Project Code: RSA408011

Project Title: Mutational analysis of estrogen receptor gene and the role of estrogen together with estrogen receptor gene locus in male osteoporosis, glucose and lipid metabolism

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Project Period: 1 December 1997-30 November 2000

In the present study we searched for single nucleotide polymorphisms (SNPs) in the coding and promotor regions of estrogen receptor-α (ERα) gene and assessed the relations of these SNPs with the risk of postmenopausal osteoporosis and skeletal responsiveness to estrogen. The roles of estrogen and these SNPs in male osteoporosis were also assessed.

Direct sequencing of the coding and promotor regions of ERα gene revealed a T262C and a G2014A SNP in exon 1 and 8, respectively. After treating 96 postmenopausal with 0.3 mg or 0.625 mg conjugated equine estrogen (CEE) for 2 years, vertebral bone mineral density (BMD) increased regardless of the T262C genotype. However, with regard to femoral neck BMD, only those homozygous for the 262C allele had an increase in femoral BMD (+5.9 ± 1.4%, mean ± SEM, $P < 0.0001$). In 228 postmenopausal women aged more than 55 years with vertebral or femoral osteoporosis (n = 106) and without osteoporosis (n = 122), the G2014A polymorphism was related to the presence of osteoporosis (odds ratio 2.7 per A allele, 95% CI 1.49-4.76) independently of body weight (odds ratio 0.93 per kg, 95% CI 0.89-0.96) and years since menopause (odds ratio 1.12 per year, 95% CI 1.08-1.19).

In 98 males aged 60 years or more, of whom 18 had vertebral or femoral osteoporosis, no significant difference in circulating estradiol was detected (90.6 ± 12.7 vs. 88.7 ± 5.0 pmol/L). The genotype distributions of the T262C SNP in exon 1 and G2014A SNP in exon 8 did not differ in subjects with and without osteoporosis. Only body weight (OR 0.86, 95% CI 0.78-0.94) was independently associated with osteoporosis. However, administration of 0.3 mg CEE to 9 hypogonadal males caused a decrease in serum CTX, a marker of bone resorption. Glucose effectiveness increased after CEE whereas no effect on insulin sensitivity or serum lipid concentrations was detected.

In conclusions, we have identify SNPs in ERα gene which is likely to be significant pharmacogenetically and prosnostically in postemenopausal osteoporosis. Further studies is needed to confirm the findings and delineate the underlying mechanisms. As compared to females, our finding suggests that the disorder in males may be genetically and pathophysiologically different.

Keywords: estrogen, estrogen receptor gene, osteoporosis

The objectives of the present study were

1. Assess the relation between the PvuII single nucleotide polymorphism (SNP) in intron 1 of estrogen-receptor-α (ER α) gene and skeletal responsiveness to estrogen.
2. Identify SNPs in exons of ERα gene which may be in linkage disequilibrium with the intronic PvuII SNP and their roles in postmenopausal osteoporosis.
3. Investigate the effect of exogenous estrogen on bone, lipid and glucose metabolism in males.
4. Assess the role of endogenous estrogen together with SNPs in ERα gene as risk factors for idiopathic osteoporosis in males.

The study was conducted during December 1997 and November 2000. The results of which are presented in 5 separate reports namely:

1. Estrogen-receptor-α Gene polymorphism affects response in bone mineral density to estrogen in postmenopausal women
2. Association of a T262C transition in exon 1 of estrogen-receptor-α gene with skeletal responsiveness to estrogen in postmenopausal women
3. Association of a G2014A transition in exon 8 of estrogen-receptor-α gene with postmenopausal osteoporosis
4. Effect of estrogen replacement on glucose sensitivity, serum lipids and bone markers in hypogonadal males
5. Circulating estradiol and estorgen-receptor-gene polymorphisms in elderly men with idiopathic osteoporosis