ANKH and Renal Stone Formation in Ankylosing Spondylitis

To the Editor:

We read with interest Pimentel-Santos and colleagues' article on the *ANKH* gene and susceptibility to and severity of ankylosing spondylitis (AS)[1]. They showed that *ANKH* is not a major determinant of susceptibility to AS and *ANKH* polymorphism does not influence severity of AS. We describe our experience of *ANKH* gene polymorphism and renal stone formation in patients with AS.

AS is a chronic inflammatory disease with main involvement of the spine and sacroiliac joints. Spine ankylosis is progressively induced by specific ossifications. It has been reported that 25% of patients with AS had renal stone formation[2]. Most of these patients had hematuria. Other studies also showed increased prevalence of renal stone in patients with AS[3]. Pyrophosphate is present in normal urine and is an inhibitor of apatite formation. Hypopyrophosphaturia is suggested to be a metabolic risk factor for renal stone formation. Mutations in a putative pyrophosphate transporter, *ANKH*, have also been associated with defects of calcifications such as craniometaphyseal dysplasia and chondrocalcinosis. Expression of *ANKH* takes place in collecting tubules of both the mouse and human kidney[4], and dysregulation of the channel or polymorphism affecting channel properties may predispose to renal stone formation[5]; thus it would be reasonable to investigate whether *ANKH* is associated with increased renal stone formation in patients with AS.

Twenty-three Turkish patients with AS and renal calculi formation were genotyped for 6 single-nucleotide polymorphisms (SNP) within the *ANKH* gene. These were *ANKH* promoter –75 CCC GTC GC ins; 5'UTR-4, G > A; intron 2, +8 G > A; exon 2, 294 GCC > GCT (rs17251667); exon 8, 963 GCA > GCG (rs2288474); and intron 8, + 15 T > G (rs187483). Genotyping was also performed in 20 ethnically matched healthy controls using a competitive allele-specific polymerase chain reaction system (Kbioscience, Hoddesdon, UK). SNP were chosen from previously reported sequence variants of possible functional importance. Allele frequencies were calculated for each genotype and differences in allele frequency between stone-forming patients with AS and controls were assessed using Fisher's exact test.

Of the 23 stone-forming patients, 10 had a history of a single calculus and 13 had recurrent stone disease. Stone-forming patients had a mean age of 42.5 years with a mean AS duration of 20 years. In the 6 SNP genotyped, no significant differences in allele frequency were noted between controls and AS patients with renal stones. We found no association between *ANKH* polymorphisms and renal stone formation in patients with AS.

Initial reports regarding *ANKH* showed no relationship with susceptibility to AS[6]. However, weakly positive findings have been reported by some authors, and the association may be strong in women[7,8]. Pimentel-Santos, *et al* showed that *ANKH* is not a major determinant of susceptibility to AS and *ANKH* polymorphism does not influence AS severity[1]. We investigated *ANKH* polymorphism in a subgroup of AS patients with a history of renal stones. We noted that an increased disease duration and hypercalciuria may play a role in the formation of renal stones in AS[2]. It can be speculated that *ANKH* gene polymorphism and renal stone formation may be related. However, we did not find an association between *ANKH* and renal stone formation in AS. Although this finding may have resulted from the small size of our sample group, it is possible that there is no relationship between *ANKH* and renal stone formation in AS. We suggested that *ANKH* polymorphism in renal stone formers with evidence of hypopyrophosphaturia requires investigation[9].

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