

GENETIC VARIATION IN ESTROGEN RECEPTOR α AND INTERLEUKIN-6 IS ASSOCIATED WITH BONE MASS ACQUISITION IN PREPUBERAL GIRLS AND BOYS: INTERACTION WITH CALCIUM SUPPLEMENTS

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Estrogens regulate interleukin-6 (IL6) expression. Polymorphisms in estrogen receptor alpha (ESR1) and in IL6 genes have been associated with BMD in post-menopausal women. Whether genetic variation in ESR1 and IL6 plays a role on bone mass acquisition however remains unknown. We examined the association of ESR1-XbaI and IL6 -174 G>C polymorphisms with BMD and their interaction with calcium intake in 139 girls and 232 boys who received calcium supplements (800 mg/d) or placebo for 1 yr. BMD at lumbar spine (LS), total hip (TH), femoral neck (FN), ultra distal (UR) and total radius (TR) was evaluated by DXA at baseline (mean age 7.6±0.4 yrs) and after 1 and 2 yrs (age 9.9±0.5 yrs). Genotypes distribution was similar in both genders. ESR1 genotypes were associated with baseline BMD at most skeletal sites (p=0.01-0.06), with a borderline interaction with sex (P=0.00). Indeed, xx females had 2-6% higher BMD compared to Xx and for Xx (LS p=0.04 and p=0.00; FN p=0.004 and p=0.05; TH p=0.009 and ns; TR p=0.005 and ns at baseline and after 2 yrs, respectively), whereas males did not. ESR1 genotypes were not associated with BMD gain in absence of calcium supplements, but a significant interaction with calcium supplements occurred on hip (P=0.03). Indeed, calcium supplements increased FN and TH BMD gain 2-3x above placebo among XX, but not among carriers of the x allele. At baseline, IL6 -174 genotypes were associated with BMD at LS (+4% in GG compared to CC and GC, p=0.001), and without evidence of interaction with sex. After two years, this association became weaker (p=0.05), since GG from both genders had a 26% lower LS BMD gain during yr 2 in absence of calcium supplements (p=0.01 vs CC and GC, adjusted for age, pubertal stage). Calcium supplements significantly increased TR and UR BMD gain in males and females (p=0.006 and p=0.05, respectively), without evidence of interaction with IL6 genotypes. In conclusions, ESR1-XbaI and IL6 promoter -174G>C polymorphisms are associated with BMD and BMD gain in prepubertal children. Whereas IL6 genetic variation appears to modulate bone mass acquisition at LS irrespective of sex and calcium intake, the broad influence of ESR1 genotypes on BMD was more prominent in females and may depend on the level of calcium intake.