therapy schedule, the physiological need of sex steroids coverage could never be achieved because of pharmacokinetic and/or pharmacodynamic issues.

Alternative explanations for the lack of difference in BMD values include the high prevalence of vitamin D deficiency in both groups, which could have undermined BMD and mitigated any differences related to chronic sex steroid deficiency. Furthermore, adrenal function was preserved in all CHH/KS subjects. Compensation of the gonadal steroid deficiency by adrenal androgen precursors, which can be locally metabolized by bone into estrogens [1], might have further mitigated the difference in BMD between the groups. Individuals with CHH/KS have lifelong low circulating follicle-stimulating hormone (FSH) levels. Since high FSH levels have been shown to be involved in bone loss independently of E2 levels, an additional protective role by chronic low FSH in these patients might not be excluded [4, 5]. Finally, it is possible that non-hormonal factors, such as physical activity, might have compensated for the chronic sex steroid deficiency in the untreated CHH/KS.

Whatever the reasons, these unexpected preliminary data suggest that the beneficial effect of sex steroid replacement therapy on bone status in this specific population may be smaller than previously thought.

Compliance with ethical standards

Conflict of interest The authors declare they have no competing interests.

Ethical approval All procedures performed in this study were in accordance with the ethical standards of the institutional research committee and with the Helsinki declaration.

Informed consent Informed consent was obtained from all individual participants included in the study.

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