

**Effect of Intravenous Calcitriol on Serum IL-6 & IL-8 in Regular Hemodialysis Patients**Mostafa Yehya<sup>1</sup>, Ehab Hassan<sup>2</sup>, Yomna Ramadan<sup>3</sup>, Hassan Eissa<sup>4</sup> and Mohamed Elsayed<sup>4</sup><sup>1</sup>Physiology Department, Faculty of Medicine, Fayoum University,<sup>2</sup>Internal Medicine Department, Nephrology Unit, Faculty of Medicine, Fayoum University,<sup>3</sup>Internal Medicine Department, Cairo University,<sup>4</sup>Physiology Department, Cairo University[ehab\\_hassan@hotmail.com](mailto:ehab_hassan@hotmail.com)

**Abstract: Introduction:** The role of vitamin D in the regulation of calcium and bone metabolism is well established. Newer physiologic functions for vitamin D have been identified. Vitamin D plays a vital and complex role in immune system function and regulation. **Aim:** is to study the effect of intravenous calcitriol treatment on the immune system in chronic regular haemodialysis patients through the study of the serum levels of IL-6 and IL-8 and to study its effect on the serum level of total calcium, ionized calcium, phosphorus, alkaline phosphatase and intact parathyroid hormone. **Methods:** This study was conducted on 45 subjects randomized into three groups. 15 healthy control subjects (Group I), 15 end stage renal disease patients on chronic hemodialysis not receiving calcitriol (Group II) and 15 end stage renal disease patients on chronic hemodialysis receiving calcitriol (Group III). Serum levels of markers of mineral metabolism ( total calcium, ionized calcium, phosphorus, intact PTH (iPTH), alkaline phosphatase (ALP), complete blood count ( CBC ) with differential, serum cytokine levels(interleukin-6 (IL-6) and interleukin 8 (IL-8) )were collected at the beginning of the study and 1 and 3 months thereafter. **Results:** Calcitriol treatment effectively suppresses iPTH, significantly increases the serum total calcium, ionized calcium and serum phosphorus levels, and decreases the serum ALP levels. Calcitriol treatment causes statistically significant decrease in the serum level of the inflammatory cytokines (IL-6 and IL-8). **Conclusion:** we concluded that haemodialysis patients with secondary hyperparathyroidism should be treated with intravenous calcitriol not only due to its role in the regulation of calcium and bone metabolism, but also due to its vital and complex role in immune system function and regulation.

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**Key Words:** Calcitriol, IL-6, IL-8, chronic kidney disease.

**1. Introduction**

Vitamin D has long been known for its effects on calcium and bone metabolism. Severe vitamin D deficiency causes a lack of bone mineralization, which manifests as rickets in children and osteomalacia in adults (1). Vitamin D can be produced very effectively by humans when ultraviolet radiation B (UVB) from sunlight or artificial sources reaches skin cells. Vitamin D is converted by a hepatic hydroxylase into 25-hydroxyvitamin D (25(OH) D). 25(OH) D is converted in the kidney to its active hormonal form 1, 25 dihydroxyvitamin D<sub>3</sub> (calcitriol) (2).

Circulating calcitriol is adversely affected by high levels of inflammatory cytokines (2). There is evidence for a role of vitamin D in the immune system. Calcitriol is able to induce the differentiation of monocytes into macrophages. In addition, calcitriol increases the activity of macrophages and facilitates their cytotoxic activity. Macrophages represent the first nonspecific defence line of the immune system. It is well known that the prevalence of infections such as pneumonia is high in infants with rickets (3).

Patients with chronic kidney disease and end stage renal disease have vitamin D deficiency that is characterized by low serum 25-hydroxyvitamin D [25(OH) D<sub>3</sub>] levels (4). Serum cytokine levels have been shown to be increased in haemodialysis patients and even in patients with early renal failure. It has been shown that vitamin D deficiency leads to impaired localized innate immunity and defects in antigen-specific cellular immunity (5).

Cross-sectional studies suggested that treatment with activated vitamin D may be associated with a better outcome in patients with end stage renal disease (6). Thus we aimed to investigate the effect of intravenous calcitriol treatment on the immune system in chronic regular haemodialysis patients and to study its effect on serum calcium, ionized calcium, phosphorus, alkaline phosphatase and intact parathyroid hormone levels.

**2. Patients and Methods**

This study was conducted on 45 subjects randomized into three groups. 15 healthy control subjects (**Group 1**) and thirty end stage renal disease patients chosen from patients presenting to the dialysis

unit, Nephrology Department, Fayoum University. These thirty patients were on chronic regular hemodialysis for at least 6 months, their hemoglobin level was above 8 g/dL, GFR < 15 ml/min/1.73m<sup>2</sup>, none of them had received calcitriol therapy during the previous 6 months. 15 of these patients were receiving treatment in the form of erythropoietin 4000 iu by dose 75 IU/Kg body weight by S.C. route per week plus 1500 mg Ca /day by oral route (calcium carbonate 500 mg **Group II**) and the other fifteen started treatment with iv calcitriol (1 µg three times per week) during the study in addition to the above treatment (**Group III**). The calcitriol treatment was interrupted if the serum calcium level rises above 11.5 mg/dl, the phosphorus level rises above 7 mg/dl.

All the patients were haemodialysed with bicarbonate-containing solutions using a polysulphone membrane dialyser with a surface area of 1.4 - 1.6 m<sup>2</sup> for 4 hours three times weekly. The patients and controls were age and sex matched. Consent was taken from all participants. Patients with autoimmune disease, those with evidence of concurrent malignancy or infection, and those on immunosuppressant agents or medications known to interfere with the immune system, non-compliance with hemodialysis are excluded from the study.

All enrolled subjects were subjected to full clinical history and physical examination. Serum markers of mineral metabolism (total calcium, ionized calcium, phosphorus, alkaline phosphatase, intact PTH), Complete blood count with differential count, serum markers of inflammatory cytokines ( interleukin-6 and interleukin-8 ) were done for all patients and controls. The blood samples were withdrawn from the arterial part of the haemodialysis set at the beginning of the study before calcitriol treatment was commenced and 1 and 3 months thereafter.

Serum total calcium, phosphorus, magnesium and ALP were analysed with the Technicon RA-XT chemistry system (Bayer, Leverkusen, Germany) using a calorimetric technique. The ionized calcium level was measured with the Ciba-Corning 288 blood gas analyser (Ciba-Corning, Instrumentation Laboratory, Medica, Nova Biomedical, Holliston, MA, USA) using an ion-selective electrode. Serum iPTH level was measured with the Immulite kit (LKPH1, Diagnostic Products Corporation, Genova, Italy) using a chemiluminescent enzyme immunometric assay. Serum cytokines (IL-6, IL-8) were detected using the RayBio® Human ELISA (Enzyme- Linked Immunosorbent Assay) kit.

#### Statistical analysis

Statistical Package for social science (SPSS) program version 9.0 was used for analysis of data. Group data was expressed as mean, SD (standard deviation). We evaluated differences between the

groups using the one way Anova for multiple group comparisons and T-test for two group comparisons.  $P < 0.05$  was considered statistically significant

### 3. Results

This study was conducted on 45 subjects randomized into three groups. 15 healthy control subjects (**Group I**) and thirty end stage renal disease patients, twenty-four males and six females (M:F=3:1), their age ranged from 30-50 years (mean ± SD = 44.58±4.98). The patients were on chronic regular hemodialysis, their hemodialysis period ranged from 10 - 50 months ( mean ± SD 28.25 ± 8.75 months). 15 of these patients were receiving treatment in the form of erythropoietin 4000 iu by dose 75IU /Kg body weight by S.C. route per week plus 1500 mg Ca /day by oral route calcium carbonate 500 mg) (**Group II**) and the other fifteen started treatment with iv calcitriol (1 µg three times per week) during the study in addition to the above treatment (**Group III**).

**Table (1)** shows comparison between hemodialysis patients (**Group II** and **III**) and the control group (**Group I**) regarding serum markers of mineral metabolism and serum cytokine levels at the beginning of the study. **Table (2)** shows changes in serum markers of mineral metabolism and serum cytokine levels before and after one and three month of therapy in **Group II** patients not receiving IV calcitriol and in **Group III** patients receiving IV calcitriol. **Table (2)** also shows statistical comparison between **Group II** (not receiving calcitriol) and **Group III** (receiving calcitriol) regarding the changes in serum markers of mineral metabolism and serum cytokine levels before and after one and three months of therapy.

**Table (1): Comparison between hemodialysis patients (Group II and Group III) and Group I (Control group) regarding serum markers of mineral metabolism and cytokine levels at the beginning of the study (Mean±SD):**

Parameter Mean ± SD	Group I	Group II	Group III
iPTH (pg/ml)	24 ± 3.52	554.6± 105.6 P < 0.05 a	596.4± 94.7 P < 0.05 b
Total Calcium (mg/dl)	10± 0.3	8.3± 0.4 P < 0.05 a	8.1± 0.3 P < 0.05 b
Ionized Calcium (mg/dl)	4.9± 0.4	3.6± 0.4 P < 0.05 a	3.6± 0.3 P < 0.05 b
Phosphorus (mg/dl)	3.6 ± 0.5	5.2± 0.7 P < 0.05 a	5.1±0.6 P < 0.05 b
ALP (U/L)	88 ± 11.4	468.6±176.5 P < 0.05 a	536±186.6 P < 0.05 b
IL- 6 (pg/dl)	37.8 ± 19.1	409.45±246.3 P < 0.05 a	439±390.2 P < 0.05 b
IL- 8 (pg/dl)	18.0 ± 7.71	81.2±45.9 P < 0.05 a	92.7±50.3 P < 0.05 b

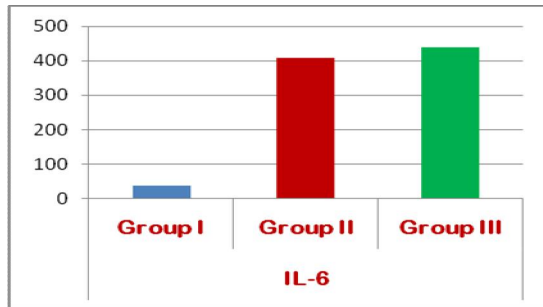
a: Group I compared with value of Group II (base line).

b: Group I compared with value of Group III (base line).

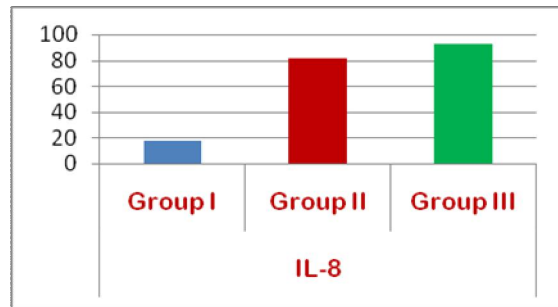
**Table ( 2):** Changes in serum markers of mineral metabolism and serum cytokine level before and after one & three months of therapy in Group II & Group III and statistical comparison between Group II& Group III regarding the same parameters after one and three months of therapy (Mean±SD):

	Group II			Group III		
	Basal	After 1month	After 3 months	Basa	After 1month	After 3 months
iPTH	554.6±105.6 0.853a	546.0±100.5 0.329b	559.4±95.5 0.012c	596.4 ± 94.7 < 0.05 a	568.4±95.3 < 0.05 b	500.6±85.0 < 0.05 c
ALP	468.6±176.5 1.000a	460.0±162.9 0.775b	471.8±177.4 0.264c	536.0±186.6 < 0.05 a	403.8±117.8 < 0.05 b	298.9±90.7 < 0.05 c
Total calcium	8.3±0.4 1.000a	8.3±0.4 1.000b	8.4±0.3 1.000c	8.1 ±0.3 < 0.05 a	8.3±.03 < 0.05 b	8.6±0.3 < 0.05 c
Ionized calcium	3.6±0.4 1.000a	3.5±0.3 1.000b	3.5±0.3 1.000c	3.6±0.3 < 0.05 a	3.8±.04 < 0.05 b	4.0±.04 0.051 c
Phosphorus	5.2±0.7 0.076a	5.1±0.7 0.418b	5.0±0.6 1.000c	5.1±0.6 < 0.05 a	5.5±0.6 < 0.05 b	5.6±0.7 < 0.05 c
IL 6	409.45±246.3	412.41±246.7 1.000 b NS	417.58±250.2 0.591 a NS 0.514 c NS	439.6±390.2 < 0.05 a	351.1±319.9 < 0.05 b	328.3±297.7 < 0.05 c
IL 8	81.2±45.9 0.610a	81.8±48.4 1.000b	84.1±44.4 0.887c	92.7±50.3 < 0.05 a	54.4±9.9 < 0.05 b	38.4±13.5 < 0.05 c

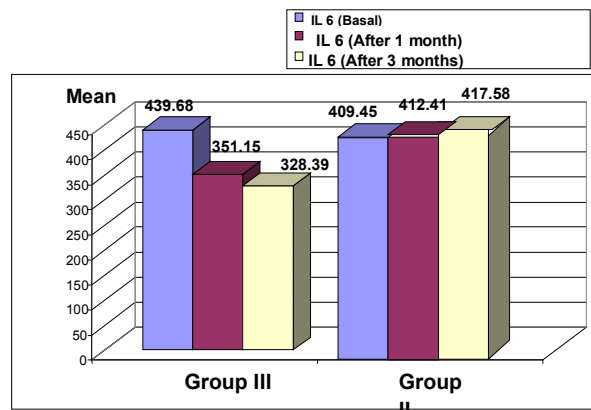
a: Baseline compared with value at 3 months.    b: Baseline compared with value at 1 month.  
c: Value at 1 months compared with value at 3 months.



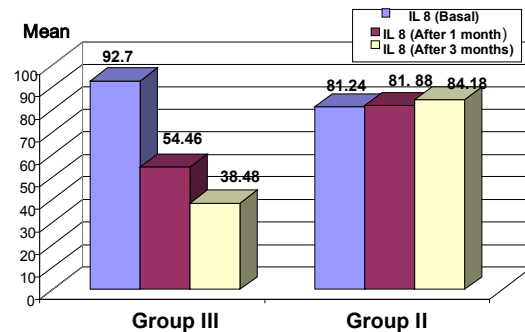
**Figure (1):** Comparison between Group II, III and I regarding IL-6 level at beginning of study:



**Figure (2):** Comparison between Group II, III and I regarding IL-8 level at beginning of study.



**Fig.(3):** Changes in serum level of IL-6 in groups II & III before and after 1 month & after 3 months of therapy



**Figure (4):** Changes in serum level of IL-8 in groups II & III before and after 1 month & after 3 months of therapy

**5. Discussion**

The role of vitamin D in the regulation of calcium and bone metabolism is well established. Newer physiologic functions for vitamin D have been

identified. Epidemiologic and genetic studies as well as research using animal models suggest vitamin D plays a vital and complex role in immune system function and regulation. Vitamin D insufficiency has

been linked with susceptibility to infection, particularly respiratory infections (7), as well as to the development of a variety of cancers (8), and autoimmune diseases (9).

Secondary Hyperparathyroidism (SHPT) is one of the main complications in patients with chronic kidney disease affecting most patients receiving hemodialysis (10). This disorder is characterized by parathyroid gland hyperplasia, increased parathormone secretion, and abnormalities in bone mineral and metabolism. The development of secondary hyperparathyroidism is attributed to decreased calcitriol production, which leads to reduced intestinal calcium absorption, hypocalcaemia and increased PTH synthesis. Failure of the kidney to synthesize calcitriol also leads to phosphate retention and hyperphosphatemia (11). SHPT is generally associated with renal high-turnover bone disease and elevated risk of bone pain and fractures (12).

Patients with uremia or other chronic inflammatory conditions have enhanced activation of T-helper type 1 (Th1) lymphocytes and monocytes secreting pro-inflammatory cytokines IL-1, IL-6, IL-8, IL-12, IFN- $\gamma$  and TNF- $\alpha$  (13).

Cytokines are a family of pleiotropic polypeptides that are produced by different cells in response to inflammatory stimuli, may modulate a variety of functions not only in circulating immune cells, but also in mesenchymal, endothelial, and epithelial cells (14). There is an increasing body of evidence that the interaction between blood and dialytic membranes induces the release of several cytokines from circulating mononuclear cells, such as IL-1, IL-6, IL-8, tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ). The specific action of any of these monocyte-derived cytokines may be relevant in the pathogenesis of clinical manifestations often observed in end-stage renal disease (ESRD) patients undergoing chronic hemodialysis (15).

***In the current study we found*** the basal serum iPTH, phosphorus and ALP levels were statistically significantly increased in Group II ( $P < 0.05$ ) and group III ( $P < 0.05$ ) (hemodialysis patients) when compared to the control group (Group I). The basal serum total calcium and ionized calcium were significantly decreased in Group II ( $P < 0.05$ ) and Group III ( $P < 0.05$ ) when compared to the control group.

Cytokines such as IL-6 and IL-8 have been implicated in the regulation of bone turnover. Increased serum levels of IL-6, IL-8 have been found to be associated with bone resorption in the nonuraemic population. Serum cytokine levels have been shown to be increased in haemodialysis patients and even in patients with early renal failure (13).

Our results showed that the basal serum levels of IL-6 ( $P < 0.05$ ) and IL-8 ( $P < 0.05$ ) were significantly increased in the hemodialysis patients (Groups II and III) than in the healthy control (Group I).

Many studies have been conducted to assess whether supplementation with vitamin D sterols can prevent or ameliorate SHPT in CKD (12). As the key to development of secondary hyperparathyroidism is the failure of the kidney to synthesize 1,25 dihydroxy vitamin D<sub>3</sub>, so it should be used in its management. There are two main forms currently used: calcitriol and alfacalcidol. The actions of both are increased intestinal calcium and phosphorus absorption, increased calcium mobilization from bone, reduced synthesis of PTH and reduced rate of cell growth within the parathyroid gland. The optimum dose, route and duration of calcitriol treatment differ from centre to centre depending on the hemodialysis programme (16).

In our study we used calcitriol 1  $\mu$ g 3times/wk intravenously and we assessed the serum markers of mineral metabolism and serum cytokine levels before and at one and 3 months of therapy. Previous studies compared oral and intravenous calcitriol effects on serum biochemical parameters and bone resorptive cytokines in hemodialysis patients and demonstrated that intravenous calcitriol has a significant depressive effect on iPTH and bone resorptive cytokines in patients undergoing hemodialysis (17, 18).

We found that the mean serum iPTH level was significantly decreased in the hemodialysis patients receiving intravenous calcitriol (Group III) at one ( $P < 0.05$ ) and three months ( $P < 0.05$ ) of therapy than before initiation of therapy when compared to patients not receiving intravenous calcitriol (Group II) ( $P = 0.3$  at one month,  $P = 0.8$  at 3 months of therapy). This is supported by **Patel et al.** (19) who reported that intravenous calcitriol lowered the serum iPTH level. Similar results were also reported by **Tentori et al.** (6).

***The present study also demonstrated*** significant increases in the serum total calcium and ionized calcium in the patients receiving intravenous calcitriol (Group III) at one ( $P < 0.05$ ) and three months ( $P < 0.05$ ) of therapy than before initiation of therapy when compared to patients not receiving it (Group II) ( $P = 1$  at one month,  $P = 1$  at 3months of therapy). This coincides with other studies which reported that there are increases in serum calcium levels and a decrease in serum iPTH level after intravenous calcitriol administration (6). These results were also in agreement with the results reported by **Valdivielso et al.** (20)

***In the study,*** there were significant increases in the serum phosphorus level in the patients receiving

intravenous calcitriol (Group III) at one ( $P < 0.05$ ) and three months ( $P < 0.05$ ) of therapy than before initiation of therapy when compared to patients not receiving it (Group II) ( $P = 1$  at one month,  $P=0.07$  at three months of therapy). The effect of calcitriol treatment on the serum phosphorus level in patients with secondary hyperparathyroidism on a haemodialysis program is unclear. In some studies the serum phosphorus level increased with intravenous calcitriol treatment (21) whereas in others there was no significant change (22). Our explanation of increased serum calcium after iv calcitriol treatment is that it increases the calcium and phosphate levels by increasing the intestinal calcium and phosphate absorption, as well as increasing the calcium and phosphate mobilization from the bone (21).

**The present work demonstrated** significant decreases in the serum ALP level in patients receiving intravenous calcitriol (Group III) but no change in patients not receiving intravenous calcitriol (Group II). The serum ALP level in patients receiving intravenous calcitriol (Group III) was statistically significantly decreased at one ( $P < 0.05$ ) and 3 months ( $P < 0.05$ ) of calcitriol therapy when compared to its level before initiation of therapy whereas there was no statistically significant difference before and after initiation of therapy in patients not receiving calcitriol (Group II) ( $P=1$  at one month,  $P=0.7$  at 3 months). Our result coincides with other studies which have shown that intravenous calcitriol treatment lowered the serum ALP level in patients with chronic renal failure and bone disease (23). It is known that the serum ALP level increases in chronic renal failure patients with osteitis fibrosa, osteomalacia and mixed uraemic bone disease. Monitoring changes in the serum ALP level allows assessment of the disease progression and the efficacy of calcitriol treatment in bone disease associated with chronic renal failure (24).

**Our study revealed** significant decreases in the serum level of IL-6 in patients receiving intravenous calcitriol (Group III) but not in patients not receiving intravenous calcitriol (Group II). The serum IL-6 level in patients receiving intravenous calcitriol (group III) was statistically significantly decreased at the end of 1 month ( $P < 0.05$ ) and 3 months ( $P < 0.05$ ) of calcitriol therapy than before initiation of therapy, but there was no statistically significant difference in IL-6 level in patients not receiving intravenous calcitriol (Group II) at the beginning of the study and 1 ( $P= 0.7$ ) and 3 month ( $P= 1$ ) thereafter. Our results were in agreement with results found by **Giulietti et al.** (25) who demonstrated that IL-6 & IL-8 have been decreased in patients receiving intravenous calcitriol.

**The present work demonstrated,** significant decreases in the serum level of IL-8 in patients

receiving intravenous calcitriol (Group III) but no change in patients not receiving intravenous calcitriol (Group II). The decrease in the serum IL-8 level in patients receiving intravenous calcitriol (Group III) at the end of 1 month ( $P < 0.05$ ) and 3 months ( $P < 0.05$ ) was statistically significant when compared to (Group II) patients not receiving calcitriol ( $P=0.6$  at one month,  $P=1$  at three months of therapy). These results coincides with a recent study which reported significant decreases in IL-8 levels in patients receiving calcitriol (26).

Vitamin D modulates the inflammatory response of immune cells, such as macrophages and monocytes. 1, 25(OH)<sub>2</sub> D<sub>3</sub> attenuates the expression of pro-inflammatory cytokines such as IL-6 (23). Vitamin D has the ability to reduce cytokines such as IL-8 from inflammatory cells. The decreased serum IL-6 and IL-8 levels in our study might also be due to a direct effect of calcitriol on pro-inflammatory cytokines. Serum IL-6, IL-8 levels were significantly decreased from baseline values after 1 month and after 3 months in (Group III), but not in (Group II). These findings suggest that the intravenous calcitriol treatment had a superior effect on the bone resorptive cytokines, which may lead to decreased bone resorption.

Calcitriol administration has been used as the primary treatment to prevent parathyroid gland hyperplasia and reduce serum PTH levels in SHPT. Vitamin D has been proven to be much more than a simple calcium hormone playing important roles in calcium, phosphorus and skeletal homeostasis. The vitamin D receptor (VDR) has been identified on macrophages and activated T lymphocytes suggesting a potential role for vitamin D in regulation of immune system. The vitamin D receptor ligand-mediated signalling cascade is important in lymphocyte/macrophage activities and cytokine release (27). Expression of 1 $\alpha$ -hydroxylase, the enzyme that catalyzes the synthesis of active 1, 25-dihydroxyvitamin D from 25-hydroxyvitamin D, is expressed by cells at extra-renal sites, including epithelial cells, keratinocytes, activated macrophages and dendritic cells (28). This not only highlights the capacity for extra-renal synthesis of the active form of vitamin D, but also the capacity to modulate innate (29) and adaptive immune function at these sites (30).

Patients with uremia or other chronic inflammatory conditions have enhanced activation of T-helper type 1 (Th1) lymphocytes and monocytes secreting pro-inflammatory cytokines IL-1, IL-6, IL-8, IL-12, IFN- $\gamma$  and TNF- $\alpha$ . (13). Vitamin D inhibits the function of T lymphocytes both directly and via effects on antigen presenting cells (APCs). It has potent anti-proliferative effects on CD4<sup>+</sup> T cells. Essentially all published studies using both human and murine models report inhibition of Th1-associated



cytokine production. Vitamin D has been reported to inhibit IL-1, IL-6, IL-8 and IL-17 production (31).

There is evidence for a role of vitamin D in the immune system. Calcitriol is able to induce the differentiation of monocytes into macrophages. In addition, calcitriol increases the activity of macrophages and facilitates their cytotoxic activity. Macrophages represent the first unspecific defence line of the immune system (32).

We concluded that intravenous calcitriol treatment significantly increased the serum total calcium, ionized calcium and phosphorus levels. Calcitriol treatment effectively suppresses iPTH, decreases serum ALP levels, significantly decreased serum inflammatory cytokines (IL -6, IL-8). Our study focused on the non-classic, non-traditional anti-inflammatory and immunoregulatory action of calcitriol. On the basis of our findings, we recommend that haemodialysis patients with secondary hyperparathyroidism would be treated with intravenous calcitriol not only due to its role in the regulation of calcium and bone metabolism, but also due to its vital and complex role in immune system function and regulation.

#### References

1. **Bischoff-Ferrari H, Willett W, Wong J, Stuck A, Staehelin H, Orav E, Thoma A, Kiel D, Henschkowski J:** Prevention of non-vertebral fractures with oral vitamin D and dose dependency: a meta-analysis of randomized controlled trials. *Arch. Intern. Med.* 2009; 169: 551-61.
2. **Zittermann A, Frisch S, Berthold H, Götting C, Kuhn J, Kleesiek K, Stehle P, Koertke H, Koerfer R:** Vitamin D supplementation enhances the beneficial effects of weight loss on cardiovascular risk markers. *Am. J. Clin. Nutr.* 2009; 89: 1321-27.
3. **Antoniucci D, Yamashita T, Portaloë A:** Dietary phosphorus regulates serum fibroblast growth factor-23 concentrations in healthy men. *J. Clin. Endocrinol. Metab.* 2006; 91:3144-49.
4. **Gonzales E, Sachdeva A, Oliver D, Martin K:** Vitamin D insufficiency and deficiency in chronic kidney disease. A single center observational study. *Am.J. Nephrol.* 2004; 24: 503-10.
5. **Wintergerst E, Maggini S, Hornig D:** Contribution of selected vitamins and trace elements to immune function. *Ann. Nutr. Metab.* 2007; 51:301-23.
6. **Tentori F, Hunt W, Stidley C et al.:** Mortality risk among hemodialysis patients receiving different vitamin D analogs. *Kid. Int.* 2006; 70:1858-68.
7. **Liu P, Stenger S, Tang D, Modlin:** Cutting edge: vitamin D-mediated human antimicrobial activity against *Mycobacterium tuberculosis* is dependent on the induction of cathelicidin. *J. Immunol* 2007; 179(4):2060-63. [PubMed: 17675463]
8. **Garland C, Garland F, Gorham E, et al.:** The role of vitamin D in cancer prevention. *Am. J. Public Health* 2006; 96(2):252-261.
9. **Cantorna M:** Vitamin D and its role in immunology: multiple sclerosis, and inflammatory bowel disease. *Prog. Biophys. Mol. Biol* 2006; 92(1):60-64.
10. **Frazer W:** Hyperparathyroidism. *Lancet* 2009; 374: 145-158
11. **Cozzolino M, Galassi A, Gallieni M, Brancaccio D:** Pathogenesis and treatment of secondary hyperparathyroidism in dialysis patients the role of paricalcitol. *Curr. Vasc. Pharmacol* 2008; 6(2):148-53.
12. **Jadoul M, Albert J, Akiba T, et al.:** Incidence and risk factors for hip or other bone fractures among hemodialysis patients in the Dialysis Outcomes and Practice Pattern Study. *Kid. Int* 2006; 70:1358-66.
13. **Fukuhara et al.,** Vitamin D and its analogues as regulators of immune activation, antigen presentation and cytokines. *Annu. Rev. Nutr* 2011; 23:117-145.
14. **Borges A, Mikhail A, Lethbridge M, Kemeny D, Macdougall:** I. Increased levels of cytokines (IFN- $\gamma$ , TNF- $\alpha$ , IL-6 and IL-8) by response to inflammatory stimuli. *J Am Soc Nephrol* 2011; 14:1776-84.
15. **Stenvinkel P, Ketteler M, Johnson R, Lindholm B, Picoitis R, Riella M, Heimbürger O, Cederholm T, Gimdt M:** IL-10, IL-6 and TNF- $\alpha$ . Central factors in the altered cytokine network of uraemia: The good, the bad, the ugly. *Kid.Int* 2005; 67:1216-1233.
16. **Jones G:** Expanding role of vitamin D in chronic kidney disease: importance of blood 25-OH-D levels and extra-renal 1 $\alpha$ -hydroxylase in the classical and non-classical actions of 1,25-dihydroxyvitamin D<sub>3</sub>. *Seminars in Dialysis.* 2007; 20(4):316-324.
17. **Turk S, Akubulut M, Yildiz A, Gurbilek M, Gonen S, Tombul Z, Yeksan M:** Comparative effect of oral and intravenous calcitriol in hemodialysis patients: the effect on IL-1, IL-6 levels and bone mineral density. *Nephron.* 2002; 90(2):188-94.
18. **Borzan A, Ustun H, Cefle A, Sekitmez N, Yilmaz A:** Comparative efficacy of oral and intravenous calcitriol treatment in hemodialysis patients: effects on serum biochemistry and

- cytokine levels. *J.Int. Med. Research* 2003;31(6):489-96.
19. **Patel T & Singh A:** Role of vitamin D in chronic kidney disease. *Semin. Nephrol* 2009 b; 29: 113-121.
  20. **Valdivielso, Block G, Klassen P, Lazarus J, et al.,:** Mineral metabolism, mortality, and morbidity in maintenance hemodialysis patients. *J. Am. Soc. Nephrol* 2011; 15:2208–18.
  21. **Dusso A, Brown A & Slatopolsky E:** Vitamin D. *Am.J.Physiol* 2005; 289: F8–F28.
  22. **Bhan T:** Serum phosphorus level in hemodialysis patients receiving intravenous calcitriol treatment. *J. Clin. Endocrinol. Metab.* 2009; 91:3144-49
  23. **Andress D:** Bone and mineral guidelines in chronic kidney disease, *Cli.J.Am.Soc. Nephrol* 2008; 3: 179-183.
  24. **Biggar A, Block G, Klassen P, Lazarus J, et al.,:** Mineral metabolism, mortality, and morbidity in maintenance hemodialysis patients. *J.Am.Soc. Nephrol* 2011; 15:2208–18.
  25. **Giulleti A, Van E, Overbergh L, Stophels K, Bouillon R, Mathieu C:** Monocytes from type 2 diabetic patients have a pro inflammatory profile, 1,25 dihydroxyvitamin D (D3) works as anti-inflammatory. *Diabetes Res Clin Pract* 2007; 77:47-57.
  26. **Sandhu and Casale:** Cytokines in hemodialysis patients receiving calcitriol. *Clin. Exp. Immunol* 2010;149:123-31.
  27. **Chia C, Jen H, Chun C, Shih B, Lia K, Wen Y, Cai M, Liang K, Kuo C:** Calcitriol inflammation attenuates inflammation and oxidative stress in hemodialysis patients with secondary hyperparathyroidism. *Tokohu J. Exp. Med* 2011; 223(3):153-159.
  28. **Adams J, Hewison M:** Unexpected actions of vitamin D: new perspectives on the regulation of innate and adaptive immunity. *Nat. Clin. Pract. Endocrinol. Metab* 2008; 4(2): 80–90.
  29. **Liu P, Stenger S, Li H, et al.,:** Toll-like receptor triggering of a vitamin D-mediated human antimicrobial response. *Science* 2006;311(5768): 1770–1773. [PubMed: 16497887].
  30. **Sigmundsdottir H, Pan J, Debes G, et al.,:** DCs metabolize sunlight-induced vitamin D3 to ‘program’ T cell attraction to the epidermal chemokine CCL27. *Nat. Immunol* 2007;8(3):285–293.
  31. **Tang J, Zhou R, Luger D, et al.,:** Calcitriol suppresses antiretinal autoimmunity through inhibitory effects on the Th17 effector response. *J. Immunol* 2009; 182 (8):4624–4632. (PubMed)
  32. **Antoniucci D, Yamashita T, Portaloe A:** Dietary phosphorus regulates serum fibroblast growth factor-23 concentrations in healthy men. *J. Clin. Endocrinol. Metab.* 2006;91:3144-49.

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