

The possible association of VDR polymorphisms to the response of asthmatic children to Vitamin D supplementation- Nabil Mohamed ElBahie - Alexandria University

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Introduction:

The association of Vitamin D and children with asthma is known and there are several individual studies on Vitamin D polymorphisms. A human body produces vitamin D as a response to sun exposure. A person can also boost their vitamin D intake through certain foods or supplements. The association between vitamin D receptor (VDR) polymorphisms and asthma risk has been inconsistently investigated, but published studies demonstrated conflicting results. The vitamin D endocrine system is central to the control of bone and calcium homeostasis. Thus, alterations in the vitamin D pathway lead to disturbances in mineral metabolism. Furthermore, a role for vitamin D has been suggested in other diseases, like cancer, diabetes and cardiovascular disease. Expression and nuclear activation of the vitamin D receptor (VDR) are necessary for the effects of vitamin D. Several genetic variations have been identified in the VDR. DNA sequence variations, which occur frequently in the population, are referred to as "polymorphisms" and can have biological effects. Expression and nuclear activation of the vitamin D receptor (VDR) are necessary for the effects of vitamin D. The vitamin D receptor (VDR also known as the calcitriol receptor) is a member of the nuclear receptor family of transcription factors. Calcitriol (the active form of vitamin D, 1,25-(OH)₂vitamin D₃) binds to VDR, which then forms a heterodimer with the retinoid-X receptor. The VDR heterodimer then enters the nucleus and binds to Vitamin D responsive elements (VDRE) in genomic DNA. VDR binding results in expression or transrepression of many specific gene products. VDR is also involved in microRNA-directed post transcriptional mechanisms. In humans, the vitamin D receptor is encoded by the VDR gene located on chromosome 12q13.11. VDR is expressed in most

tissues of the body, and regulates transcription of genes involved in intestinal and renal transport of calcium and other minerals. Glucocorticoids decrease VDR expression. Many types of immune cells also express VDR. Several genetic variations have been identified in the VDR. DNA sequence variations, which occur frequently in the population, are referred to as "polymorphisms" and can have biological effects. Mutations in this gene are associated with type II vitamin D-resistant rickets. A single nucleotide polymorphism in the initiation codon results in an alternate translation start site three codons downstream. Alternative splicing results in multiple transcript variants encoding the same protein. VDR gene variants seem to influence many biological endpoints, including those related to osteoporosis. The vitamin D receptor plays an important role in regulating the hair cycle. Loss of VDR is associated with hair loss in experimental animals. Experimental studies have shown that the unliganded VDR interacts with regulatory regions in cWnt (wnt signaling pathway) and sonic hedgehog target genes and is required for the induction of these pathways during the postnatal hair cycle. These studies have revealed novel actions of the unliganded VDR in regulating the post-morphogenic hair cycle. Researchers have focused their efforts in elucidating the role of VDR polymorphisms in different diseases and normal phenotypes such as the HIV-1 infection susceptibility and progression or the natural aging process. The most remarkable findings include the report of VDR variants that bolster vitamin-D action and that are directly correlated with AIDS progression rates, that VDR association with progression to AIDS follows an additive model and the role of FokI polymorphism as a risk factor for enveloped virus infection as revealed in a meta-analysis. The importance of this gene has

also been noted in the natural aging process were 3'UTR haplotypes of the gene showed an association with longevity. The VDR gene encodes the nuclear hormone receptor for vitamin D. The most potent natural agonist is calcitriol (1,25-dihydroxycholecalciferol) and the vitamin D2 homologue ercalcitriol, 1-alpha,25-dihydroergocalciferol) is also a strong activator. Other forms of vitamin D bind with lower affinity, as does the secondary bile acid lithocholic acid. The receptor belongs to the family of trans-acting transcriptional regulatory factors and shows similarity of sequence to the steroid and thyroid hormone receptors. Downstream targets of this nuclear hormone receptor include many genes involved in mineral metabolism. The receptor regulates a variety of other metabolic pathways, such as those involved in the immune response and cancer. To test whether there is a linkage between VDR polymorphisms and diseases, epidemiological studies are performed. In these studies, the presence of a variation of the gene is studied in a population of patients, and then compared to a control group. Thus, association studies are performed, and a link among gene polymorphisms and diseases can be established. Since the discovery of VDR polymorphisms a number of papers have been published studying its role in bone biology, renal diseases, diabetes, etc. The purpose of this review is to summarize the vast amount of information regarding vitamin D receptor polymorphisms and human diseases, and discuss its possible role as diagnostic tools. The actions of Vit D are mainly mediated through Vit D receptors (VDR). Different trials studied the possible association between the VDR genetic variants, for e.g. Apal and TaqI and asthmatic populations in different ethnic groups. During this study, patients were given a daily oral 600 IU of Vit D in addition to their inhaled corticosteroids for 3 months. 64% of the population showed a polymorphism of Apal and 66.3% of TaqI including both homozygous and heterozygous polymorphisms.

Based upon the clinical asthma control level improvement, the patients were categorized as responders (Rs); 62.1% and Non Responders (NRs); 37.9%. The genotypic distribution of both polymorphisms was significantly different between Rs and NRs. Low Vit D mean serum level was detected at the beginning of the study and was significantly increased after 3 months of Vit D supplementation. Pulmonary function tests (PFTs) results were also significantly ameliorated. While the Rs of different genotypic groups performed significantly better in the PFTs, there was no significant difference between the Vit D serum level between the Rs and the NRs before and after the intervention for the whole population. Daily low dose of Vit D supplementation was beneficial to the asthmatic children as 62.1% of the study population showed a favorable outcome while the role of these specific polymorphisms is not clear yet.