Polymorphisms in Vitamin D-Related Genes

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Vitamin D deficiency represents a major healthcare problem. Vitamin D status is influenced by genetic and environmental determinants. Several observational studies have evaluated the association of single-nucleotide polymorphisms (SNPs) in vitamin D-related genes and vitamin D levels. Nevertheless, little is known about the role of these SNPs in the response to vitamin D supplementation. We conducted an interventional study to define the association between SNPs in vitamin D-related genes and the response to vitamin D supplementation in 100 self-reported healthy women of Arab ancestry for the majority. Methods. A total of 100 healthy female subjects received a weekly oral dose of 50,000 IU vitamin D for 12 weeks. Serum vitamin D concentration and metabolic profiles were measured at baseline and 12 weeks post-vitamin D supplementation. The genotypes of 37 SNPs selected from previously reported vitamin D-related genes have been assessed by Fluidigm genotyping assay. Results. Rs731236 (VDR gene) and rs7116978 (CYP2R1 gene) showed a significant association with vitamin D status. The rs731236 GG genotype and the rs7116978 CC genotype were associated with a “vitamin D sufficiency” state. Rs731236 GG and rs7116978 CC genotypes showed a higher response to vitamin D supplementation. Transcription factor binding site prediction analysis showed altered binding sites for transcription factors according to the different rs7116978 alleles. Interestingly, the 37 SNPs previously established to play a role in vitamin D-related pathways explained very little of the response to vitamin D supplementation in our cohort, suggesting the existence of alternative loci whose number and effect size need to be investigated in future studies. Conclusion. In this paper, we present novel data on vitamin D-related SNPs and response to vitamin D supplementation demonstrating the feasibility of applying functional genomic approaches in interventional studies to assess individual-level responses to vitamin D supplementation.

Keywords: vitamin D ; polymorphisms ; vitamin D deficiency ; Qatar

1. Introduction

Vitamin D plays an important role in the endocrine system, and it takes part in several biological processes such as blood pressure regulation, calcium and phosphate homeostasis, nerve conduction, skeletal development, erythropoiesis, and so forth. [1][2][3]. The active form of vitamin D, 1,25-dihydroxyvitamin D [1,25(OH)2D], regulates the expression of vitamin D-related genes involved in calcium transport and bone matrix protein [4][5]. Nevertheless, vitamin D deficiency has been well documented worldwide [6]. Several factors have been shown to contribute to vitamin D deficiency, including low skin exposure to sunlight, low dietary intake of vitamin D, high body mass index (BMI), genetic predisposition, the gut microbiome, and the immune system [7][8][9][10][11]. The Middle East regions are also affected by vitamin D deficiency [3][12][13][14]. In fact, despite having ample sunshine, these regions register the highest rate of vitamin D deficiency [13]. This is partially explained by the limited sun exposure due to cultural practices. Other common risk factors in these regions include female gender and clothing style, multiparity, sedentary lifestyle, and low intake of vitamin D and calcium from the diet [14][15].

There are two forms of vitamin D: vitamin D2 and vitamin D3. Vitamin D2 mainly comes from fortified foods like breakfast cereals, milk, and other dairy items, while vitamin D3 is made by the body on exposure to sunlight [16]. In the bloodstream, vitamin D2 and vitamin D3 are converted to the major circulating form of vitamin D, which is 25-hydroxyvitamin D (25(OH)D) [17]. Serum 25(OH)D level is thus considered the best indicator of vitamin D supply to the body from both cutaneous synthesis and nutritional intake. Ethnic differences in the prevalence of common genetic polymorphisms provide an additional explanation for low vitamin D levels. Studies related to the role of the genetic background on the responsiveness to vitamin D supplementation are yet in their infancy [18][19].

Noteworthy, while current studies provide data about vitamin D deficiency, they have been mainly focused on the Western populations [20][21][22], thus their conclusions do not necessarily apply to populations with a different genetic background. Additional research is warranted to understand the role of the genetic background in responsiveness to vitamin D supplementation, especially in regions disproportionally affected by vitamin D deficiency such as the Arab populations.

2. History and Development

To date, observational and functional studies have been performed on vitamin D in Middle Eastern countries, however, interventional studies are currently lacking. The evidence from observational studies in humans is often susceptible to bias and confounders, thus provides limited evidence for causality. We designed this interventional study to test the hypothesis whether genetic polymorphisms in genes involved in the effect and/or metabolism of vitamin D3 influence the outcome of vitamin D3 supplementation by recruiting participants with low vitamin D levels (deficient or insufficient). We believe this question to be particularly relevant since little is known about the role of the genetic background in vitamin D deficiency and/or responsiveness to supplementation in the Arab population.

When selecting SNPs (single-nucleotide polymorphisms), we aimed at choosing the ones previously reported to be associated with vitamin D-related traits in addition to a few SNPs we wanted to explore [5]. These SNPs were selected from genes associated with vitamin D and included cytochrome P450 family 2, R (CYP2R1) [5][22][23][24][25][26][27], cytochrome P450 family 24 subfamily A member 1 (CYP24A1) [22][27][28][29][30][31], the 1-alpha-hydroxylase (CYP27B1) [32][33][34][35], the 7-dehydrocholesterol reductase/NAD synthetase 1 (DHCR7/NADSYN1) [26][36], the vitamin D receptor (VDR) [37][38], and the vitamin D-binding protein GC (group-specific component) [20][21][22][26][28][39][40].

3. Findings

Vitamin D is a fat-soluble vitamin that is produced when the skin is exposed to UVB radiation [46]. Vitamin D deficiency is associated with chronic liver [47] and kidney [48] diseases.

The actions of vitamin D are mediated by several proteins. VDR (vitamin D receptor) is a ligand-activated transcription factor that acts through vitamin D response elements located near the start sites of target genes to regulate gene expression [49]. GC (group-specific component) encodes for a vitamin D binding protein that plays an important role in the transport and metabolism of vitamin D, being the major plasma carrier for vitamin D and its metabolites [50]. The vitamin D pathway also involves a series of cytochrome P450-containing sterol hydroxylases that generate and degrade the active hormone serving as a ligand for the vitamin D receptor-mediated transcriptional gene expression [51]. Among these hydroxylases, CYP2R1 is the principal enzyme carrying the hydroxylation of vitamin D to 25-hydroxyvitamin D in the liver [52]; the 1a-hydroxylation of 25(OH)D in the kidney by CYP27B1 generates the fully active vitamin D metabolite [51][52]. Cytochrome P450 family 24 subfamily A member 1 (CYP24A1) gene encodes a mitochondrial monooxygenase which catalyzes the 24-hydroxylation of 1,25-dihydroxyvitamin D3 [51].

Recent studies have suggested that SNPs within the genes above may influence the level or activity of vitamin D, but studies exploring the association of SNPs in vitamin D-related genes with the response to supplementation of vitamin D are still lacking.

The present interventional study assessed the association between SNPs previously established to play a role in vitamin D-related genes and the responsiveness to vitamin D supplementation after the intervention. Our data showed that both rs731236 (VDR gene) and rs7116978 (CYP2R1 gene) have a significant association with the vitamin D status, where the rs731236 GG and the rs7116978 CC genotypes were associated with a “vitamin D sufficiency” state. In addition, rs731236 GG and rs7116978 CC genotypes were associated with a higher response to vitamin D supplementation. With the exception of rs731236 and rs7116978, the remaining SNPs previously established to play a role in vitamin D-related pathways explained very little the response to vitamin D supplementation in our cohort, suggesting the existence of alternative loci whose number and effect size warrant future studies.

Rs7116978 is located in an intronic region. Whereas the recognition of functional variants in the coding region is relatively simple, detecting changes in the noncoding region is more challenging due to the lack of a clear connection between nucleotide differences and regulatory functions. Some introns have been shown to contain transcription factor binding sites [53][54] and to influence gene expression by several known and unknown mechanisms such as intron-mediated enhancement [55][56]. In this study, we speculated that the two alleles of rs7116978 may change potential binding sites for different transcription factors. We have performed TFBS (transcription factor binding site) prediction analysis in silico to verify this hypothesis. The two alleles were predicted to modify transcription binding sites of several transcription factors, including transcription factor 4 (TCF4) and the human glucocorticoid receptor (GR). Several studies have shown the link between these transcription factors with vitamin D metabolism. Beildeck et al. found that 1,25(OH)2D3 induces the expression of TCF4 in several human cell lines via a VDR-dependent mechanism [57]. As per the proposed model, TCF4 upregulation would enhance the repression of β-catenin/TCF target genes. With regards to the human glucocorticoid receptor (GR), cross-sectional studies have shown that the chronic use of glucocorticoids is associated with low levels of 25(OH)D [58]. It appears that the glucocorticoids can upregulate the renal expression of CYP24A1 which in turn

catabolizes 25(OH)D and 1,25(OH)2D to water-soluble inactive agents, thus mediating deficiency of vitamin D [58][59]. Another link between the use of glucocorticoids and vitamin D is that 1,25(OH)2D/VDR and glucocorticoids/glucocorticoid receptor (GR) intracellular signaling pathways cross-talk so that the increased levels of vitamin D may enhance the responsiveness of certain target cells to glucocorticoids [60][61][62]. Glucocorticoids with their cognate receptors translocate from the cell cytoplasm to the nucleus where they bind to glucocorticoid response element (GRE) to regulate gene transcription. As VDR and GR share some coactivators, VDR may promote individual gene transcription induced by GR; additionally, it has been reported that vitamin D may upregulate the binding of GR to GRE [60]. These may result in vitamin D enhancing the cellular responsiveness to glucocorticoids. Functional studies are warranted to understand the importance of rs7116978 polymorphism as a potential regulator of gene expression.

The vitamin D molecular pathway is a complex process that varies across individual genetic profiles and according to their health status. As this current topic is still in its infancy, additional studies are warranted to elucidate how genetic variation contributes to vitamin D supplementation outcomes.

4. Conclusions

In conclusion, the present interventional study shows novel data about the association of vitamin D-related SNPs with responsiveness to vitamin D supplementation in individuals of Arab ancestry. Our findings should be validated in additional studies employing a cohort of a bigger size.

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