The effects of calcitriol with calcium carbonate supplementation on inflammatory biomarkers in chronic kidney disease patients’ with low vitamin D

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Abstract

Introduction: Chronic kidney disease (CKD) patients’ are at risk of low vitamin D and chronic inflammation. We studied the effect of 12 weeks calcitriol and calcium carbonate supplementation on inflammatory mediators serum; interleukin-6 (IL-6), interleukin-10 (IL-10) and highly sensitive C-reactive protein (hs-CRP).

Material and methods: A prospective randomized study in CKD stages 2-4 with serum 25-hydroxyvitamin D (25-OHD) levels < 30 ng/ml. Patients were randomized into the Vitamin D + Calcium (Vitamin D+C) or Calcium group. Serums were analyzed at baseline, week 6 and 12.

Results: Fifty patients, median age of 53 (13.5) years were recruited. Their median IL-10 was 13.35 (25.22) pg/ml. At week 12, serum IL-6 was reduced in both groups (p = 0.001), serum IL-10 was maintained in the Vitamin D + C group (p = 0.06) and was reduced in the Calcium group (p = 0.001). CKD-diabetic patients had reduced serum IL-6 in both study groups (p = 0.001) and a reduction was seen in the Vitamin D + C group of the non-diabetics counterparts (p = 0.005). Serum IL-10 was reduced in the Calcium group (p < 0.05) whereas serum 25-OHD rose in both groups, regardless of their diabetic status (p < 0.05).

Conclusions: Twelve weeks, calcitriol supplementation maintained IL-10, had no effects on hs-CRP and had no additional benefit compared to calcium carbonate in reducing serum IL-6 except in non-diabetics.

Key words: inflammation, vitamin D, diabetes, chronic kidney disease, calcitriol.

Introduction

Vitamin D has a diverse biological action in addition to regulating calcium homeostasis[1]. The major circulating vitamin D metabolite is 25-hydroxyvitamin D (25-OHD)-nutritional vitamin D, and the active metabolite is 1,25-dihydroxyvitamin D [1,25-(OH)2D]-active vitamin D. Active vitamin D has immuno-modulatory effects [1]. Vitamin D metabolizing enzymes and their receptors are present in many cell types including various immune cells such as antigen-presenting-cells, T cells, B cells and monocytes.

Besides disordered bone mineralization, vitamin D plays an important role in reducing the risk of many chronic diseases such as diabetes mellitus, cancers, heart disease, multiple sclerosis and psoriasis [2]. Diabetes remains the major cause of chronic kidney disease (CKD) in Malaysia and other countries [3]. Low vitamin D also predisposes CKD patients to chronic infections and subclinical inflammation. Previous studies demonstrated that vitamin D deficiency was associated with increased susceptibility to infections such as tuberculosis and a higher rate of acute respiratory infections [4]. Vitamin D enzymes are unique; the actions of 25-OHD are suggested to be independent of active vitamin D and may have direct effects on the bone health. Synthesis of active vitamin D is not dependent on 25-OHD. However in CKD, this is not hold true and synthesis of active vitamin D is dependent on higher concentration of 25-OHD [5]. The 25-OHD level is used to reliably monitor nutritional vitamin D therapy, however the active vitamin D level is
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Material and methods

A prospective randomized controlled study included 50 CKD patients’ stages 2 to 4 (eGFR 89-15 ml/min/1.73 m²) under the Nephrology Clinic follow up at our institution, who consented to participate. Abbreviated Modification of Diet in Renal Disease (MDRD) study equation was used for estimation of GFR (eGFR) and it was based on serum creatinine at randomization. We included patients aged 20-65 years old who had serum 25-OHD levels < 30 ng/ml. Our exclusion criteria were acute kidney injury, dialysis dependence, chronic liver disease, granulomatous diseases (i.e. tuberculosis, sarcoidosis), malabsorption syndrome or already on any medications that may interfere with vitamin D metabolism. The patients were randomized into 2 groups; Calcium group (oral CaCO₃ 500 mg daily) or Vitamin D + C group (oral CaCO₃ 500 mg daily and oral calcitriol 0.5 μg daily) using computer generated software.

Calcitriol 0.5 μg once a day was chosen because it is an active form of vitamin D and is the lowest minimal dose shown to increase serum active vitamin D [15]. In order to ensure adequate absorption of this Calcitriol, minimum dose of calcium is needed. Therefore, we decided CaCO₃ 500 mg daily to be added and also to be given to the other group to minimize the confounding factor. Baseline data were collected and patients were followed for 12 weeks.

Blood tests for 25-OHD, 1,25-(OH)₂D, IL-6, IL-10, hs-CRP and serum calcium were taken at baseline, week 6 and 12. Serum 25-OHD was measured in duplicates via radio-immuno-assay (RIA) method using commercially available kits from DiaSorin (Minnesota, USA). Mean serum active vitamin D (1,25-(OH)₂D) was measured in duplicates by immuno-extraction and quantitation using enzyme-immunoassays (EIA) using commercially available kits from DiaSorin as well. Plasma interleukins (IL-6 and IL-10) concentrations were assessed using commercially available kits BD OptEIA (San Jose, USA) which use Enzyme-Linked Immuno-sorbent Assay (ELISA) technique. Serum concentrations for hs-CRP were determined using Immulite® 2000 system analyser by Siemens (USA) and it is a solid phase, chemiluminescent immunometric assay.

Statistical analysis was performed using SPSS software version 19. Normally distributed data were expressed as mean ± standard deviation (SD) whereas non-normally distributed data were expressed as median (IQR). For normally distributed data, Student’s t test was used. For non-normally distributed data, the median value of the two groups was compare using Mann-Whitney U test. Within the groups, Wilcoxon rank sum test was used. For qualitative data, χ² test and Fisher’s exact test were used and data for each group were compared using ANOVA and also Kruskal Wallis test. A p value < 0.05 was considered significant.

This study was approved by the Research and Ethics committee of our institution and funded by the Research Grant of the same institution (FF 137-2011) and Malaysian Society of Nephrology (MSN).

Results

Our study cohort consisted of 50 CKD patients with 14% CKD stage 2, 60% CKD stage 3 and 26% CKD stage 4 with median MDRD eGFR of 36 mls/min/1.73 m². Their baseline demographic characteristics and laboratory parameters are shown in Table 1. The median serum IL-6 difficult to measure and interpret due to an exceedingly low circulating calcitriol concentration [6]. Therefore there is no reliable indicator for monitoring active vitamin D treatment in CKD patients.

Factors contributing to the low vitamin D in CKD includes poor sunlight exposure, dietary restriction of vitamin D rich food, chronic uraemia, reduced kidney mass, reduced glomerular filtration rate (GFR), decreased renal 1-α hydroxylase activity, increased serum fibroblast growth factor-23 (FGF 23), defective 25-OHD uptake by the failing kidneys and protein losses [7]. It remains unknown whether sufficient non-renal 1-α hydroxylase activity is available to activate 25-OHD in late stage CKD patients.

Traditionally, vitamin D therapy in CKD patients is used for the prevention and treatment of metabolic bone disease [8]. However in recent years, there have been more data suggesting the role of vitamin D in regulating the renin-angiotensin system, promotion of vascular endothelial growth factor release, vascular calcification as well as immune modulation hence reducing overall mortality rates [1].

Chronic infection and inflammation seem to be important causes of morbidity and mortality in CKD patients [9]. This chronic inflammation is a well-known major risk factor for cardiovascular complications in CKD. Inflammation is facilitated by stress hormone through induction of interleukins (IL), tumour necrosis factor-α (TNF-α) and C-reactive protein (CRP) which are mediated by cytokines [10].

Several oral vitamin D preparations are available, including calcitriol, paricalcitol and doxercalciferol. Paricalcitol has been shown to reduce a highly sensitive CRP (hs-CRP) level and albuminuria in CKD patients [11]. Studies have also shown that supplementation with calcitriol 0.5 μg daily induces significant changes in serum IL-1, IL-6 and TNF-α in the end stage renal disease [12, 13]. Although promising, results on the use of vitamin D therapy on these inflammatory biomarkers and infection rates have been variable [14]. Current practice advocates routine active vitamin D prescription only in chronic dialysis patients for prevention or treatment of secondary hyperparathyroidism. We performed this study to evaluate whether supplementation with Calcitriol will improve the inflammatory biomarkers in these patients with low serum vitamin D levels.
levels were 8.40 (7.48) pg/ml and 80% of all patients had elevated baseline IL-6 (> 3.96 pg/ml). The median serum IL-10 was 13.35 (25.22) pg/ml, whereas the median hs-CRP was 1.87 (3.88) mg/l and 70% had a value above the range.

Serum 25-OHD, active vitamin D and calcium levels at baseline, week 6 and 12 post-supplementation in both groups are shown in Table 2. The sub-analysis of the CKD with diabetes and non-diabetes (serum IL-6, IL-10, hs-CRP, 25-OHD, and 1, 25-(OH)2 D) at various time points are shown in Table 3.

The effect of supplementation on serum IL-6, IL-10, and hs-CRP is shown in Fig. 1 (panel A, B and C).

**Table 1.** Baseline characteristics of the two study groups

| Characteristic               | Vitamin D + C group (n = 25) | Calcium group (n = 25) | p    |
|-----------------------------|------------------------------|------------------------|------|
| Age in years                | 55 (9.5)                     | 52.0 (20.5)            | 0.50 |
| Gender [n, (%)]             |                              |                        |      |
| Male                        | 16 (64)                      | 13 (52)                | 0.39 |
| Female                      | 9 (36)                       | 12 (48)                |      |
| Race [n, (%)]               |                              |                        |      |
| Malay                       | 23 (92)                      | 18 (72)                |      |
| Chinese                     | 1 (4)                        | 6 (24)                 | 0.10 |
| Indian                      | 1 (4)                        | 1 (4)                  |      |
| SBP (mm Hg)                 | 127.4 ±18.2                  | 135.6 ±17.6            | 0.11 |
| DBP (mm Hg)                 | 74.9 ±10.4                   | 76.4 ±10.9             | 0.63 |
| Aetiology of CKD [n, (%)]  |                              |                        |      |
| Diabetic nephropathy        | 16 (64)                      | 15 (60)                |      |
| Glomerulonephritis          | 5 (20)                       | 8 (32)                 |      |
| Hypertensive nephrosclerosis| 2 (8)                        | 0 (0)                  | 0.16 |
| Obstructive uropathy        | 0 (0)                        | 2 (8)                  |      |
| Others (NSAIDS/ADPKD)       | 2 (8)                        | 0 (0)                  |      |
| Co-morbidities [n, (%)]     |                              |                        |      |
| Diabetes mellitus           | 16 (51.6)                    | 15 (48.4)              | 0.77 |
| Hypertension                | 25 (54)                      | 21 (46)                | 0.11 |
| Dyslipidaemia               | 22 (55)                      | 18 (45)                | 0.15 |
| Stroke                      | 2 (50)                       | 2 (50)                 | >0.99|
| Ischaemic heart disease (IHD)| 5 (56)                       | 4 (44)                 | >0.99|
| Se creatinine (μmol/l) (NR, 44-80) | 158.0 (91.0)                  | 155.0 (87.5)          | 0.47 |
| Se eGFR (ml/min/1.73 m²)    | 36.0 (36.5)                  | 35.0 (19.0)            | 0.29 |
| CKD stages [n, (%)]         |                              |                        |      |
| Stage 2                     | 6 (24)                       | 1 (4)                  |      |
| Stage 3                     | 13 (52)                      | 17 (68)                | 0.15 |
| Stage 4                     | 6 (24)                       | 7 (28)                 |      |
| Se IL-6 (pg/ml) (NR, 0-3.96) | 9.25 (8.73)                   | 8.26 (6.75)            | 0.33 |
| Se IL-10 (pg/ml) (NR, 0-7.8) | 6.63 (22.10)                  | 20.64 (22.42)          | 0.016|
| Se hs-CRP (mg/l) (NR, < 1)   | 1.63 (5.01)                  | 1.91 (3.11)            | 0.82 |
| Se 25-OHD (ng/ml) (NR, > 30) | 15.2 ±7.2                    | 17.0 ±5.0              | 0.30 |
| Se 1,25-(OH)2 D (pmol/l) (NR, 39-193) | 91.88 (72.58)              | 86.22 (44.91)          | 0.96 |

Data are expressed as mean ± SD or median (IQR)
SD – standard deviation; IQR – inter-quartile range; NR – normal range
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Table 2. Serum 25-OHD, active vitamin D (1,25-(OH)2D) and calcium at baseline, week 6 and week 12

| Parameters                      | Study groups       | Baseline       | Week 6          | Week 12         | Intra-group p |
|--------------------------------|--------------------|----------------|-----------------|-----------------|---------------|
| 25-OHD (ng/ml) (NR, > 30)       | Calcium            | 17.70 (8.05)   | 21.74 (8.84)    | 23.36 (16.38)   | 0.001         |
|                                | Vitamin D + C      | 15.80 (9.37)   | 22.90 (13.85)   | 25.10 (35.57)   | 0.001         |
| Inter-group p                  | 0.44               | 0.93           | 0.87            |                 |               |
| 1,25-(OH)2D (pmol/l) (NR, 39-193) | Calcium           | 86.22 (44.91)  | 79.35 (58.73)   | 77.13 (45.9)    | 0.12          |
|                                | Vitamin D + C      | 91.88 (72.53)  | 81.58 (68.39)   | 76.32 (70.46)   | 0.88          |
| Inter-group p                  | 0.96               | 0.94           | 0.93            |                 |               |
| Calcium (mmol/l) (NR, 2.14-2.58) | Calcium           | 2.34 ±0.10     | 2.28 ±0.11      | 2.34 ±0.11      | 0.007         |
|                                | Vitamin D + C      | 2.30 ±0.10     | 2.38 ±0.19      | 2.42 ±0.18      | < 0.001       |
| Inter-group p                  | 0.125              | 0.003          | 0.052           |                 |               |

Data were expressed as mean ± SD or median (IQR)
SD – standard deviation; IQR – inter-quartile range; NR – normal range

Discussion

CKD is a risk factor for low vitamin D and low vitamin D is associated with dysregulation of immunity. Chronic inflammatory state is being increasingly recognized as playing an important role in pathological states such as cardiovascular disease, obesity, diabetes, cancer and malnutrition. Although there are numbers of pro-inflammatory and anti-inflammatory cytokines that orchestrate the inflammatory response, IL-6 and its soluble receptor are the central regulators of the process [16].

We found that 80% of the patients had elevated baseline serum IL-6 and their mean levels of IL-6 were more than twice the upper limit of normal. This result corroborates with the high prevalence of increased IL-6 in CKD populations [17]. Supplementation with calcitriol and calcium carbonate (Vitamin D + C group) significantly reduced serum IL-6 at the end of 12 weeks supplementation and is consistent with previous studies [18, 19]. Surprisingly, we found that patients in the Calcium group also had reduced serum IL-6 levels. A study by Tsukomoto et al. demonstrated that pro-inflammatory cytokines (IL-1β and TNF-α) were suppressed by calcitriol whereas CaCO3 suppressed TNF-α only [20]. Since TNF-α stimulates IL-6 production, it is logical that reduction of TNF-α by either calcitriol or CaCO3 or both will in turn lower IL-6 levels as seen in our study.

Sub-analysis of the diabetic subgroup showed a marked reduction in serum IL-6 in both treatment arms however serum IL-6 only reduced in the Vitamin D + C arm in non-diabetic subgroup. This suggests that the diabetics CKD patients will benefit from the calcium supplementation with or without calcitriol but non-diabetics needed the added benefit of the calcitriol.

Interleukin-10 (IL-10) has an anti-inflammatory role. We found that serum IL-10 levels in the Vitamin D + C group was maintained (p = 0.06) whereas the Calcium group showed a significant reduction at week 6 and 12. These findings suggested that the given dose of calcitriol was able to maintain this anti-inflammatory cytokine. A similar effect was also seen in chronic heart failure patients who were treated with combination of vitamin D3 + Calcium [21].

CRP or hs-CRP is the most commonly used biomarker of inflammation and strongly implicated in the pathogenesis of atherosclerosis. Although we found that serum hs-CRP was elevated in 70% of our CKD patients, but the level of hs-CRP at which it is clinically significant remains unclear [22, 23]. Calcium supplementation with or without calcitriol in our study had no effect on hs-CRP levels independent of their diabetic’s status and is consistent with previous studies [23].

Various studies have demonstrated that vitamin D and its analogues were able to increase serum 25-OHD even though levels may not be normalized [24]. In our patients both treatment arms had an increment in their median serum 25-OHD levels at 12 weeks but the increment was higher in the Vitamin D + C group. This increment can be explained due to the rise in serum calcium which in turn leads to a reduction in intact parathyroid hormone (iPTH) level thus less conversion of serum 25-OHD to the active form of vitamin D [25].

Although a previous study found that 0.5 μg of calcitriol supplementation increased serum active vitamin D levels [15], our study did not demonstrate this. This may be because our population is suffering from CKD. As expected, with the calcium and calcitriol supplementation, the serum calcium levels were raised but as showed in this study the degree of elevation was still within the normal range of our laboratory value and a close monitoring is strongly suggested.

In conclusion, we found that within 12 weeks of the study duration calcitriol supplementation did not offer any additional benefit compared to calcium carbonate alone in reducing serum pro-inflammatory biomarkers (IL-6) and hs-CRP in CKD patients with low vitamin D except for the reduction of IL-6 in the non-diabetics. Calcitriol supplementation demonstrated stabilization of serum anti-inflammatory biomarkers, IL-10. All of these effects are independent of serum vitamin D levels.
Table 3. Serum IL-6, IL-10, hs-CRP, 25-OHD, active vitamin D (1,25-(OH)_2D) and calcium in non-diabetic and diabetic CKD patients’

| Parameters          | Study groups | Non-diabetic (n = 19, C = 10, Vit. D + C = 9) | Diabetic (n = 31, C = 15, Vit. D + C = 16) | p         |
|---------------------|--------------|-----------------------------------------------|-------------------------------------------|-----------|
|                     |              | Baseline | Week 6 | Week 12 | p          | Baseline | Week 6 | Week 12 | p          |
| 25-OHD (ng/ml)      | Calcium      | 19.14 (6.0) | 22.8 (8.58) | 41.05 (55.33) | 0.008 | 16.19 (8.01) | 19.38 (10.61) | 21.92 (7.64) | 0.01 |
|                     | Vitamin D + C | 19.71 (10.28) | 26.34 (10.93) | 48.44 (66.16) | 0.003 | 14.43 (13.41) | 18.46 (18.0) | 19.44 (32.8) | 0.009 |
| Inter group p       |              | 0.51     | 0.33    | 0.87     | 0.27 | 0.48 | 0.58 | 0.51 | 0.33 | 0.87 | 0.27 | 0.48 | 0.58 |
| 1,25-(OH)_2D (pmol/l) | Calcium      | 90.42 (30.32) | 84.78 (45.99) | 90.25 (63.24) | 0.50 | 71.73 (55.28) | 75.73 (71.87) | 64.87 (37.02) | 0.20 |
|                     | Vitamin D + C | 123.64 (70.82) | 121.36 (58.97) | 171.22 (101.57) | 0.61 | 66.0 (58.55) | 71.16 (57.27) | 57.43 (57.84) | 0.63 |
| Inter group p       |              | 0.17     | 0.18    | 0.10     | 0.36 | 0.58 | 0.32 | 0.17 | 0.18 | 0.10 | 0.36 | 0.58 | 0.32 |
| hs-CRP (mg/l)       | Calcium      | 1.37 (3.85) | 1.59 (1.46) | 1.20 (3.37) | 0.23 | 2.32 (3.47) | 1.39 (3.15) | 1.55 (7.07) | 0.28 |
|                     | Vitamin D + C | 1.10 (2.80) | 1.07 (2.21) | 1.46 (3.91) | 0.24 | 3.02 (11.14) | 2.03 (4.59) | 2.82 (9.64) | 0.65 |
| Inter group p       |              | 0.87     | 0.51    | 0.81     | 0.86 | 0.43 | 0.92 | 0.87 | 0.51 | 0.81 | 0.86 | 0.43 | 0.92 |
| IL-6 (pg/ml)        | Calcium      | 5.90 (5.38) | 4.87 (2.24) | 2.99 (4.83) | 0.41 | 8.60 (6.88) | 4.98 (2.55) | 1.10 (2.78) | 0.001 |
|                     | Vitamin D + C | 4.74 (10.45) | 4.87 (1.93) | 1.80 (1.44) | 0.005 | 10.06 (7.86) | 5.11 (3.38) | 1.54 (3.56) | 0.001 |
| Inter group p       |              | > 0.99   | 0.78    | 0.62     | 0.29 | 0.58 | 0.41 | > 0.99 | 0.78 | 0.62 | 0.29 | 0.58 | 0.41 |
| IL-10 (pmol/l)      | Calcium      | 28.88 (21.49) | 2.0 (4.63) | 10.61 (12.92) | 0.001 | 16.72 (25.95) | 2.0 (9.41) | 3.29 (6.17) | 0.001 |
|                     | Vitamin D + C | 5.20 (11.61) | 2.0 (3.05) | 2.0 (3.08) | 0.34 | 10.27 (24.62) | 5.39 (10.81) | 3.8 (9.67) | 0.16 |
| Inter group p       |              | 0.02     | 0.89    | 0.82     | 0.22 | 0.14 | 0.40 | 0.02 | 0.89 | 0.82 | 0.22 | 0.14 | 0.40 |
| Se calcium (mmol/l) | Calcium      | 2.32 (0.12) | 2.27 (0.09) | 2.32 (0.10) | 0.02 | 2.39 (0.14) | 2.29 (0.22) | 2.34 (0.21) | 0.28 |
|                     | Vitamin D + C | 2.24 (0.18) | 2.28 (0.11) | 2.34 (0.22) | 0.12 | 2.33 (0.09) | 2.45 (0.14) | 2.46 (0.26) | 0.19 |
| Inter group p       |              | 0.16     | 0.21    | 0.84     | 0.41 | 0.01 | 0.03 | 0.16 | 0.21 | 0.84 | 0.41 | 0.01 | 0.03 |

Data were expressed as median (IQR)  
IQR – inter-quartile range; C – Calcium group; Vit. D + C – Vitamin D + C group; NR – normal range
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Fig. 1. Summarized the effects of supplementation on serum IL-6, IL-10 and hs-CRP levels at various visit; baseline, week 6 and 12. Panel A showed IL-6 level, panel B showed serum IL-10 and panel C showed result for serum hs-CRP; p = NS

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The authors declare no conflict of interest.

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