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ORIGINAL RESEARCH

Medicine Science 2017;6(3):393-7

Medicine Science International Medical Journal

Vitamin D and pro-inflammatory cytokine IFN-γ and the anti-inflammatory cytokines IL-4 and IL-10 in peritoneal dialysis patients

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Received 01 November 2016; Accepted 21 December 2016
Available online 23.12.2016 with doi: 10.5455/medscience.2016.05.8575

Abstract
Several clinical trials in patients with chronic disease have found that active vitamin D usage lowers pro-inflammatory cytokines. The aim of this study was evaluate whether supplementation of cholecalciferol in peritoneal dialysis patients with vitamin D deficiency would lead any chance in the pro-inflammatory cytokine IFN-γ and the anti-inflammatory cytokines IL-4 and IL-10, and pentraxin 3 and peripheral blood mononuclear cell subpopulations (CD3, CD4, CD8, CD45)and CD4/CD8 ratio. We analyzed fasting blood samples from 31 continuous peritoneal dialysis patients (15 males, 16 females, mean age 48,6±14,8 yrs) for serum 25-hydroxyvitamin D [25(OH)D)] and specific plasma cytokine concentrations (interferon-gamma [IFN-γ], interleukin [IL]-4, and IL-10), pentraxine 3, CD3, CD4, CD8 and CD45 before and after cholecalciferol replacement. Before and after cholecalciferol replacement mean 25 (OH) level was 6,1±2,1 ng/dL and 39,7±10,9 ng/dL respectively (p<0,05). There was no difference in CD3, CD4, CD8, CD4 to CD8 ratio, and CD45, serum IL4, IL 10, and pentraxin 3 levels after vitamin D replacement, but there was a significant decrease in white blood cell count, IFN-γ levels ($P < 0.05$). Cholecalciferol replacement resulted in decrease in proinflammatory cytokine IIFN-γ wherease cholecalsiferol replacement could not induce any change in the serum levels of antiinflammatory cytokines IL4, IL 10 and peripheral blood mononuclear cell subpopulations we studied. It seems that although there are stimuli that simultaneously may induce generation of many cytokines, each cytokine is derived from a distinct pathway that may be affected differentially by vitamin D .

Keywords Dialysis, Vitamin D, pro-inflammatory cytokines, anti-inflammatory cytokines, peripheral blood mononuclear cell subpopulations

Introduction

The biologically active form of vitamin D_3, 1,25-dihydroxyvitamin D_3 ($1,25(OH)_2D_3$), has been shown to influence the differentiation and function of both the innate and adaptive immune cell types and to augment cytokine production differentially [1,2]. Vitamin D_3 has been described to exhibit immunomodulatory effects with the uncovering of vitamin D receptors (VDR) expression on activated $CD4^+$ and $CD8^+$ T lymphocytes and antigen-presenting cells (APC) such as monocytes, dendritic cells and macrophages [3,4].

1-alpha hydroxylase (CYP1a) is a mitochondrial cytochrome p450 super-family enzyme that catalyzes hydroxylation and metabolic activation of 25-hydroxyvitamin D_3 (25 (OH) D) into $1,25(OH)_2D_3$. CYP1a expression in activated macrophages, dendritic cells, B and T cells enables them to synthesize functional vitamin D [5,6]. Some studies demonstrate that vitamin D supplementation as cholecalcipherol or ergocalciferol improves cytokine profiles in patients with chronic diseases, such as congestive heart failure and osteoporosis [7,8].

Patients with chronic kidney disease are recognized to have serologic evidence of an activated inflammatory response [9,10]. Dialysis patient are given active vitamin D to decrease parathroid hormone (PTH). The dose of active vitamin D are adjusted according to PTH levels. Mostly active vitamin D is prescribed once a day. Vitamin D deficiency is very common in patients on chronic dialysis [11,12]. We do not know whether the dose of active vitamin D adjusted according to PTH levels is sufficient for immunomodulatory effects of vitamin D on dialysis patients with vitamin D deficiency. The life time of active vitamin D as a drug is short being for 4-6 hours [12].

In normal physiological conditions, 25 (OH) D is a constant source of active vitamin D. Body can have active vitamin D anytime according the requirement of the body. It is possible that whereas the half-life is shorter as medicaments active vitamin D, and therefore the same effect may not be available continuously.

We hypothesized that supplementation of cholecalciferol in peritoneal dialysis patients with vitamin D deficiency

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would lead any chance in the pro-inflammatory cytokine IFN-γ and the anti-inflammatory cytokines IL-4 and IL-10, and Pentraxin 3 and peripheral blood mononuclear cell subpopulations (CD3, CD4, CD8, CD45)and CD4/CD8 ratio.

Material and Methods

We analyzed fasting blood samples from 31 (15 males, 16 females, mean age 48,6±14,8 yrs) continuous peritoneal dialysis patients for vitamin D status (serum 25-hydroxyvitamin D [25(OH)D)] and specific plasma cytokine concentrations (interferon-gamma [IFN-γ], interleukin [IL]-4, and IL-10), CD3, CD4, CD8 and CD45. This study was approved by the institutional ethical committee. Clinically unstable patients, those with tumors or inflammatory diseases (such as chronic pulmonary disease, and malnutrition), and those treated with immunosuppressives were excluded. No patient showed signs of inflammation or infection during the study period. In all patients 25 (OH)D level was less than 20 ng/mL (<50 nmol/L).

In our clinic we prescribe cholecalciferol to all CKD patients whose 25(OH) D levels are less than 30 ng/ml (75 nmol/L). This study included the patients prescribed colecalciferol as a rutin protocol, 50 000 IU orally once per week for 4-8 weeks or $Devit_3$ ampule (300,000 IU cholecalciferol) in a single dose per month orally for 2-3 months. The levels of 25(OH) was rechecked and, if still deficient, the patient was given another course of cholecalciferol. Calcitriol and alphacalciferol dosing (if patients were on either of these drugs) was recorded.

Patients were seen in the PD clinic every 4 weeks. At the beginning of the study serum levels of corrected total calcium, phosphorus, albumin, total protein, iPTH, and 25 (OH)D were measured. Usage of active vitamin D (1 alpha calcidiol) were documented.

Fasting samples of venous blood were obtained from an antecubital vein between 08:30 and 09:00 h in all subjects for general analytical data. Blood samples to measure IL 4,10, Interferon gamma and 25 (OH)D were centrifuged immediately, and the serum samples were stored at −20°C until analysis of other measurements. Blood samples were analysed on the same day for total and differential white cell counts and CD3, CD4, CD8, and CD45 using a coulter counter.

25(OH) D levels were measured by High performance liquid chromatography method (Recipe Chemical Instrument GmbH, Munich Germany). Levels of IL-4, IL10, pentraxine 3, Interferon gama were measured by ELISA (Basic Radim Immunoassay Operator, Radim Spa, Pomezia, Italy). Cells were phenotypically analyzed by flow cytometry (BD FACS CANTO II, USA).

Statistical analysis

All the numerical variables are given as the mean ± SD. Differences between repeated measurements were analyses with Paired - Samples T test or Wilcoxon test where appropriate. Differences between patients on alphacalciferol and on not were tested using Mann-Whitney *U* or Student's *T* testing where appropriate. All reported probability values are 2-tailed, and a *P*-value<0.05 was considered statistically significant. Categorical data were expressed as percentages and compared using X^2 analysis or Wilcoxon test.

Results

The mean age was 48,6±14,8 years. Duration of dialysis was 66,19±57,1 months. Baseline mean 25 (OH) level was 6,1±2,1 ng/dL and after cholecalcipherol replacement mean 25 (OH) level was 39,7±10,9 ng/dL (p<0,05). Table 1 showed etiological factors of the chronic kidney disease. Twenty four (77.4 %) of the patients were on alphacalciferol to control PTH. The dosage of the alphacalciferol was 0,48±0.35 mcg/day. There was no change in dose of alphacalciferol during the cholecalciferol replacement.

Table 1: Etiology of chronic kidney disease

	N	%
Hypertension	12	38.7
Chronic glomerulonephritis	5	16.2
Unknown	4	12.9
Others	4	12.9
Diabetes Mellitus	3	9.7
Nephrolithiasis	3	9.7

There was no difference in total serum calcium, phosphore, total protein, albumin, iron, ferritin levels, plateletes number, CD3, CD4, CD8, CD4 to CD8 ratio, and CD45, IL4, IL 10 levels (P > 0.05) after vitamin D replacement, but there was a significant decrease in white blood cell count, PTH, IFN-γ levels (P < 0.05) (Table 2).

Table 2: Laboratory results of the patients after and before cholecalciferol replacement

	Before cholecalciferol replacement Mean±standart deviation N:31	After cholecalciferol replacement Mean±standart deviation N:31	p
BUN (mg/dL)	59.1±18,3	57.5±15,4	0.364
Creatinine (mg/dL)	9.4±2,8	9.2±2.6	0.366
Albumin (gr/dL)	3.1±0.4	3.1±0.5	0.315
Calcium (mg/dL)	9.1±0.8	9.1±0.9	0.825
Phosphore (mg/dL)	4.7±1.1	4.9±1.2	0.215
PTH (pg/mL)	543.0±462.2	450.4±388.0	**0.004**
Iron (µg/dL)	63.7±28.8	60.2±24.1	0.322
Iron binding cap.(µg/dL)	169.1±47.8	171.4±42.7	0.724
Ferritine (ng/mL)	478.8±417.1	454.7±422.0	0.050
CRP (mg/dL)	1.16±2.0	1.28±1.4	**0.008**
WBC (10^3/mL)	8.2±2.1	7.8±2.3	**0.042**
Lymphocyte (%)	19.15±5.71	20.03±9.5	0.938
HGB (g/dL)	10.7±1.3	10.3±1.5	**0.041**
PLT (10^3/mL)	253.7±67.1	251.6±62.9	0.761
25(OH)D (ng/mL)	6.1±2.1	39.7±10.9	**0.000**
Cd3 (%)	73.3±9.4	73.7±8.7	0.953
Cd4 (%)	44.1±8.4	43.9±9.4	0.802
Cd8 (%)	32.6±9.3	33.9±8.6	0.210
Cd45 (%)	97.4±4.2	97.9±5.2	0.176
CD4-8(%)	1.53±0.74	1.43±0.65	0.117
Interleukin 4 (pg/mL)	2.3±1.3	2.1±1.1	0.236
Interleukin 10 (pg/mL)	9.8±6.7	9.1±5.4	0.095
Interferon -γ (IU/mL)	0.14±0.03	0.12±0.04	**0.030**
Pentraxin-3 (ng/mL)	0.61±0.43	0.71±0.78	0.496

Discussion

Several clinical trials in patients with chronic disease have found that active vitamin D usage (which improves status) lowers pro-inflammatory cytokines [7,8,13]. The effect of 1,25-(OH)2D3 deficiency, as well as of replacement therapy with 1 alpha-hydroxyvitamin D_3[1 alpha-$(OH)D_3$], on the production of tumor necrosis factor-alpha (TNF-alpha) by peripheral blood mononuclear cells and on the serum levels of soluble TNF receptors (sTNFRs) in hemodialysis (HD) patients was investigated by Harran et al [14]. These authors reported that therapy with 1 alpha-hydroxylated vitamin D_3 analogs normally given to HD patients for the management of renal osteodystrophy may also regulate the in vivo activity of TNF-alpha [18].

Tabata et al [15] reported that four weeks of oral administration of 0.5 micrograms/day of 1 alpha-OHD_3 enhanced the IL-2 production of peripheral blood mononuclear cells from the patients. This fact suggests that 1 alpha-OHD_3 therapy may be useful for the restoration of IL-2 production in hemodialysis patients, and that the vitamin D_3 deficiency may be responsible for the impairment of cellular immunity associated with IL-2 production disorder in hemodialysis patients.

Turk et al [16] treated 28 hemodialysis patients either oral or intravenous (IV) pulse calcitriol treatment in a study. These authors reported that oral and IV calcitriol caused a significant fall in IL-1 beta and IL-6 levels at the 6th month of treatment. These effects were prominent in IV calcitriol group.

Wu et al [17] in 25 patients treated with calcitriol treatment for 16 weeks reported significant decrease in inflammatory markers (CRP and IL-6) inflammatory cytokine (CD4(+) IFN-γ) and increase in anti-inflammatory cytokine (CD4(+) IL-4).

Borazan et al [13] compared the effect of oral and intravenous calcitriol treatment on bone-resorptive cytokines in hemodialysis patients. Serum IL-1, IL-6 and TNF-α levels were significantly decreased from baseline values after 3 months in the intravenous study group, but not in the oral group. These authors reported that the decreased serum IL-1 and IL-6 levels might also be due to a direct effect of calcitriol on pro-inflammatory cytokines [13].

It was reported that increased vitamin D intake or increased exposure to sunlight, to raise blood concentrations of $25(OH)D_3$ above 30 mg/ ml, are necessary for maximal extrarenal production of $1,25(OH)_2D_3$ in a wide variety of tissues and cells in the body, including colon, breast, prostate, lung, activated macrophages, and parathyroid cells. In patients on dialysis, including anephric individuals, high doses of ergocalciferol or $25(OH)D_3$ can raise the serum levels of $1,25(OH)_2D_3$ [18,19].

Some experimental data showed that cholecalciferol is able to suppress the release of TNF-α and to enhance IL-10 synthesis [20-21]. High blood concentrations of 25(OH)D were associated with high IL-10 concentrations [22]. Several tissues, such as cytokine-producing immune cells, express 1-α-hydroxylase [23] and are thus able to make calcitriol for themselves from circulating 25(OH)D. Although serum calcitriol concentrations are usually homeostatically regulated, local calcitriol production depends on the concentration of circulating 25(OH)D [12, 22].

Schleithoff et al [8] reported that a daily supplement of 50 µg vitamin D for 9 months is able to increase serum concentrations of the antiinflammatory cytokine IL-10 and to prevent an increase in serum concentrations of the proinflammatory cytokine TNF-α in chronic heart failure patients [12].

In English literature there are few studies evaluated the direct relationship between serum 25 (OH)D levels or replacement of cholecalciferol and cytokines in dialysis patients.

Stubbs et al [24] in seven HD patients with 25(OH)D insufficiency assessed changes after cholecalciferol and paricalcitol therapies serum levels of inflammatory cytokines. Cholecalciferol therapy increased serum 25(OH)D levels four-fold, monocyte vitamin D receptor expression three-fold, and 24-hydroxylase expression; therapy decreased monocyte 1 -hydroxylase levels. Cholecalciferol therapy reduced circulating levels of inflammatory cytokines, including IL-8, IL-6, and TNF. These authors suggest that nutritional vitamin D therapy has a biologic effect on circulating monocytes and associated inflammatory markers in patients with ESRD.

Oral cholecalciferol was prescribed once a week in the first 12 weeks (50,000 IU) and in the last 12 weeks (20,000 IU) to 30 HD patients not receiving vitamin D therapy, and presenting with 25(OH)D levels of <30 ng/mL by Bucharles et al [25]. After 6 months of cholecalciferol supplementation, as well as a significant reduction in interleukin-6 levels (after 6 months of supplementation) were observed.

Assimon et al [26] in a pilot study treated 20 HD patients on doxercalciferol with ergocalciferol. These authors could not show any change in IL-6, TNF-α.

In our study replacement with cholecalciferol resulted in decreased levels of the proinflammatory cytokine IIFN-γ wherease cholecalsiferol therapy could not induce an increase in the serum levels of antiinflammatory cytokines IL4 and IL 10. It is difficult to assess why vitamin D had a greater effect on proinflammatory cytokine IFN-γ levels whereas treatment had no effect on the anti inflammatory cytokines IL4 and IL10. One potential explanation is that although there are stimuli that simultaneously may induce generation of many cytokines, each cytokine is derived from a distinct pathway that may be affected differentially by vitamin D. Seventy seven percent of our patients were on alphacalciferol theraphy during the study. However, we could not find any difference according to IL4, IL 10, pentaxin 3 and IFN-γ levels between patients on alphacalciferol and not before and after cholechalciferol replacement.

Khoo et al [2] investigated if and to what extent seasonality of vitamin D_3 levels are associated with changes in T cell numbers and phenotypes. Every three months during the course of the entire year, human peripheral blood mononuclear cells and whole blood from 15 healthy subjects were sampled and analyzed using flow cytometry. These authors observed that elevated serum $25(OH)D_3$ and $1,25(OH)_2D_3$ levels in summer were associated with a higher number of peripheral CD4 + and CD8 +T cells. In addition, an increase in naı¨ve CD4+CD45RA + T cells with a reciprocal drop in memory CD4 + CD45RO+ T cells was observed. These authors reported that the increase in CD4 + CD45RA + T cell count was a result of heightened proliferative capacity rather than recent thymice migration of T cells.

However, in our study there was no significant change in CD3, CD4, CD8, CD4 to CD8 ratio, and CD45 counts after vitamin D supplementation.

Several studies have shown the evidence for a T and B cell defects in dialyses patients, but it has not been determined precisely how the T and B-cell function comes to be damaged. Various hypotheses attribute the damage of the T -cell function to protein-caloric malnutrition, D3 and B6 vitamin deficiency, lowered blood zinc level , blood transfusion and a fraction of serum very low density lipoprotein [27-29].

Our study has several limitations. Firstly, the small sample size limits the power of our study. Secondly It is not a placebo controlled drug study. We prescribe cholecalciferol to all patients with vitamin D deficiency as a routine approach. This study examined effect of our this routine approach on the pro-inflammatory cytokines IFN-γ and the anti-inflammatory cytokines IL-4 and IL-10 in PD patients on active vitamin D in order to suppress PTH. Thirtly we could not measure 1,25 (OH) D levels. Vitamin D studies in patients on dialysis have predominantly used active vitamin D compounds and focused on $1,25(OH)_2D$ deficiency. We suggest that there is evidence for a proinflammatory state that may be attenuated by vitamin D replacement in CAPD patients with vitamin D deficiency.

As a conclusion, our results show that pro-inflammatory cytokines IFN-γ decreased after vitamin D replacement in PD patients with vitamin D deficiency even the patients had been on active vitamin D. However, anti-inflammatory

cytokines IL 4 and 10 levels did not change after vitamin D replacement. Prospective larger clinical trials are needed to more clearly define these relations.

Acknowledgement: This study was supported by Inonu University Medical Research Center.

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