INVITED COMMENTARY

Delayed puberty and peak bone mass

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The accrual of bone mass during childhood and adolescence is a major determinant of peak bone mass (PBM), and thereby of the risk of osteoporotic fractures occurring in advanced age (1). The development of non-invasive techniques, such as dual-energy X-ray absorptiometry (DXA), has made it possible to determine with precision and very low radiation exposure the pattern of bone mineral mass accumulation at various sites of the axial and appendicular skeleton during infancy, childhood and adolescence. At the end of the growth period, a wide variance in areal bone mineral density (aBMD, in g/cm²) or content (BMC, in g) in either the axial or the appendicular skeleton is observed both in healthy females and males (1). This broad variance is barely reduced after correction for standing height. It is already present before puberty, but at certain skeletal sites, such as lumbar (L) spine and proximal femur, this height-independent variance in aBMD/BMC still tends to become broader (1).

The mechanical resistance of bone depends upon several factors among which the size of the bone, the amount of bony tissue within the periostal envelope (i.e. the volumetric density) and its space distribution (i.e. the micro- and macroarchitecture) appear to be the most important determinants. The aBMD variable as measured by DXA is directly related both to the volumetric mineral density (vBMD) and to the size of the bone in the axis of the beam generated by the energy source. The integration of these two important components of mechanical resistance can explain why it is not surprising that inverse relationships have repeatedly been found between aBMD and the incidence of osteoporotic fractures (2).

During development the increase in aBMD at several skeletal sites is essentially due to an augmentation in bone size with an increase in cortical thickness which mainly results from the process of periosteal apposition. In contrast, in the parts of the skeleton with both compact and spongy bony tissue as, for instance, in vertebral bodies, the volumetric trabecular density appears to increase very little from birth to the age at which peak bone mass is attained (1). The gender difference in either aBMD or BMC observed at the level of the radial or femoral diaphysis in young adults is essentially generated during pubertal maturation, with a greater gain in bone size in males than in females (1). Likewise in the lumbar spine, where the gender difference in BMC observed at PBM (2) appears to result essentially from a greater increase in the size of the male vertebral bodies during pubertal maturatation (3). In both clinical practice and trials in human subjects the measurement of aBMD provides important information on the factors that can affect bone mineral mass accrual and loss (4). The operational definition of osteoporosis as endorsed by the World Health Organisation is based on the measurement of aBMD, the risk of fragility fractures being inversely related to the value of aBMD (4).

Puberty is a crucial time in bone mineral mass development. Thus, at the lumbar spine level the mass of bone mineral more than doubles from 9 to 15 years and from 11 to 17 years in females and males respectively (1, 3). Epidemiological studies have provided suggestive evidence that late menarche is a risk factor of osteoporosis. Osteopenia has been reported in a cohort of men with a history of delayed puberty (5). Delayed puberty or adolescence has been defined as the absence of any sign of puberty in a subject who has attained the upper normal limit of chronological age for the onset of puberty. This means an absence of increase in testicular volume at 14 years in a boy or an absence of any breast development in a girl at 13 years of age (6). The causes of delayed adolescence have been classified in permanent and temporary disorders. The permanent ones can be due to either hypothalamo–pituitary or gonadal failure (6). Among the temporary disorders, some can be explained by the presence of chronic systemic diseases, nutritional disorders, psychological stress, intensive competitive training, or hormonal disturbances such as hyposecretion of thyroid hormones or growth hormone, or hypercortisolism (6). However, the most common cause of delayed adolescence is the so-called ‘constitutional delay of growth and puberty’ (CDGP). It is a transient disorder with, in some cases, a familiar history of late menarcheal age of the mother or sisters, or a delayed growth spurt in the father (6). This condition has been considered so far as an extreme form of the physiological variations of the timing of the onset of puberty of which the ‘normal’ range is about 8–12 and 9–13 years of age in girls and boys respectively (7). The onset of puberty is a complex process involving the activation of the hypothalamic–pituitary–gonadal axis and other endocrine systems such as the growth hormone–insulin-like growth factor (IGF) axis (6, 7) of which the targets include factors
influencing the bone mineral balance and the growth rate of the skeleton (8).

The mechanism whereby CDGP may lead to a low peak bone mass is unknown. Only some speculation can be made. A first possibility is that the timing of the pubertal maturation onset is an important determinant of the amount of bone which will be accumulated after this 'critical' chronological mark. According to this model a significant inverse relationship should exist between the age of the onset of puberty and the bone mass gained from the beginning of pubertal maturation to the attainment of peak bone mass. As mentioned above the 'normal' range of the age at which pubertal maturation starts extends over a four-year period in both genders. To our knowledge such an inverse relationship has not been documented in adolescents considered as 'normal' with respect to their age of puberty onset. As a variant to this first model one could still envisage that there is an upper limit of age, i.e. some kind of time threshold, beyond which the potential of peri- and postpubertal bone mass accrual would be reduced. Again, to our knowledge there are no studies indicating that the yearly bone mass gain of CDGP subjects would be normal before but reduced after the onset of puberty.

A second possibility is that the deficit in bone mass gain occurs well before the onset of puberty. According to this second hypothesis, the low peak bone mass would be unrelated to the late onset of pubertal maturation. The mass of bone accumulated during the peri- and postpubertal period would be proportional to that gained during the prepubertal years. In other words the CDGP subjects would just keep their prepubertal low standard deviation (S.D.) score or percentile (the distribution of bone mineral mass varies being Gaussian, S.D. scores and percentiles can be considered as equivalent) after the onset of pubertal maturation and until the attainment of peak bone mass. Such a model implies that without substantial change in the environmental factors bone mass like body height tends to track. Indeed, recent evidence obtained in prepubertal girls indicates that as for body height there is a high correlation between the S.D. score of several bone variables including spinal and femoral aBMD or BMC when measured at yearly intervals (9). Furthermore, bone variables and, as expected, body height were significantly correlated between prepubertal daughters and their mothers (9). These results strongly suggest that tracking observed during the prepubertal period is likely to last during the entire period of bone growth. Note that these observations do not preclude the possibility that tracking for most bone traits may be definitively altered by changing environmental factors such as dietary calcium (10) or physical activity (11).

In the current issue of this Journal, Moreira-Andrés and her colleagues (12) provide data in favor of the second model described above, so that in CDGP subjects the low bone mass could be already present before the onset of puberty. In this study BMC, bone area, and aBMD of L1-L4 were measured by DXA in 56 children (28 boys and 28 girls) aged 5–11 years, whose height was below the 10th percentile for chronological age (12). In about half of these children the diagnosis of 'possible CDGP' was made based on a bone age of at least 1.75 years below their chronological age, a family history of CDGP, or midparental height above the 25th percentile. The other half were considered as familial short stature (FSS). Spinal BMC, bone area and aBMD mean values were respectively 26, 16 and 16% lower in 'possible CDGP' than in FSS. These differences were highly significant. Furthermore, the larger relative difference in BMC than in bone area suggests that the deficit bears on both the size and the amount of bony tissue contained within the 4 lumbar vertebrae. This study did not provide an estimate of bone mineral apparent (volumetric) density (BMAD), as it can be calculated by dividing BMC by a volume derived from the projected area and height of L1-L4. However, multiple regression analysis supports the notion that L1-L4 BMC remains lower even after adjustment for the projected bone area (12). The present study cannot explain what might be the nature of the apparent deficit in the amount of bone within the bone. It could be related to various determinants of volumetric bone mineral density, including cortical thickness, trabecular bone volume, and/or degree of matrix mineralization.

The authors of this interesting report are well aware that their data are only suggestive, since a very long period of follow-up, more than 8–10 years for the youngest subjects, will be necessary to ascertain if the prepubertal subjects classified as 'possible CDGP' will actually have a significant delay in the onset of their pubertal maturation. More years of follow-up will still be required before information will be available on the bone mass accumulation during pubertal maturation and finally on the peak bone mass value of this cohort. Among the subjects considered as 'possible CDGP' some may have no delay in the timing of pubertal maturation. Indeed, a subgroup may well belong to the lower range of the normal distribution of bone mineral mass. The fact that the subjects were first subdivided according to their bone age value does not exclude a bias of selection since there is a tight correlation between bone age, as classically assessed by X-ray of the hand and wrist, and aBMD/BMC as measured by the DXA technique.

If the second model is correct, the mechanism by which these children have a low bone mass gain as well as the reason why such an alteration during the prepubertal years would delay the onset of pubertal maturation will still need to be explained. In other words and assuming that the FSS subjects of this cohort will mature normally, it would imply that in CGDP the mechanism responsible for the slow tempo of pubertal bone mass accumulation, but not that of standing height, is coupled to that determining the time of the pubertal maturation onset. Bone development and
pubertal maturation are under the influence of complex interactions between the growth hormone—IGF-I system and the sex steroids (13). Observations of delayed skeletal maturation in individuals with estrogen receptor defects or mutations in the aromatase gene underline the crucial role of estrogen in promoting bone mass accrual in both females and males (13, 14). Some more subtle alterations in estrogen production and/or action could underlie CDGP. Finally, experimental evidence indicates that alterations in the maternal estrogenic levels during pregnancy can not only influence the early phases of fetal bone tissue development but can also exert long term imprinting effects on bone cellular activity and eventually on adult skeletal mass (15). In this respect recent retrospective cohort studies have suggested that weight in infancy is a significant predictor of spinal and femoral BMC of women during adulthood (16). Furthermore, an association has also been found between birthweight and menarcheal age (17), suggesting an influence of the early environment on this physiological event. Therefore, CDGP could already be programmed in utero. It is the merit of the report by Moreira-Andrés and her colleagues (12) on CDGP that it raises key questions on the mechanisms that govern bone mass development from fetal life to peak bone mass and thereby influence the risk of osteoporosis in adulthood.

References


Received 14 May 1998
Accepted 14 May 1998