Influence of estrogen receptor polymorphisms on bone mass, body composition, lipid profile and response to hormone therapy

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ABSTRACT

The basic work for this PhD dissertation was carried out at the Center for Clinical and Basic Research, Ballerup (2000-2002) and during my one year scholarship granted by the University of Aarhus (2004-2005). The thesis consists of three published or accepted articles and one submitted manuscript currently in peer review.

The aim was to study whether some women responded differently than others in plasma lipids and bone mineral density (BMD) during treatment with estrogen ± progestin hormone therapy (HT), and whether selected polymorphisms of the estrogen receptor (ER) genes influenced the HT response. Additionally, potential associations between body fat distribution, serum lipids, fasting glucose, BMD of spine and arm, prevalence of vertebral fractures and annual rate of bone loss with the ER gene polymorphisms were investigated.

The total study population comprised 1098 postmenopausal Danish women, who were examined twice with a mean follow-up period of 11.4 years. Genomic DNA was amplified by PCR followed by cleavage with PvuII and XbaI restriction enzymes for the ERα polymorphism and the AluI restriction enzyme for the ERβ polymorphism. Body composition, fat distribution and BMD were determined by dual energy X-ray absorptiometry. Vertebral fractures and plasma lipid measurements were obtained using standard methods.

Baseline plasma lipids, BMD, prevalence of spinal fractures, and response to HT were not significantly associated with polymorphisms in the ER genes. However, the AluI polymorphism of ERβ was significantly associated with bone loss from the distal forearm in women, who had never received HT.

Body composition and fat distribution were significantly associated with the PvuII polymorphism of ERα. Thus, women with at least one mutant P-allele had significantly more central fat (1 kg difference), a lower percentage of lean tissue mass, and the most unfavourable ratios of central-to-peripheral fat. In addition, a gene-environmental interaction between smoking and the PvuII polymorphism was observed.

In a large Caucasian population of postmenopausal women, body composition and fat distribution variables were influenced by the PvuII polymorphism in the ERα gene, thereby partly accounting for the genetic determinants of anthropometrics.

The selected ER polymorphisms were not associated with BMD or lipid profile at baseline or with the responses to HT in bone and lipids; but the ERβ genotype modulated bone loss from the distal forearm in non-treated women.

Further studies are needed to determine the clinical relevance of the observed associations between the PvuII polymorphism of ERα with body composition, as well as the clinical importance of ERβ polymorphism in bone loss and risk of osteoporotic fractures.