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Association of VDR gene polymorphisms with heart disease in chronic renal failure patients

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Introduction

It has been postulated that vitamin D receptor (VDR) polymorphisms influence mortality in chronic renal failure (CRF) by directly modifying VDR protein levels or VDR sensitivity in target organs. There is growing evidence that low vitamin D status adversely affects cardiac function (figure 1). Here we aimed at evaluating the possible association of VDR FokI and BsmI gene polymorphisms with co-morbid conditions of CRF at different stages.

Design, setting, participants, and measurements

The patients included in this study were a Sicilian cohort of 171 subjects, at CRF stage 1-2 (n=49), stage 3 (n=34), stage 4-5 (n=34), and hemodialysis (HD)(n=54). Almost 70% of patients were also suffering from heart disease, with/without diabetes and/or hypertension, and 40% were also suffering of hypertension, with/without diabetes and/or heart disease; only around 20% had no co-morbid conditions.

Results

A highly significant association was found between the BsmI B minor allele and heart disease in all CRF stages. Indeed, the Odds ratio calculation showed that patients bearing either the bB or BB genotype had, respectively, a seven-fold and around twelve-fold increased risk for heart disease. Instead, the presence of bb wild-type genotype was associated with a fifty-fold reduced risk for heart disease, suggesting that the b allele may display a protective effect. No association was found for FokI genotypes with the different co-morbid conditions.

Table 1 –Clinical and biochemical features of the CRF study cohort.

Biochemical data	*CRF 1-2 (n=49)*	*CRF3 (n=34)*	*CRF4-5 (n=33)*	*HD (n=55)*	*Reference range*
Calcium (mg/dL)	9.0 ± 0.6***	8.5 ± 1.6*	8.2 ± 1.5	7.4 ± 2.3	9-10.7
Phosphate (mg/dL)	3.4 ± 0.6***	3.3 ± 0.6***	3.6 ± 0.5**	4.4 ± 1.5	2.4-4.1
25-OH-Vitamin D (ng/mL)	45.4 ± 23.7***	26.5 ± 16.7	17.9 ± 8.7	22.0 ± 17.2	40-120
Parathormone (pg/mL)	26.1 ± 10.1***	32.2 ± 13.9***	53.8 ± 44.4***	308.8 ± 273.9	11-54
Co-morbid conditions	*Number of patients*	*Number of patients*	*Number of patients*	*Number of patients*	*Total number of patients*
None	7	6	6	14	33 (19.3%)
Diabetes	2	-	-	3	5 (2.9%)
Hypertension	4	2	5	1	12 (7.1%)
Heartdisease	15	9	8	28	60 (35.1%)
Diabetesmellitus/Heartdisease	1	-	-	6	7 (4.1%)
Diabetesmellitus/Hypertension	1	2	-	2	5 (2.9%)
Hypertension/Heartdisease	14	9	12	-	35 (20.4%)
Diabetes mellitus/ Heart disease/Hypertension	5	6	2	1	14 (8.2%)

*Legend:*p<0.05, **p<0.01, ***p<0.0001, significant value in comparison with HD patients.*

Figure 1:

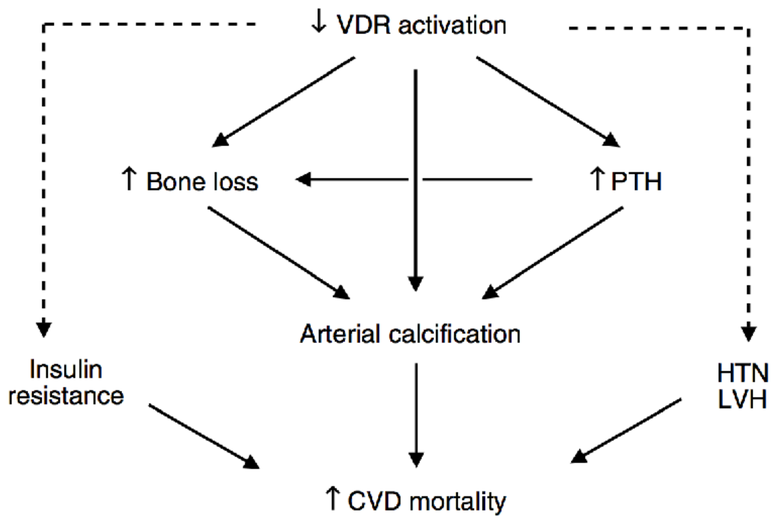

Figure 1. Role of VDR activation on CVD mortality (from Xiang W, et al:. Am J Physiol Endocrinol Metab 2005

Table 2 – Distribution of VDR FokI and BsmI genotypes in the different CRF groups.

PATIENTS (n=171)	*FokI ff* (n=17)	*FokI fF* (n=57)	*FokI FF* (n=97)	*BsmI bb* (n=53)	*BsmI bB* (n=81)	*BsmI BB* (n=37)
CRF 1-2 (n=49)	5 (10.2%)	16 (32.7%)	28 (57.1%)	13 (26.5%)	24 (49.0%)	12 (24.5%)
CRF 3 (n=34)	4 (11.8%)	11 (32.3%)	19 (55.9%)	9 (26.5%)	17 (50.0%)	8 (23.5%)
CRF 4-5 (n=34)	2 (5.9%)	18 (52.9%)	14 (41.2%)	14 (41.2%)	14 (41.2%)	6 (17.6%)
HD (n=54)	6 (11.1%)	12 (22.2%)	36 (66.7%)	17 (31.5%)	26(48.1%)	11 (20.4%)

Table 3 – Association of VDR FokI and BsmI polymorphisms with co-morbid conditions in CRF patients recruited for this study.

Polymorphism / CRF co-morbid condition	*FokI* ff (n=17)	*FokI* Ff (n=57)	*FokI* FF (n=97)	*BsmI* bb (n=53)	*BsmI* Bb (n=81)	*BsmI* BB (n=37)
Diabetes (n=31)	5 (29.4%)	12 (21.1%)	14 (14.4%)	10 (18.9%)	17 (21.0%)	4 (10.8%)
Hypertension (n=66)	9 (52.9%)	26 (45.6%)	31 (32.0%)	19 (35.8%)	32 (39.5%)	15 (40.5%)
Heart disease (n=116)	11 (64.7%)	39 (68.4%)	66 (68.1%)	10 (18.9%) ***	71 (87.7%) ***	35 (94.6%) ***

*Legend: ***p<0.0001, significant value in comparison with all other genotypes.*

Conclusion

We first demonstrated that the VDR BsmI B allele may be considered as a genetic determinant for heart disease and hypertension in CRF, independently from disease stage. Thus, the screening for VDR variants should be regarded as a way to better address preventive strategies and improving the management of CRF co-morbid conditions

Main References

Testa A, et al **J Bone Miner Res 2010**;25:313-9.; El-Shehaby AM, et al. **Scand J Clin Lab Invest 2013**;73:75-81; Santoro D, et al. **Nutrients 2014**;6:1029-37.

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