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Review

INFLUENCE OF HEREDITY AND ENVIRONMENT ON PEAK BONE DENSITY: A REVIEW OF STUDIES IN CROATIA

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One of the main determinants of who will develop osteoporosis is the amount of bone accumulated at peak bone density. There is poor agreement, however, on when peak bone density occurs. Ethnic differences were observed in age at peak bone density and their correlates. Since the diagnosis of osteoporosis and osteopaenia is based on the comparison between patients' bone mineral density (BMD) and optimal peak bone density in healthy young people (T-score), it is of great importance that each country should provide its own reference peak bone density data.

This review article presents our published results on peak bone density in Croatia and compares them with findings in other populations. Our research included 18 to 25-year-old students from Zagreb University and their parents. The results showed that peak bone mass in young Croatian women was achieved before the age of twenty, but BMD continued to increase after the mid-twenties in the long-bone cortical skeleton. BMD was comparable to the values reported by the National Health and Nutrition Examination Survey (NHANES) and other studies that included the same age groups, except for the cortical part of the radius, where it was significantly lower. Men achieved peak bone density in the spine later than women, which cannot be explained by different diet or physical activity. As expected, heredity was more important for peak bone density than the environmental factors known to be important for bone health. However, the influence of heredity was not as strong as observed in most other populations. It was also weaker in the cortical than in the trabecular parts of the skeleton.

Future research should include young adolescent population to define the exact age of achieving peak bone density in different skeletal sites.

KEY WORDS: *calcium intake, heredity, peak bone density, physical activity*

Peak bone mass is the largest amount of bone tissue that a person achieves at certain point in life. Up to 90 percent of peak bone mass is acquired by the age of 20, and it keeps growing until around the age of 30 (1-6). At that point, bones have reached their maximum strength and density. It is very difficult to estimate the exact peak bone density because the development of the skeleton and bone loss are dynamic processes. Some bones may still be gaining mass while others have started to lose it. Peak bone mass may be influenced by a combination of heredity and environmental factors. Heredity may be responsible for up to 70 % to 75 % of bone mass formation and environmental factors for the remaining 25 % to 30 % (7). Even though genetic studies have discovered several potential regions of linkage, the underlying

genes are still widely unknown. One important genetic component of bone mass is the allelic variation in the receptor for 1,25 dihydroxy-vitamin D. These alleles (VDR) have a co-dominant effect on bone turnover and on bone mineral density (BMD). (8) The most important environmental factors are diet, especially calcium intake, and physical activity. Calcium is the most important nutrient for bone and its deficiency in young people may increase the risk of fracture later in life (9). As regards physical activity, weight-bearing exercises are the best exercises for bones. Young people who exercise regularly usually achieve greater peak bone mass than those who do not (10). Unhealthy habits, such as alcohol use and smoking may adversely affect peak bone bass (11).

Peak bone mass tends to be higher in men than in women. Before puberty, boys and girls acquire bone mass at similar rates, but men start to gain greater bone mass in puberty, which is related to hormonal changes.

Variations in BMD between populations and ethnic groups have been confirmed in many population-based studies. The European Study of Vertebral Osteoporosis (EVOS) (12) has shown substantial differences in bone density between European nations. There is also evidence that peak BMD in the young healthy subjects from the Middle East is lower than in young American subjects (13).

In addition, levels and timing of peak bone density seem to vary between ethnic groups (7, 12).

Osteoporosis and osteopaenia are diagnosed based on the T-score (14). The T-score is the number of standard deviations below the average for a young adult at peak bone density. There are different T-scores, depending on which group of young adults is used as reference (for example, Caucasian women, Hispanic men). As BMD varies across ethnic groups, it is important that every nation has its own reference bone density. Many nations use their own reference data sets in densitometer machines. Croatia, however, still lacks its own reference peak BMD and has instead been using white adult American population data collected by the National Health and Nutrition Examination Survey (NHANES) III to calculate the T-score.

This article gives a review of our epidemiological studies of peak bone density in Croatia. Due to different demographic, ethnic characteristics which influence bone density, these studies were aimed to determine the specific age of peak bone density and the risk factors affecting it in general Croatian population.

PEAK BONE DENSITY IN GENERAL CROATIAN POPULATION

Even though it is widely accepted that most of the skeletal mass is acquired by the age of 20, more recent studies suggest that bone density is at its peak by the end of adolescence (1, 16). We wanted to see whether this was true and measured bone density in the spine, femur, and the cortical part of the radius in a healthy young population aged between 18 and 25. We also investigated the influence of heredity, dietary calcium, physical activity, weight, and height on bone density (15).

Another study of ours (18) comprised a student population from Zagreb University and their parents (220 girls, 51 boys, and 83 parents-couples, mothers and fathers). The first part of our research was focused on female population, and we found a significant negative correlation between age and bone density in young women, which suggests that bone loss has started in their early twenties. An exception was the cortical bone of the radius, as its bone mass did not correlate inversely with age. Moreover, Z-scores (the number of standard deviations the bone mineral density measurement is above or below the young-normal mean bone mineral density) for the radius were negative in most subjects, in contrast to positive Z-scores for other sites. This suggests that the peak bone mass of the cortical bone in radius is achieved later than in other parts of the skeleton. Our results have shown that young women in Croatia have a lower peak bone mass in the cortical bone of the radius than the American reference values reported by NHANES. However, the positive correlation between age and cortical BMD suggests that cortical bone density of the radius will continue to rise in our young women. This rise will probably be slight, and we expect that the cortical peak bone density will finally be lower in Croatian young women than in their American counterparts.

Other studies also showed that BMD peaks at different times across the skeleton. Lin et al. (2) and Lu et al. (5) confirmed that peak BMD at the proximal femur was observed earlier than in the spine or total body. Matković et al. (1) also suggested that BMD of the spine and femur peaked as early as in adolescence or young adulthood. Several studies were consistent

with our results that the bone mass of the cortical bone continued to rise after the age of 18 (6, 17).

The second part of our research was focused on comparing BMD patterns between parents and children and assessing the risk of children having low BMD if their parents had low BMD (Figure 1). It is difficult to directly compare the BMD between children and their parents as parents vary in age more than children. The study group consisted of 83 families (48 daughters and 35 sons recruited from Zagreb University and their parents (18). We wanted to see to which extent heredity accounted for the variation in bone mineral density in children (the parents′ BMD) and as opposed to several environmental/lifestyle characteristics known to affect bone health (calcium intake, physical activity, and smoking). Our results showed that heredity accounted for 24 % to 42 % of the variation in children's BMD, depending on the site of measurement. In contrast, environmental and lifestyle influence on the variation was relatively low. Findings from other studies are controversial; some have found a stronger influence of heredity (up to 80 %) on BMD (19-21) and some lower. In Jouanny's study (22), parent BMD, child body mass index (BMI) and mother BMI accounted for 41.4 % of the variance in child BMD. Ferrari et al. (23) showed that only 18 % to 37 % of bone density in pre-menopausal daughters was directly determined by maternal bone density. Moreover, Ulrich et al. (24) suggested that behavioural and hormonal factors were more important for BMD than heredity between mothers and daughters. In another study by Mc Guigan et al. (25). the strongest predictor of BMD in women was body weight, accounting for 16.4 % of the variance in the spine BMD, and the second was vitamin D receptor genotype (3.8 %).

We continued our research to see whether bone density peaked at different times between young men and women. We used the dataset obtained from the same student population sample and found that boys had a higher areal bone density (g cm^{-2}) at all measured sites (26). However, estimated volumetric bone mineral apparent density (BMAD; g cm^{-3}), which minimizes the effect of skeletal size on BMD, was higher in girls. This means that the difference in areal BMD between boys and girls is owed to a greater increase in bone size in boys during growth. We could not determine any differences in peak bone density between boys and girls that would be related to lifestyle habits, as the two groups had similar diet and physical activity.

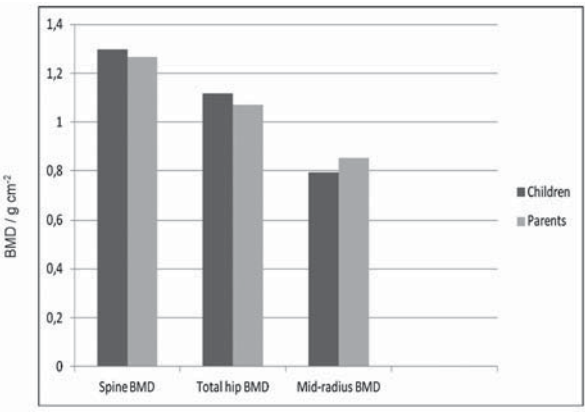

Figure 1 *Bone mineral density (BMD) at different skeletal sites in Croatian student population of both sexes, aged 18 to 25 years, and in their parents.*

Our students reached their peak bone density in their early twenties and had already started to lose bone. The exception was the spine in boys, as it did not correlate inversely with age. Since it is expected that men will gain a higher peak bone density than women, we can conclude that male students have not yet achieved their peak bone density in the spine. In addition, the insignificant negative correlation between age and BMD of the femur and radius suggests that boys reach peak bone density later than girls.

A study by Kaštelan et al. aimed to establish a reference bone density for the general population in Croatia using quantitative ultrasound (QUS). It included 1002 healthy male participants, aged 20 to 99 from all over Croatia (27). Their qualitative ultrasound index (QUI) and speed of sound (SOS) values peaked in the third decade, whereas broadband ultrasound attenuation (BUA) peaked in the fourth decade of life. These findings confirm our own, as our study participants continued to gain bone density after the age of 25. However, the two studies cannot be directly compared because we studied a mixed population and used dual energy absorptiometry (DXA) for measuring bone density, while Kaštelan et al. recruited a male population and performed ultrasound bone densitometry.

The same group of authors analysed the influence of cytosine-adenine dinucleotide (CA)n repeat polymorphisms of the insulin-like growth factor I (IGF-1) gene n alleles on peak bone mass attainment in 92 unrelated healthy men, aged 21 to 35. The results suggest a negative effect of the IGF-1 (CA)18 allele on bone mass gain in men (28).

CONCLUSIONS

Studies of peak bone density in Croatia are rare. We still do not have national reference peak bone density values for T- or Z-scores and for diagnosing osteoporosis according to the WHO criteria, but use reference values from other nations instead.

Our epidemiological studies suggest that peak bone density in Croatian population is achieved before the age of twenty, but later in the long-bone cortical skeleton. BMD in our young women is slightly higher than peak BMD of young American women, except in the cortical part of the radius, where it appears to be lower.

Future research should aim at defining the exact age of achieving peak bone density in different skeletal sites in order to establish reference peak bone density values for the Croatian population.

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Sažetak

UTJECAJ NASLJEĐA I OKOLIŠA NA VRŠNU KOŠTANU GUSTOĆU: PREGLED ISTRAŽIVANJA U HRVATSKOJ

Vršna koštana gustoća je jedna od najvažnijih pretpostavki za nastanak osteoporoze. Poznati su rizični faktori za vršnu koštanu gustoću, ali vrijeme njezinog postizanja nije u potpunosti definirano. S obzirom na to da se dijagnoza osteoporoze i osteopenije temelji na usporedbi mineralne gustoće kosti (BMD) pojedinca s prosječnom vršnom koštanom gustoćom u mladoj, odrasloj populaciji (T vrijednost), vrlo je značajno da svaka zemlja utvrdi vrijednosti vršne koštane gustoće za svoju populaciju.
U ovom smo radu prikazali naša istraživanja i objavljene rezultate o vršnoj koštanoj gustoći u hrvatskoj populaciji i usporedili rezultate s drugim istraživanjima u svijetu. Naše je istraživanje obuhvatilo studentsku populaciju u dobi od 18 do 25 godina i njihove roditelje.
Rezultati su pokazali da se u našoj populaciji vršna koštana gustoća postiže prije 20. godine na trabekularnoj kosti, a na kortikalnom dijelu skeleta nakon 25. godine života. Vrijednosti vršne koštane gustoće u našoj populaciji slične su onima iz studije National Health and Nutrition Examination Survey (NHANES), kao i iz ostalih studija koje su obuhvatile istu dobnu skupinu, osim na kortikalnom dijelu skeleta, gdje su u našoj populaciji nađene značajno niže vrijednosti. Kasnije postizanje vršne koštane gustoće u muškaraca nego u žena bilo je najizraženije na kralježnici, što se nije moglo objasniti različitim prehrambenim navikama i razinom tjelesne aktivnosti među spolovima. Nasljeđe je imalo veći utjecaj na koštanu gustoću od okolišnih faktora, ali taj utjecaj nije bio toliko značajan kao u većini drugih istraživanja. Utjecaj nasljeđa na vršnu koštanu gustoću bio je manji na kortikalnom nego na trabekularnom dijelu skeleta.
Bilo bi važno proširiti istraživanje na mladu adolescentnu populaciju i tako točnije definirati vrijeme postizanja vršne koštane gustoće na pojedinim dijelovima skeleta.

KEY WORDS: *nasljeđe, unos kalcija, tjelesna aktivnost, vršna koštana gustoća*

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