Vitamin D receptor (VDR) polymorphism and the risk of cardiovascular events

Polimorfizm receptora witaminy D (VDR) a ryzyko zdarzeń sercowo-naczyniowych

Grażyna Sygitowicz, Łukasz Pera, Dariusz Sitkiewicz

Department of Laboratory Medicine, Biochemistry and Clinical Chemistry, Medical University of Warsaw, Warsaw, Poland

INTRODUCTION

The present-day understanding of the role of vitamin D in the human body goes far beyond its primary function as regulator of calcium and phosphate metabolism. The role played by vitamin D in normal energy metabolism in the body, in the functioning of the immune system and cardiovascular system is receiving increasing attention. A relationship between vitamin D deficiency in the serum and the occurrence of risk factors of cardiovascular diseases, such as hypertension [1], hyperlipidaemia [2], diabetes [3] and known cardiovascular events, including coronary heart disease, stroke and myocardial infarction [4] has been demonstrated.

The described effects result from a regulation of gene transcription by a vitamin D active metabolite, namely 1α,25-dihydroxyvitamin D_3 [1,25$(OH)_2D_3$], which acts through the vitamin D nuclear receptor [5]. The VDR activated by 1,25$(OH)_2D_3$ interacts with the promotor region of target genes after the formation of a transcription complex with ligands. Vitamin D receptor (VDR) acting as a transcription factor has an influence on hormonal secretion, immunological response, cell division and differentiation [6].

The present paper considers studies of the effect of respective VDR polymorphisms on the risk of cardiovascular events. Propositions trying to elucidate observations are also presented.

VDR

VDR belongs to a nuclear receptor family that consists, for example, of steroid-dependent receptors and retinoic acid receptors. VDR forms homodimers or heterodimers with one of the retinoid X receptors (RXRα, RXRβ, RXRγ) according to the cell type and finally interacts with its DNA binding site (VDRE) [7].

An activated VDR as a transcription factor has an effect on the activity of genes associated with innate immunity of the body (increases synthesis of antimicrobial peptides and cytokines) (Table 1) [8]. VDR possesses immunomodulating properties. An inhibition of genes encoding interleukin 17 and 17A protein and CCR-6 chemokine receptor [9] by VDR has been demonstrated. Furthermore, an inhibition *in vitro* of neoplastic cell proliferation (breast cancer, prostate cancer, colonic carcinoma) by activated VDR was observed. This effect is probably connected with an increase in synthesis of inhibitors of cyclin-dependent kinases, such as p21, p27, with concurrent inhibition of synthesis of transcription factors c-myc and c-fos. An induction of apoptosis in neoplastic cells through inhibition of synthesis of Bcl-2 by VDR has been also demonstrated [10].

Table 1. Influence of vitamin D receptor on selected signalling molecules

Effect	Influence on signalling molecules
Immunomodulating effect	↑ AMPs, cathelicidins, IL-4
	↓ INF-γ, TNF-α, MMP-9, IL-17, IL-17A, IL-1β, MCP-1, ICAM-1, VCAM-1, CCR6
Regulation of calcium and phosphate metabolism	↑ CaBP, osteocalcin, osteoponin
	↓ collagen
Anti-proliferative effect	↑ p21, p27
	↓ Bcl-2, c-fos, c-myc

↑ amplification, ↓ inhibition; AMPs —antimicrobial proteins; IL — interleukin; INF-γ — interferon-γ; TNF-α — tumour necrosis factor-α; MMP-9 — matrix metalloproteinase-9; MCP-1 — monocyte chemotactic protein-1; ICAM — intercellular adhesion molecule; VCAM — vascular cell adhesion molecule; CCR — C-C chemokine receptor; CaBP — calcium-binding protein; p21, p27 — cyclin-dependent kinase inhibitors; Bcl-2 — antioncogen; c-fos, c-myc — protooncogenes

Address for correspondence:
Dr Grażyna Sygitowicz, Department of Laboratory Medicine, Biochemistry and Clinical Chemistry, Medical University of Warsaw, ul. Banacha 1, 02–097 Warszawa, Poland, e-mail: gsygitowicz@poczta.onet.pl

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VDR GENE

More than 470 VDR single nucleotide polymorphisms (SNPs) have been determined so far. The VDR encoding gene is located on chromosome 12 and contains nine exons [11]. The greater part of the studies describing VDR SNP have concerned five SNPs in the Caucasian population: rs10735810 – Foc1 in exon 2, rs1544410 – BsmI in intron 8, rs731236 – Taq1 in exon 9, rs7975232 – Apa1 in intron 8, and rs757343 – Tru91 in intron 8. The significance of the respective SNPs results from their different locations in the VDR encoding gene. The FocI polymorphism is located at the site encoding a DNA-binding domain sequence of VDR protein. The other SNPs are located in DNA sequences encoding ligand domains [12].

Special attention has been paid to the BsmI and FocI polymorphism. The presence of BsmI SNP leads to an alternative VDR mRNA splicing *in vitro* [13]. The VDR FocI gene single nucleotide polymorphism determines two potential VDR gene transcription start points, which results in the synthesis of two alternative versions of the VDR protein: a long and a short one. A greater regulatory ability of the VDR protein short version has been observed [14].

VDR POLYMORPHISM AND RISK OF CORONARY HEART DISEASE

The risk of coronary heart disease (CHD) according to VDR polymorphism has been the subject of cohort studies that have covered populations differing in quantity and ethnicity.

In the study carried out by van Shooten et al. [15] that covered 41 Caucasian patients with documented CHD, a result close to statistical significance indicating a higher incidence of CHD in carriers of *bb* allele pair of BsmI VDR (OR 4.2; 95% CI 0.8–22.5; p = 0.06) was obtained. Unlike van Shooten et al. [15], Ortlepp et al. [16] demonstrated an increased risk for CHD among carriers of BB allele pair of BsmI VDR. This study was carried out in 293 Caucasian patients (OR 1.32; 95% CI 1.1–1.58; p = 0.05) [15].

Moreover, two successive studies performed by Shanker et al. [17] (287 patients of Indian origin) and Pan et al. [18] (152 patients of Chinese origin) have not shown a relationship between VDR BsmI and FocI single nucleotide polymorphism and increased risk of CHD. An increased risk of CHD in carriers of VDR BsmI single nucleotide polymorphism has also not been confirmed in the study carried out by Ortlepp et al. (3,441 Caucasian patients) [16].

VDR POLYMORPHISM AND ARTERIAL HYPERTENSION

The VDR BsmI and FocI gene polymorphism was the only one shown to be associated with a risk of arterial hypertension. Muray et al. [19] carried out genotyping in 590 healthy persons (260 men, 330 women). A higher systolic blood pressure was found in men who were carriers of VDR BsmI gene bb homozygote compared to other genotypes ($p < 0.006$) [19]. Unlike Muray et al. [19], Lee et al. [20] demonstrated among 798 healthy persons of Korean origin a statistically significant higher systolic (by 2.7–3.7 mm Hg) and diastolic pressure (by 1.9–2.5 mm Hg) in carriers of B allele of VDR BsmI gene. Arterial hypertension was found more frequently in this group than in persons with a different VDR polymorphism (OR 2.1; 95% CI 1.0–4.4; p = 0.05) [20].

Wang et al. [21] have also shown among 695 men an increased risk of arterial hypertension in carriers of VDR BsmI gene bb homozygote and VDR FocI gene ff homozygote (OR 1.25; 95% CI 1.04–1.51; $p > 0.05$; and OR = 1.32; 95% CI 1.03–1.70; $p > 0.05$; respectively) [21].

VDR POLYMORPHISM AND OTHER CARDIOVASCULAR EVENTS

El-Shehaby et al. [22] carried out genotyping of VDR BsmI single nucleotide polymorphism in 80 patients with chronic renal failure. It was shown that left ventricular hypertrophy — a risk factor which is a prognostic indicator of chronic renal failure — is found statistically significantly more often in carriers of B-allele of VDR BsmI gene single nucleotide polymorphism than in carriers of different genotypes (b-allele of VDR BsmI, other SNPs) [22].

At the same time, Ortlepp et al. [23] demonstrated an increased risk of myocardial infarction in carriers of B-allele of BsmI VDR (OR 1.38; 95% CI 1.07–1.79; p = 0.016). However, the authors emphasised that the behavioural (tobacco smoking, alcohol consumption) risk of myocardial infarction is, after all, of greater importance than that of genetic risk factors including BsmI polymorphism.

These observational studies were an attempt to identify the role of the VDR polymorphism in cardiovascular events. $1,25(OH)_2D_3$ acting through VDR regulates the transcription of genes responsible for several key reactions in the body. A proposition based on *in vitro* studies and clinical observations that the protective effect of vitamin D on the cardiovascular system is manifested by regulation of inflammatory reaction, which is of key importance in the atheromatous plaque formation (Table 2), was submitted. Furthermore, vitamin D has an antiproliferative effect on monocytes in cardiac-muscle hypertrophy and regulating action on the renin–angiotensin system.

A relationship between specific VDR polymorphism and risk of cardiovascular events was not unequivocally indicated by the studies presented above. However, further research should undoubtedly look into whether VDR mediates the biological activities of cardioprotective vitamin D in order to elucidate this mechanism of action.

Conflict of interest: *none declared*

Tabela 2. Potential mechanisms of the cardioprotective effect of vitamin D [24]

Potential mechanism of action	Observations
Anti-inflammatory	• Inhibition of maturation of antigen-presenting cells • Inhibition of NF-κB activity • Inhibition of release of MMP-9 and C-reactive protein • Restriction of TNF-α and TGF-β release induced by high concentration of glucose and liposaccharides • Inhibition of synthesis of MCP-1, angiotensinogen and PAI-1; the above effects were demonstrated by *in vitro* studies
Anti-proliferative	• Inhibition of smooth muscle cell proliferation • Decrease in LVH
Regulation of RAS	• An increase in serum vitamin D concentration decreases renin concentration • A vitamin D supplementation reduces blood pressure • Disturbances of vitamin D receptor activity in mice led to LVH, an elevation of blood pressure and an increase in renin concentration • Activated vitamin D receptor acts as a repressor of renin encoding gene transcription

NF-κB — nuclear factor-kappa B; MMP-9 — matrix metalloproteinase-9; TNF-α — tumour necrosis factor-α; TGF-β — transforming growth factor-β; MCP-1— monocyte chemotactic protein-1; PAI-1 — plasminogen activator inhibitor-1; LVH — left ventricular hypertrophy; RAS — renin–angiotensin system

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