Vitamin D endocrine system and the genetic susceptibility to diabetes, obesity and vascular disease. A review of evidence

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SUMMARY

The Vitamin D endocrine system regulates multiple aspects of calcium metabolism and cellular differentiation and replication in the immune system, endocrine pancreas, liver, skeletal muscles and adipocytes. It plays an important role in glucose homeostasis, notably, in the mechanism of insulin release. Actions of vitamin D are mediated by the binding of 1, 25-(OH)2D3 to a specific cytosolic/nuclear vitamin D receptor (VDR), a member of the steroid/thyroid hormone receptor superfamily. Several frequent polymorphisms are found in the *VDR* gene and were reported to be associated with a variety of physiological and pathological phenotypes in many populations. In this paper, we will review the evidences suggesting associations of allelic variations in the *VDR* gene and phenotypes related to body weight, glucose homeostasis, diabetes and its vascular complications.

Key-words: Vitamin D · Vitamin D receptor (VDR) · Vitamin D binding protein (DBP) · Type 1 diabetes · Type 2 diabetes · Obesity · Insulin secretion · Insulin sensitivity · Cardiovascular disease.

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RÉSUMÉ

Vitamine D et prédisposition génétique au diabète, à l'obésité et aux maladies artérielles. Une revue de la littérature récente

Le système hormonal de la vitamine D joue de multiples rôles physiologiques. En dehors de ses cibles classiques impliquées dans l'homéostasie calcique, la forme active de l'hormone, 1, 25-(OH)2D3, aurait une action biologique dans nombreux tissus, organes ou systèmes, parmi lesquels on peut citer le système immunitaire, le pancréas endocrine, le foie, les muscles et les adipocytes. La vitamine D joue un rôle important dans la sécrétion physiologique d'insuline et dans le maintien d'une tolérance normale au glucose. La forme active de l'hormone, 1, 25-(OH)2D3, se lie à un récepteur intracellulaire spécifique (VDR), qui fait partie de la super-famille des récepteurs nucléaires des hormones stéroïdes. Plusieurs variants, fréquents dans la population générale, ont été identifiés dans le gène VDR, et des associations avec différents traits phénotypiques ont été rapportées dans de nombreuses populations. Dans cette revue, nous résumons et discutons les résultats plus significatifs de la littérature concernant les associations alléliques du gène VDR avec les variations du poids corporel, l'homéostasie glucidique, les diabètes sucrés et leurs complications vasculaires.

Mots-clés : Vitamine D · Récepteur de la vitamine D (VDR) · Protéine de liaison de la vitamine D (DBP) · Insulino sécrétion · Sensibilité à l'insuline · Diabète de type 1 · Diabète de type 2 · Obésité · Maladie cardiovasculaire.

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The vitamin D endocrine system regulates multiple aspects of calcium metabolism and cellular differentiation and replication in many target organs in addition to those directly involved in calcium homeostasis (bones, intestinal tract, kidneys and parathyroid gland). These include the immune system, endocrine pancreas, liver, skeletal muscles and adipocytes [1-3]. It is now clear that the vitamin D endocrine system plays an important role in glucose homeostasis and, notably, in the mechanisms of insulin release. In animal models and in humans, vitamin D deficiency is associated with impaired insulin secretion, which is normalised by vitamin D administration [4-6]. Correlations between serum concentrations of vitamin D metabolites, plasma glucose and insulin secretion were observed in humans [5, 7]. The molecular pathways by which 1, 25-dihydroxyvitamin D3 [1, 25-$(OH)_2D_3$] regulates insulin synthesis are not precisely defined [8]. However, it was shown that vitamin D promotes general activation of protein synthesis in pancreatic η-cells [9], modulates the glycolytic pathway [10], enhances Ca^{++} influx into η-cells [11] and stimulates the conversion of proinsulin to insulin [12].

The circulating metabolites of vitamin D bind with high affinity to the vitamin D-binding protein (DBP) [13], a single-chain serum glycoprotein. DBP is encoded by the *Gc* gene, a member of a multigene cluster that includes albumin and ζ-fetoprotein genes, located at chromosome 4q11-q13 [13]. Studies in knocked-out mice demonstrated the important role DBP plays in maintaining stable serum stores of vitamin D metabolites and modulating their bioavailability, activation and end-organ responsiveness [14]. Sequence variations in the *Gc* gene give rise to three major electrophoretic variants of DBP [15]. These variants differ by amino acid sequence as well as by attached polysaccharide structures. They also differ by their binding affinity for vitamin D and its metabolites [16]. Several studies in non-Caucasian populations have suggested associations of DBP phenotypes or related genotypes with type 2 diabetes mellitus or with glucose or insulin levels [17-23]. However, these results were not confirmed in larger cohorts of American or French Caucasian subjects [24, 25].

The actions of the vitamin D endocrine system are mediated both by genomic and non genomic pathways [26]. The former are activated by the binding of 1, 25-$(OH)_2D_3$ to a specific cytosolic/nuclear vitamin D receptor (VDR), a member of the steroid/thyroid hormone receptor superfamily [5]. Non genomic pathways are activated via a putative membrane vitamin D receptor (mVDR) and might be responsible for rapid effects of vitamin D [27]. The *VDR* gene is located on chromosome 12q12-q14 in humans. Rare loss of function mutations in its coding regions are associated in homozygous carriers with an autosomal recessive form of familial vitamin D-resistant rickets [28]. Several frequent polymorphisms are also found in the *VDR* gene *(fig 1)* [29], and were reported to be associated with a variety of physiological and pathological phenotypes in many populations. These include variations in circulating levels of 1, 25-$(OH)_2D_3$ [30], variations in bone mineral density [31, 32], modulation of intrauterine and early postnatal growth [33, 34] and adult height [34]. Other studies showed associations with variations in body weight [35], insulin sensitivity [36], insulin secretion in response to glucose [37, 38], susceptibility to type 1 [39] or type 2 diabetes [36] and severity of coronary artery disease [40]. However, not all associations were consistently found in all populations.

In this paper, we will review the evidences suggesting associations of allelic variations in the *VDR* gene and phenotypes related to body weight, glucose homeostasis, diabetes and its vascular complications.

VDR allelic variation and susceptibility to type 1 diabetes

VDR is expressed in many cell types of the immune system [41] and immune defects are observed in VDR knockout mice [42]. These observations are consistent with a physiological role for vitamin D in the modulation of immune responses. An increasing body of data in mice and humans suggest that vitamin D could modulate the pathophysiological process leading to autoimmune diabetes [43]. Thus, studies in NOD mice showed increased diabetes incidence in animals with vitamin D deficiency in the early weeks of life [44]. Conversely, oral administration of vitamin D or vitamin D analogues was shown to prevent diabetes onset in the animals as long as treatment was maintained [45]. Epidemiological data in humans showed a threefold increase in the incidence of type 1 diabetes when vitamin D deficiency was present in the first months of life [46].

These observations led investigators to look for possible associations of VDR polymorphisms with type 1 diabetes. A first study was performed in Southern Indian families with type 1 diabetes and in this population the *"b"* allele of the *Bsm*I variant or *"b"*-allele containing haplotypes were shown to be preferentially transmitted by parents to affected offspring [39]. Several populations with different genetic backgrounds have been studied since [47-53]. *VDR* polymorphisms were found to be associated with risk for type 1 diabetes in many but not all of these investigations, but the statistical power of some studies was probably low. Different risk alleles, genotypes or haplotypes were found in different populations (data summarised in *table I*). One possible explanation for these contrasting results could be the presence of variable degrees of linkage disequilibrium between the variants and the putative functional mutation or mutations in the different populations. The map of single nucleotide polymorphisms (SNP) of the *VDR* gene region was developed [54], and a recent study analysed associations of 98 *VDR* SNPs in up to 3,763 type 1 diabetic families from the UK, Finland, Norway, Romania, and USA