Vitamin D supplementation is associated with improved cardiac autonomic tone in IgA nephropathy

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Background

- **Cardiovascular disease is the leading cause of death in patients with chronic kidney disease (CKD), despite treatment of traditional risk factors**
- **Altered cardiac autonomic tone (CAT), specifically withdrawal of contribution from the parasympathetic limb of the cardiac autonomic nervous system, has been shown to predict poor cardiac outcomes in both healthy and end-stage CKD populations**
- **Vitamin D deficiency has also been shown to be independently associated with poor cardiovascular outcomes**
- **We sought to determine the influence of vitamin D supplementation on CAT in response to a vascular stressor in an earlier stage of CKD, IgA nephropathy**
- **We hypothesized that subjects with IgA nephropathy would demonstrate unfavourable CAT responses pre-supplementation compared to post-supplementation during infusion of angiotensin II (AngII)**

Objectives

- **To elucidate the role of vitamin D supplementation in altering CAT during a vascular stressor in subjects with IgA nephropathy**

Methods

- ***Subjects:*** **15 healthy, non-smoking IgA nephropathy patients with no history of cardiovascular disease**
- ***Study design:*** **AngII challenge (3ng/kg/min x 30 min, 6ng/kg/min x 30 min) was conducted on two study days while subjects wore an ambulatory heart monitor**
- **Following the pre-supplementation study day 1, subjects ingested 10,000IU cholecalciferol/day for 4 weeks followed by the post-supplementation study day 2**
- ***Outcomes:*** **CAT at baseline and in response to AngII pre- and post-vitamin D supplementation**
  - ***LF (low-frequency sympathetic tone)***
  - ***HF (high-frequency vagal tone)***
  - ***LF:HF (sympathovagal balance)***
- ***Statistical Analysis*****: Pre- and post-supplementation CAT responses were compared using non-parametric methods**

Table 1. Baseline characteristics

	Pre-supplementation (n=15)	Post-supplementation (n=15)
Age (yrs)	41 ± 4	
Male (%)	13 (87%)	
25OH vitamin D (nmol/L)	63 ± 7	136± 12*
1,25(OH)$_2$ vitamin D (pmol/L)	107 ± 9	126 ± 13
Calcium (mmol/L)	2.30 ± 0.02	2.30 ± 0.02
Phosphate (mmol/L)	0.97 ± 0.05	0.96 ± 0.08
PTH (ng/L)	46 ± 4	44 ± 4
HDL (mmol/L)	1.2 ± 0.06	1.2 ± 1.0
LDL (mmol/L)	2.68 ± 0.20	2.57 ± 0.20
NE (nmol/L)	2.3 ± 0.4	1.9 ± 0.5
Epi (pmol/L)	71 ± 7	82 ± 12
Urinary sodium (mmol/day)	310 ± 22	324 ± 29
Urinary protein (g/day)	1.03 ± 0.3	108 ± 0.3
eGFR (ml/min/1.73m^2)	101 ± 7	96 ± 6

BMI, body mass index; PTH, parathyroid hormone; HDL, high-density lipoprotein (cholesterol); LDL, low-density lipoprotein (cholesterol), NE, norepinephrine; Epi, epinephrine; eGFR, estimated glomerular filtration rate.

Data is expressed as mean ± SE.

Table 2. Responses to AngII challenge

	Baseline	3ng/kg/min AngII	6ng/kg/min AngII	Recovery
Heart rate (bpm)				
Pre	64 ± 3	66 ± 4	68 ± 4	69 ± 3
Post	61 ± 2	65 ± 3	66 ± 4	64 ± 3
LF (nu)				
Pre	63 ± 5	69 ± 5	63 ± 3	63 ± 3
Post	66 ± 4	65 ± 3	65 ± 4	64 ± 4
HF (nu)				
Pre	27 ± 4	32 ± 5	32 ± 3*	32 ± 4
Post	32 ± 4	35 ± 3	37 ± 3*	34 ± 4
LF:HF				
Pre	1.61 ± 0.2	1.72 ± 0.1*	1.51 ± 0.1^	1.65 ± 0.2^
Post	1.60 ± 0.2	1.39 ± 0.08*†	1.39 ± 0.09*^	1.51 ± 0.2^
SBP (mmHg)				
Pre	124 ± 4	140 ± 5*	149 ± 5*	134 ± 4
Post	126 ± 4	142 ± 5*	151 ± 6*	131± 5
DBP (mmHg)				
Pre	75 ± 3	86 ± 4	91 ± 3*	80 ± 3
Post	75 ± 4	90 ± 4	93 ± 4	77 ± 4
Renin (pmol/L)				
Pre	0.51 ± 0.1	0.41 ± 0.2*	0.35 ± 0.1*^	0.36 ± 0.3*^
Post	0.50 ± 0.2	0.45 ± 0.1*	0.35 ± 0.2*^	0.33 ± 0.2*^
Aldo (pmol/L)				
Pre	150 ± 16	366 ± 36*	457 ± 44*^	298 ± 27*
Post	158 ± 21	340 ± 45*	428 ± 61*^	288 ± 36*

*LF, low-frequency; HF, high-frequency; LF:HF, low- to high-frequency ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; Aldo, aldosterone. Data is expressed as mean ± SE. *p < 0.05 vs. baseline; ^p < 0.05 vs. response at 3ng/kg/min Ang II.*

Figure 1. LF:HF response to AngII, pre- and post- vitamin D supplementation

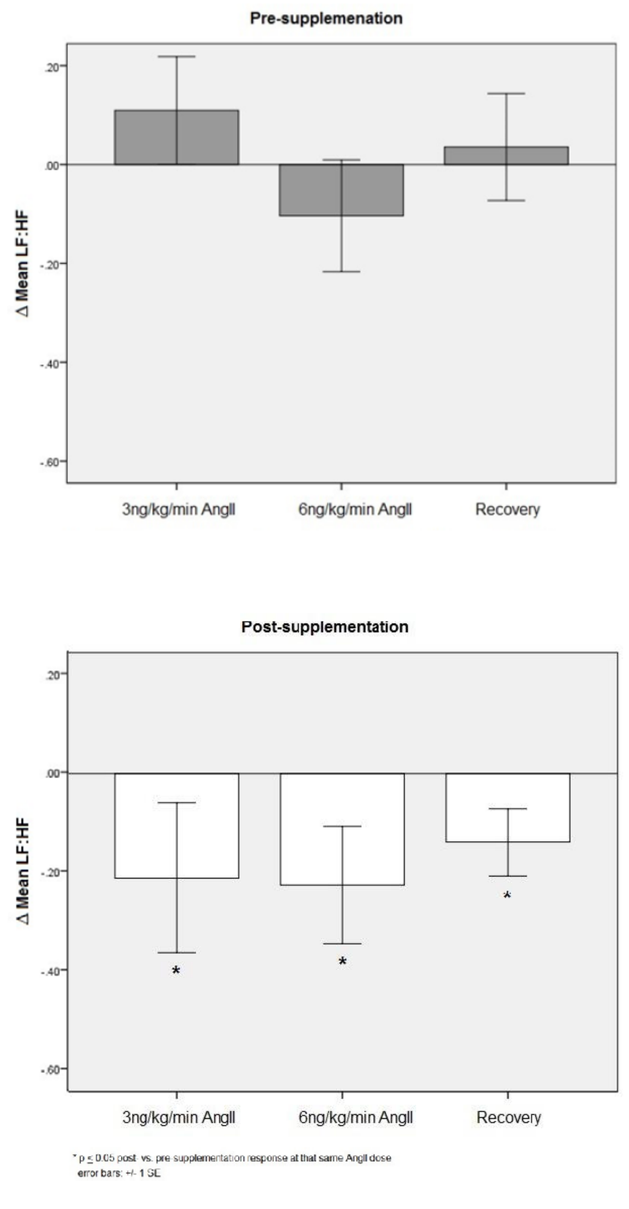
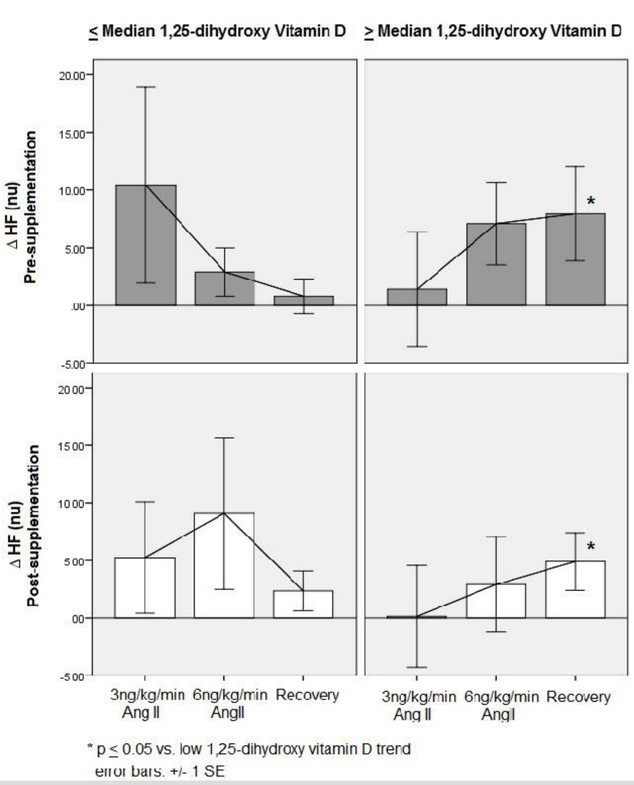


Figure 2. HF response to AngII, pre- and post- vitamin D supplementation stratified by 1,25(OH)$_2$ vitamin D level



Conclusions

- **Vitamin D supplementation is associated with changes in CAT during acute vascular stress, specifically with favourable enhancement of vagal tone in IgA nephropathy**
- **Activated 1,25(OH)$_2$ vitamin D serum level appears to predict cardiac vagal control during a vascular stressor**
- **Oral vitamin D supplementation and subsequent increases in vitamin D serum levels may reduce the risk of cardiovascular-related mortality in CKD by promoting more stable CAT during vascular stress**

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