HLA class I, Cw*01 and Cw*15 alleles can play a preventing role in serum IL-17 elevation associated with postmenopausal osteoporosis in Hungary

Ilona Bohaty1, Mónika Jurásné-Lukovics1, Éva Somogyiné-Vári2, László Kozma1, Katalin Dankó3, Ildikó Molnár1
Regional Centre of Hungarian National Blood Transfusion Service1, Immunendoocrinology and Osteoporosis Centre2, 3rd Department of Internal Medicine, University of Debrecen Medical and Health Science Center3, Debrecen, Hungary

BACKGROUND

IL-17 (named as IL-17A) is a novel family of inflammatory cytokines regulating neutrophil-recruitment and granulopoiesis. IL-17 up-regulates the granulocyte colony-stimulating factor (G-CSF) therefore can accelerate osteoclastogenesis. Bone-wasting effect of IL-17 was demonstrated in multiple myeloma, periodontal bone loss and rheumatoid arthritis. TNF-α is a potent osteoclast maturing factor. Its secretion is stimulated by estrogen deficiency and its action can be potentiated with IL-17. HLA class I antigens are involved in cytokine immune responses binding to lymphocytes with CD8 molecules. HLA class II antigens are connected to lymphocytes expressing CD4 molecules.

The linkage between bone mineral density and immune system highlights an immunological aspect of osteoporosis. Trabecular bone loss is associated with estrogen deficiency and can be inhibited by addition of IL-17 monoclonal antibody.

PATIENTS AND METHODS

Sixty four postmenopausal women were divided into four subgroups according to BMDs and IL-17 levels. Subgroup OL: postmenopausal osteoporotic women with low IL-17 levels (2.85±0.12 ng/ml), n=6, mean age of 60±6 years, mean lumbar BMD and T-score values: 0.695±0.05 g/cm² and -3.2±0.47. Subgroup OH: postmenopausal osteoporotic women with high IL-17 levels (3.79±0.55 g/ml), n=35, mean age of 68±10 years, mean lumbar BMD and T-score values: 0.8±0.07 g/cm² and -3.31±0.63. Subgroup PL: postmenopausal osteoporotic women with low IL-17 levels (2.9±0.12 ng/ml), n=8, mean age of 63±8 years, mean lumbar BMD and T-score values: 0.82±0.04 g/cm² and -2.01±0.47. Subgroup PH: postmenopausal osteoporotic women with high IL-17 levels (3.48±0.38 g/ml), n=15, mean age of 62±8 years, mean lumbar BMD and T-score values: 0.83±0.05 g/cm² and -1.98±0.47.

The HLA-A, -B, -DRB1 and -DQB1 alleles were tested for all individuals with polymerase chain reaction (Biocent HLA PCR SSP kit, Biocent Bio-Rad Medical Diagnostics GmbH, Germany). The serum IL-17A levels were measured with enzyme-linked immunosorbent assay (ELISA) (PeproTech, USA). The bone density (BMD g/cm²) of lumbar spines (L1-L4) was measured by dual energy X-ray absorptiometry (DXA) using Hologic Discovery WII.

RESULTS

The results using Hardy-Weinberg equilibrium (HWE) test, did not show remarkable difference among the subgroups (Table 1). The postmenopausal women with high IL-17 (subgroup OH) levels showed increased number of alleles in comparison with those found in subgroup with low IL-17 levels (OL) (Table 2).

In women with high IL-17, the allele frequencies of HLA-Cw*01 and -Cw*15, as well as the haplotype frequencies of HLA-A*02-DQB1*01 or HLA-A*02-DQB1*06, and HLA-Cw*01-DQB1*06 were significantly increased in osteoporotic women compared with osteoporotic ones (Table 3 and 4).

The pair of loci for HLA-Cw*01-DQB1*06 was not in linkage disequilibrium in subgroup OL (Table 5).

The genetic distances between subgroups with high IL-17 (subgroups OH and PH) were closer together compared with subgroups with low IL-17 (OL and PL subgroups) (Figure 1).

CONCLUSION

Our results revealed in postmenopausal osteoporosis that the high IL-17 levels, which cytokine is a bone-wasting accelerating factor, showed HLA associations at loci of HLA-A, -C and -DQB1. The absence of HLA-Cw*01 and -Cw*15 alleles, as well as HLA-A*02-Cw*01, -A*02-DQB1*06 and -Cw*01-DQB1*06 haplotypes was connected to high IL-17 levels. The HLA-allele association showed shorter genetic distances between subgroups with high IL-17 than between osteoporotic and osteopenic subgroups with low IL-17. In postmenopausal osteoporosis, the presence of HLA-Cw*01 and -Cw*15 alleles, as well as of HLA-A*02-Cw*01, -A*02-DQB1*06 and -Cw*01-DQB1*06 haplotypes demonstrated preventive role in the increase of IL-17.

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info@endomed.hu