High dose vitamin D treatment regulates the gene expression pattern in T helper cells of type 1 diabetes patients

M. Penna-Martinez1, H. Hess1, C. Döring2, N. Nejatian1, D. Bogdanou1, F. Shoghi1, M-L. Hansmann2 and K. Badenhoop1
1Department of Internal Medicine, Division of Endocrinology, 2Senckenberg Institute of Pathology, University Hospital Frankfurt am Main, Germany

Introduction / Objectives

Dysregulated T helper cells and vitamin D (VD) deficiency are important factors in the pathogenesis of Type 1 diabetes mellitus (T1D). Therefore, we investigated the immune effects of high dose VD treatment on gene expression pattern (GEP) in T helper cells (Th) before and after VD-therapy in patients with T1D.

Patients and Methods

Seven T1D patients with 25(OH)D3 levels below 20 ng/mL received three months 4000 IU/d Vigandol oil as part of the RCT VDDIA1. The 25(OH)D3 concentration and gene expression within Th cells were measured at baseline (V1) and after three months treatment (V3). Th helper cells were isolated from freshly collected EDTA-blood by density gradient centrifugation, subsequently enriched by magnetic sorting and total RNA was isolated. After cDNA synthesis the gene expression profile was investigated using GeneChip Human 1.0 ST (Affymetrix). 25(OH)D3 plasma concentrations were measured by radioimmunoassay. VD-therapy effects on the gene expression were evaluated using the differences between V1 and V3 (expressed in fold change<FC) within each patient by the statistical computing environment R version 3.0.2 [R Development Core Team, 2005].

Results

Figure 2: 25(OH)D3 level after VD therapy.

The 25(OH)D3 concentration increased in median from 14 to 38 ng/mL (median differences 24.4 ng/mL; p = 0.02) after high dose VD.

Table 1: Validation of GEP using real time RT-PCR. The data are expressed as median (interquartile range = IQR). The microarray results were checked in seven randomly selected genes using real time PCR. The upregulation of the genes JUNB (p < 0.05) and DUSP2 (p<0.05) was confirmed in T1D patients.

Conclusions

The elevation of 25(OH)D3 induced by Vigandol therapy (4000 IU/day) leads to differential gene expression pattern in Th cells from T1D patients (four genes upregulated/fourty-four genes down regulated). The Th cell response to vitamin D results in an upregulated gene set (IFNAR1, NUDC and ZNF830). Our data as validated by RT-PCR suggest an indirect VD effect particularly on the upregulated gene set (DUSP2 and JUNB) probably via activation of transcription factor such as activator protein 1 (AP-1). These data can help to explain how vitamin D treatment can tip a balance from a pro- to an anti-inflammatory cellular environment.

References