The association between FOK-I vitamin D receptor gene polymorphisms and bone mineral density in patients with systemic lupus erythematosus

Sirs,

Bone loss is a frequently occurring complication in patients with systemic lupus erythematosus (SLE), but the relationship between vitamin D receptor (VDR) gene polymorphisms and bone mineral density (BMD) in SLE has not been investigated.

The VDR is located on chromosome 12q13.11 (1). The Fok-I (rs10735810) VDR polymorphism is associated with an increased risk of SLE (2). The FOK-I VDR polymorphism changes the structure of the VDR, resulting in a VDR that is 3 amino-acids longer (f) than the wild-type VDR (F). The longer VDR might have reduced transcriptional activity (3), which in turn may affect vitamin D serum levels and bone metabolism. However, the influence of VDR polymorphisms on VDR function is still largely unknown.

Increased 25-hydroxyvitamin D (25(OH)D) levels in subjects carrying the Fok-I ff genotype compared to subjects carrying the FF genotype have been observed in SLE patients (4), as well as in healthy controls and multiple sclerosis patients (5). Because vitamin D deficiency and osteoporosis are both highly prevalent in SLE patients (6) and low 25(OH)D levels have been associated with lower BMD in SLE (6, 7), bone mass in SLE might be influenced by the Fok-I genotype.

The aim of this study was to assess the relationship between Fok-I VDR polymorphisms and BMD in SLE. We hypothesise that the ff genotype might be associated with a higher BMD and decreased bone loss in SLE patients.

Demographic and clinical data of 123 SLE patients were collected. Genotyping was performed by restriction fragment length polymorphism analysis as previously described (5, 8). BMD measurements of the hip and the lumbar spine were performed using dual x-ray absorptiometry at baseline and follow-up. Differences between groups were determined by using χ-square test, independent samples *t*-test, Mann-Whitney U-test and univariate linear regression.

Of the 123 included patients (mean age 42.5±12.3 (SD) years, 89% female, 72% Caucasian ethnicity), 47% carried the FF genotype, 39% the Ff genotype and 14% the ff genotype. Mean ± SD follow-up duration between the two BMD measurements was 5.3±2.9 years. Demographic and clinical variables were not significantly different between the three genotypic groups.

Compared to patients with the FF and Ff genotypes, patients carrying the Fok-I ff genotype had significantly higher mean BMD values in the lumbar spine, but not in the hip (Table I).

The observed association between Fok-I ff genotype and higher mean spine BMD might partially be mediated by higher mean 25(OH)D levels in the Fok-I ff SLE patients (data not shown), which finding is in line with the results of studies in Brazilian SLE patients (4), multiple sclerosis patients, and healthy controls (5).

In contrast, studies in healthy subjects demonstrated higher BMD in subjects carrying the FF genotype compared to subjects with ff or Ff genotypes. A supposed interaction between the VDR gene and the immune system might provide an explanation for this finding. An *in vitro* study demonstrated higher transcriptional activity for proinflammatory cytokines for cells expressing the F genotype as opposed to cells expressing the f genotype (9), which in turn may induce increased bone loss. Indeed, lower mean BMD and higher C-reactive protein levels were observed in ankylosing spondylitis patients carrying the Fok-I FF genotype compared to the ff genotype (10).

In our study, BMD changes in the hip and spine during follow-up were not significantly different between the three allelic groups. Possibly, our study population was too small and/or the follow-up duration was too short to detect a difference in BMD changes related to Fok-I polymorphisms.

A larger prospective study is needed to elucidate the role of VDR polymorphisms on bone metabolism in SLE.

J. JACOBS[1] *MD*
A.E. VOSKUYL[1] *PhD. MD*
L.-A. KORSWAGEN[1] *MD*
R. THEUNISSEN[2]
J.W. COHEN TERVAERT[2] *PhD, MD*
I.E.M. BULTINK[1] *MD, PhD*

[1]Department of Rheumatology, VU University Medical Center, Amsterdam, The Netherlands; [2]Clinical and Experimental Immunology, Maastricht University, The Netherlands.

Address correspondence to:
Irene E.M. Bultink, MD, PhD, Department of Rheumatology, VU University Medical Center PO Box 7057, 1007 MB Amsterdam, The Netherlands.
E-mail: iem.bultink@vumc.nl

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Table I. BMD and BMD change in the three different genotypic groups.

	VDR FOK-I polymorphism					
	All patients (n=123)	FF (n=58)	Ff (n=48)	ff (n=17)	*p*-value[a] FF/Ff *vs*. ff	Beta* FF/Ff *vs*. ff
BMD hip, mean ± SD g/cm^2	0.90 ± 0.13	0.90 ± 0.14	0.89 ± 0.12	0.92 ± 0.11	0.55	-0.06
T-score hip	-0.45 ± 0.97	-0.47 ± 1.01	-0.55 ± 0.95	-0.13 ± 0.84	0.15	-0.13
Z-score hip	-0.10 ± 1.00	-0.10 ± 1.09	-0.19 ± 0.93	+0.11 ± 0.86	0.36	-0.09
Mean % BMD change/year in hip	-0.31 ± 1.4	-0.27 ± 1.27	-0.38 ± 1.60	-0.26 ± 1.34	0.86	-0.02
BMD spine, mean ± SD g/cm^2	1.00 ± 0.15	1.00 ± 0.16	0.98 ± 0.14	1.07 ± 0.12	0.04	-0.18
T-score spine	-0.52 ± 1.36	-0.57 ± 1.40	-0.74 ± 1.31	+0.33 ± 1.02	0.01	-0.24
Z-score spine	-0.03 ± 1.46	-0.06 ± 1.59	-0.25 ± 1.28	+0.66 ± 1.42	0.03	-0.19
Mean % BMD change/year in spine	-0.16 ± 1.6	-0.07 ± 1.55	-0.40 ± 1.76	+0.18 ± 1.22	0.35	-0.09

a: univariate linear regression.
*negative Beta: higher values in the ff group compared to the FF/Ff group; BMD: bone mineral density; VDR: vitamin D receptor.