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## Serum 25-hydroxyvitamin D is not related to cardiac natriuretic peptide in nulliparous and lactating women

Hussein F Saadi\*<sup>1</sup>, M Gary Nicholls<sup>2</sup>, Christopher M Frampton<sup>2</sup>,  
Sheela Benedict<sup>1</sup> and Javed Yasin<sup>1</sup>

Address: <sup>1</sup>Department of Internal Medicine, Faculty of Medicine and Health Sciences, UAE University, Al Ain, United Arab Emirates and  
<sup>2</sup>Department of Medicine, Christchurch School of Medicine and Health Sciences, Christchurch Hospital, Christchurch, Canterbury, New Zealand

Email: Hussein F Saadi\* - saadih@uaeu.ac.ae; M Gary Nicholls - Gary.Nicholls@cdhb.govt.nz;  
Christopher M Frampton - Chris.Frampton@cdhb.govt.nz; Sheela Benedict - Sheela.Benedict@uaeu.ac.ae; Javed Yasin - javid.yasin@uaeu.ac.ae

\* Corresponding author

Published: 29 January 2009

Received: 7 May 2008

BMC Endocrine Disorders 2009, 9:4 doi:10.1186/1472-6823-9-4

Accepted: 29 January 2009

This article is available from: <http://www.biomedcentral.com/1472-6823/9/4>

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### Abstract

**Background:** Vitamin D deficiency is associated with heightened risk of cardiovascular disease. Potential mechanisms include involvement of vitamin D in regulation of renin-angiotensin system and manufacture and secretion of cardiac natriuretic peptides. Our aim was to document relationships between 25 hydroxyvitamin [25(OH)D] and N-terminal pro B-type natriuretic peptide (NT-proBNP) and plasma renin activity (PRA) levels and to document the effect of vitamin D administration on NT-proBNP and PRA levels in vitamin D deficient subjects.

**Methods:** Serum 25(OH)D, parathyroid hormone (PTH), plasma or serum NT-proBNP and PRA levels were measured at baseline in nulliparous and lactating women and after 2 months of oral vitamin D<sub>2</sub> (2,000 IU/day or 60,000 IU/month) supplementation to lactating women.

**Results:** Baseline levels of 25(OH)D were low (<50 nmol/L) in most women whereas PRA and NT-proBNP levels were within the normal range. There were no significant correlations between baseline 25(OH)D or PTH with NT-proBNP and PRA. Vitamin D administration over a 2-month period in lactating women was associated with a decline in NT-proBNP (by  $9.1 \pm 2.0$  pmol/L;  $p < 0.001$ ) and PRA (by  $0.32 \pm 0.17$  nmol/L/hr;  $p = 0.064$ ). However, there were no significant correlations between the changes from baseline in 25(OH)D and either NT-proBNP ( $r = -0.04$ ,  $p = 0.8$ ) or PRA ( $r = -0.04$ ,  $p = 0.8$ ).

**Conclusion:** We found no significant correlations between 25(OH)D or PTH with NT-proBNP and PRA in vitamin D deficient women. Further information is required to clarify the effects of vitamin D administration on cardiac structure and function.

### Background

In addition to metabolic bone disease, new evidence links vitamin D deficiency with many disease states including autoimmune diseases, multiple sclerosis, some forms of cancer (breast, ovarian, colon), metabolic syndrome and

type 2 diabetes [1-3]. More recently, vitamin D deficiency has been linked with heightened risk of hypertension and cardiovascular disease [4-8]. Potential mechanisms that may explain this link include involvement of vitamin D in the regulation of the renin-angiotensin system [9-11], and

the negative vascular effects of secondary hyperparathyroidism [12]. In addition, activation of nuclear vitamin D receptors present in the myocardium can inhibit cardiac growth and hypertrophy whilst also suppressing the manufacture and secretion of the cardiac natriuretic peptides in both atrial and ventricular myocytes [13].

In some Arab countries, vitamin D deficiency is particularly common especially amongst women [14,15], and it has been proposed that correction of low vitamin D status in such a cohort might reduce the incidence of cardiovascular disease, especially heart failure [16]. Circulating levels of B-type natriuretic peptide (BNP) and the 1–76 amino-terminal fragment of pro-BNP (NT-proBNP) are elevated in acute and chronic cardiac impairment in proportion to the degree of hemodynamic compromise [17,18]. NT-proBNP rises more steeply than pro-BNP as cardiac function deteriorates and may be a more sensitive marker of cardiac dysfunction [18]. It was recently demonstrated that both BNP and NT-proBNP correlated inversely with 25 hydroxyvitamin D [25(OH)D] concentrations ( $r_s = -0.60$ ,  $p = 0.007$  and  $r_s = -0.64$ ,  $p = 0.003$ , respectively) in patients on maintenance peritoneal dialysis [19].

The objectives of the present study were to document relationships between plasma levels of NT-proBNP and serum 25(OH)D concentrations and to document the effect of vitamin D administration on NT-proBNP and plasma renin activity (PRA) levels in vitamin D deficient subjects.

## Methods

The study protocol was approved by the human research ethics committee of the Al Ain Medical District and subjects received both oral and written information and gave informed consent. We recruited 88 generally healthy nulliparous Emirati women in the reproductive age group, many of whom were medical students and interns working at Tawam hospital in Al Ain city, and 90 lactating women (15 UAE, 61 other Arab, and 14 South Asian) at the time of their first postnatal visit to the Maternal and Child Health center in Al Ain city (latitude 24°N and longitude 55°E) [14]. Lactating women were eligible if they planned to continue breast-feeding for the next 3 months. Exclusion criteria included pregnancy, history of metabolic bone disease or calcium disorders and treatment with vitamin D (other than multivitamins) within the past 1 year. Enrolment began in September 2005 and finished in February 2006.

This was an open label randomized parallel group clinical trial of lactating and nulliparous women [14]. Consenting subjects in each group were randomly allocated to either 2000 IU daily dose or 60,000 IU monthly dose of vitamin

D<sub>2</sub> in a 1:1 ratio within permuted blocks of size 10. Of the 88 nulliparous women enrolled initially, 55 completed 1 month, 27 completed 2 months and 23 completed the 3-month study period. Most subjects who withdrew from the study were contacted and none specified any particular reason for withdrawal. Sufficient follow-up serum samples were also not available except for very few subjects. We therefore measured NT-proBNP only in baseline samples from subjects with sufficient stored serum ( $n = 53$ ) using an electrochemiluminescence immunoassay (Roche Elecsys 1010/2010 system). Intra-assay variability was <1.5%.

Of the 90 lactating women enrolled initially, 69 completed 1 month, 58 completed 2 months and 48 completed the 3-month study period. There were no significant differences in baseline characteristics between women who completed the study and those who dropped out. Venous samples drawn at baseline ( $21 \pm 3.4$  days, mean  $\pm$  SEM, post partum) and monthly thereafter showed peak levels of 25(OH)D at 2 months [14]. We therefore measured NT-proBNP and PRA in baseline and 2 month samples from subjects with sufficient stored plasma ( $n = 53$  subjects for PRA and  $n = 46$  subjects for NT-proBNP). Original samples were taken into chilled tubes containing EDTA and centrifuged at +4°C and the plasma stored at -80°C. One aliquot of plasma from each subject was couriered on dry ice to the Endolab in Christchurch, New Zealand where NT-proBNP and PRA were measured in single assay runs to avoid inter-assay variability [18]. Intra-assay variability varied between 3.7% for PRA and 6.7% for NT-proBNP. Reference ranges were NT-proBNP 2–50 pmol/L, and PRA 0.4–2.3 nmol/L/hr. Serum calcium was measured with Beckman Synchron autoanalyzer. Serum 25(OH)D concentrations were determined by a radioimmunoassay that measures both 25(OH)D<sub>2</sub> and 25(OH)D<sub>3</sub> equally (DiaSorin; Stillwater, Minnesota). The intra- and inter-assay coefficients of variation (CVs) were 8.3% and 3.2%, respectively. Serum 25(OH)D concentration <50 nmol/L (20 ng/ml) was considered to reflect vitamin D deficiency based on studies in the literature (19, 25). Serum intact parathyroid hormone (PTH) was measured by immunoradiometric assay (Diagnostic Products Corporation; Los Angeles, California). The intra- and inter-assay coefficients of variation (CVs) were 6% and 5.1%, respectively.

Data were analysed with SPSS statistical software (version 15; SPSS Inc, Chicago). Data are shown as mean  $\pm$  SEM unless mentioned otherwise. Differences between groups were assessed by two-tailed *t*-tests for continuous variables and by chi-square tests for categorical variables. Paired observations were analysed using paired two-tailed *t*-tests. Correlations between different variables were

examined using Spearman's correlation coefficients. P-values < 0.05 were considered significant.

## Results

### Baseline data

The baseline characteristics of nulliparous and lactating women are shown in Table 1. Subjects were generally healthy and none suffered from diabetes mellitus, hypertension or heart disease. Baseline serum concentrations of 25(OH)D were low (<50 nmol/L) in all subjects except in one nulliparous and one lactating woman and they correlated negatively with PTH ( $r = -0.1$ ,  $p = 0.6$  in nulliparous women and  $r = -0.5$ ,  $p < 0.001$  in lactating women). In nulliparous women, NT-proBNP values were undetectable in more than half (51%) of the subjects. In lactating women, NT-proBNP levels were within the normal range (Table 2) but they dropped significantly with increasing postpartum days until they reached a plateau at ~14 days postpartum (Fig 1). There were no statistically significant correlations between NT-proBNP and either 25(OH)D ( $r = 0.01$ ,  $p = 0.9$ ) or PTH ( $r = -0.1$ ,  $p = 0.4$ ) in nulliparous women. There were also no statistically significant correlations between 25(OH)D and either NT-proBNP ( $r = 0.003$ ,  $p = 1.0$ ) or PRA ( $r = -0.1$ ,  $p = 0.5$ ) or between PTH and either NT-proBNP ( $r = 0.1$ ,  $p = 0.5$ ) or PRA ( $r = -0.1$ ,  $p = 0.4$ ) in lactating women.

### Follow-up data

Of the 58 lactating women who completed 2 months of the study, sufficient stored plasma was available in 53 subjects. Twenty-six women were allocated to the daily

and 27 were allocated to the monthly regimen. No significant differences in baseline characteristics were found among subjects based on the allocated regimen or availability of sufficient stored samples (data not shown). As expected, mean concentration of 25(OH)D increased significantly ( $p < 0.001$ ) over the 2 month period of vitamin D supplementation from  $26.6 \pm 1.5$  to  $39.0 \pm 1.7$  nmol/L (Table 3). Similarly, mean serum PTH concentration decreased but not statistically significantly (Table 3). Over the same time period, plasma levels of NT-proBNP declined in 33 of 46 women, and overall substantially (by 26%) and significantly ( $p < 0.001$ ) by  $9.1 \pm 2.0$  pmol/L whilst PRA fell in 32 of 53 women, but overall only slightly (by  $0.32 \pm 0.17$  nmol/L/hr) and not statistically significantly ( $p = 0.064$ ). The above changes were not significantly different between the daily and intermittent supplementation regimen groups (Table 3). Overall, there were no significant changes in mean serum calcium concentrations, blood pressure, and weight. There were no significant correlations between the changes from baseline in 25(OH)D and NT-proBNP ( $r = -0.04$ ,  $p = 0.8$ ) whether the baseline sample was drawn <14 or  $\geq 14$  days postpartum ( $r = -0.3$ ,  $p = 0.2$  and  $r = 0.1$ ,  $p = 0.6$ ; respectively) (Fig 2). In the 10 (18.9%) women who achieved 25(OH)D concentrations of  $\geq 50$  nmol/L at 2 months, the changes from baseline in 25(OH)D and NT-proBNP also showed no significant correlation ( $r = 0.5$ ,  $p = 0.2$ ). There were also no significant correlations between the changes from baseline in 25(OH)D and PRA ( $r = -0.04$ ,  $p = 0.8$ ) or between the changes from baseline in PTH and either NT-proBNP ( $r = -0.02$ ,  $p = 0.9$ ) or PRA ( $r = -0.1$ ;  $p = 0.5$ ).

**Table 1: Baseline characteristics of study subjects**

Characteristic	Nulliparous	Lactating
	n = 63	n = 53
Ethnicity <sup>1</sup>		
UAE (%)	98.4 [62]	15.1 [8]
Other Arab (%)	1.6 [1]	67.9 [36]
South Asian (%)	0 [0]	17.0 [9]
Age (y) <sup>2</sup>	24.0 $\pm$ 0.6	29.8 $\pm$ 0.9
Weight (kg) <sup>2</sup>	63.7 $\pm$ 2.9	72.2 $\pm$ 1.7
BMI (kg/m <sup>2</sup> ) <sup>2</sup>	24.2 $\pm$ 0.7	28.4 $\pm$ 0.6
Systolic Bp (mm Hg) <sup>2</sup>	108 $\pm$ 1	120 $\pm$ 1
Diastolic Bp (mm Hg) <sup>2</sup>	70 $\pm$ 1	76 $\pm$ 1
Parity <sup>3</sup>	0	3.0
Health <sup>3,4</sup>	1	1
Sunlight exposure (min/day) <sup>2</sup>	5.6 $\pm$ 1.8	0.8 $\pm$ 0.5
Multivitamin use (%) <sup>1</sup>	3.2 [2]	49 [26]
Vitamin D intake (mcg/day) <sup>2</sup>	3.7 $\pm$ 0.3	4.5 $\pm$ 0.4
Calcium intake (g/day) <sup>2</sup>	0.5 $\pm$ 0.05	0.6 $\pm$ 0.05

<sup>1</sup> n in brackets;

<sup>2</sup> Mean  $\pm$  SEM;

<sup>3</sup> Median;

<sup>4</sup> Self reported general health status (1–5): excellent, very good, good, fair, poor.

**Table 2: Baseline biochemical variables in nulliparous and lactating women<sup>1</sup>**

Group	Nulliparous women (n = 63)	Lactating women (n = 53)
Serum 25OHD (nmol/L)	19.0 ± 1.4	26.6 ± 1.4
Serum PTH (pmol/L)	7.3 ± 0.4	4.6 ± 0.4
Serum calcium (mmol/L)	2.3 ± 0.01	2.4 ± 0.01
NTproBNp (pmol/L)	1.6 ± 0.3	19.2 ± 2.2
PRA (nmol/L/hr)	-----	2.0 ± 0.1

<sup>1</sup> Mean ± SEM;

25(OH)D, 25-hydroxyvitamin D; PTH, parathyroid hormone; NT-proBNP, N-terminal pro B-type natriuretic peptide; PRA, plasma renin activity.

## Discussion

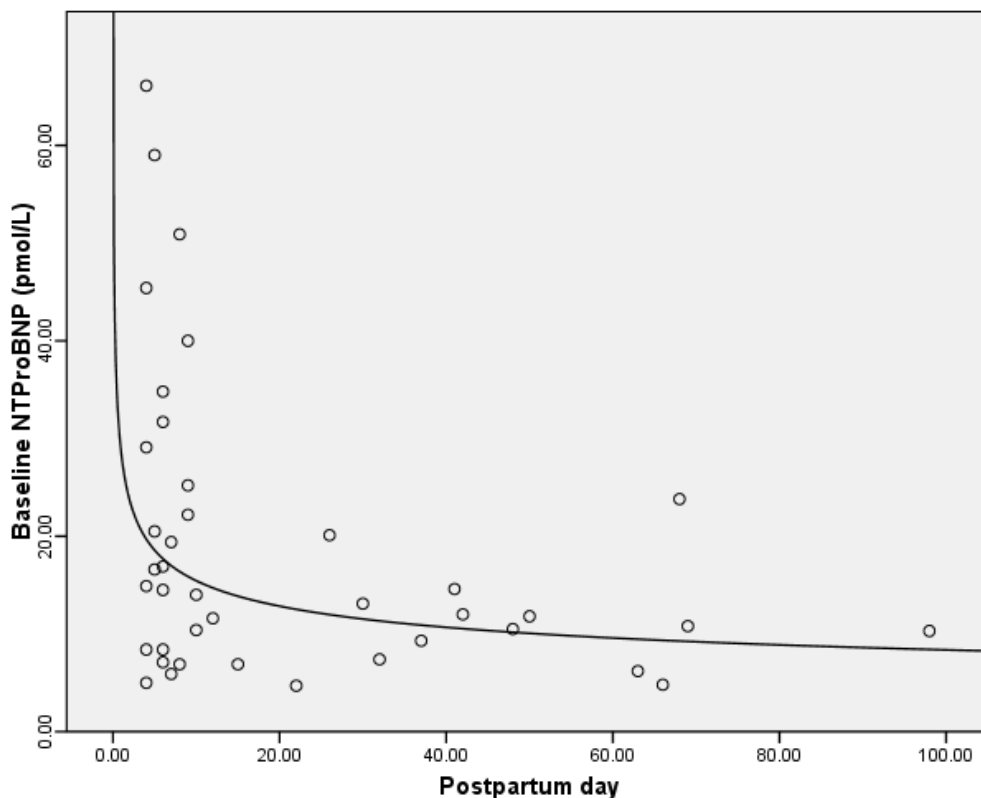
Vitamin D deficiency may adversely affect cardiac function [6-8,20] and vitamin D administration under these conditions may be beneficial [21]. Park and colleagues reported that calcitriol, administered intravenously twice weekly over 15 weeks, reduced left ventricular mass and suppressed circulating levels of renin, angiotensin II and ANP in patients on chronic hemodialysis with secondary hyperparathyroidism [22]. Similar findings of regression of cardiac hypertrophy (together with reduced QT dispersion) during calcitriol administration in a similar cohort of patients were reported subsequently by the same group [23]. Other investigators also found that vitamin D administration for patients with congestive heart failure improved pro-inflammatory and anti-inflammatory cytokine levels but there was no significant decline in NT-proBNP levels [21]. Our results show no significant correlations between baseline 25(OH)D concentrations and NT-proBNP levels in vitamin D deficient nulliparous women or between baseline 25(OH)D concentrations and NT-proBNP and PRA in vitamin D deficient lactating women. Although vitamin D administration over a 2-month period in lactating women was associated with a statistically significant decline in NT-proBNP levels and a non-statistically significant decline in PRA, there were no significant correlations between the change from baseline in 25(OH)D concentrations or PTH with the change from baseline in NT-proBNP and PRA levels. This suggests that the decline we observed in NT-proBNP is unlikely related to vitamin D administration but is probably related to other factors such as postpartum blood volume changes. Pregnancy represents a state of physiologic volume expansion as maternal blood volume increases ~40%–45% above non-pregnancy volumes [24]. By 1 week after delivery, the blood volume returns nearly to its non-pregnancy value [25]. NT-proBNP levels, on the other hand, increase by 2-fold within the first 28 hours after delivery suggesting a role in postpartum diuresis [26]. Our results suggest that NT-proBNP levels drop quickly thereafter until they reach a plateau at ~14 days postpartum.

Our data also confirm previous studies showing a high prevalence of severe vitamin D deficiency among women in the Middle East due to sunshine deprivation and inadequate vitamin D intake [14,15,27]. Our current study did not evaluate seasonal changes in serum 25(OH)D concentrations but our previous studies showed no significant seasonal variation in 25(OH)D concentrations between September and February in the UAE, where there is abundant sunshine year-round [15]. In addition, vitamin D fortification of food is not mandatory in many Middle Eastern countries, and the current dietary intake of vitamin D is relatively low [15]. Vitamin D<sub>2</sub> supplementation with 2000 IU daily or 60,000 IU monthly for 2 months in this study increased serum 25(OH)D concentrations significantly but these concentrations reached an acceptable level ( $\geq 50$  nmol/L) in only a small proportion of studied women [14]. Although the mean increment observed in 25(OH)D concentration in our study was slightly higher than that reported by other investigators [28] (0.4 nmol/L per 100 IU of vitamin D<sub>2</sub>) it remained lower than that reported for equimolar doses of vitamin D<sub>3</sub> [29-31]. This could be related to greater potency of vitamin D<sub>3</sub> compared to vitamin D<sub>2</sub> [32,33] although this has been recently questioned [34].

Our data must be viewed with appropriate caution. First, neither PRA nor NT-proBNP was elevated at baseline, making physiological significance an unresolved issue. Second, we had no time-matched control women (not receiving vitamin D) and serum 25(OH)D concentrations at 2 months remained below the optimal level of 75 nmol/L in all subjects studied. Additionally, pre- and post-treatment assessments by cardiac echocardiography were unfortunately not performed as that would have provided a useful correlate for the NT-proBNP measurements.

## Conclusion

We found no significant correlations between 25(OH)D or PTH with NT-proBNP and PRA in vitamin D deficient women. There were also no significant correlations between the change from baseline in 25(OH)D concen-



**Figure 1**  
Scatter plot of baseline NT-proBNP in relation to the postpartum day of sample collection.

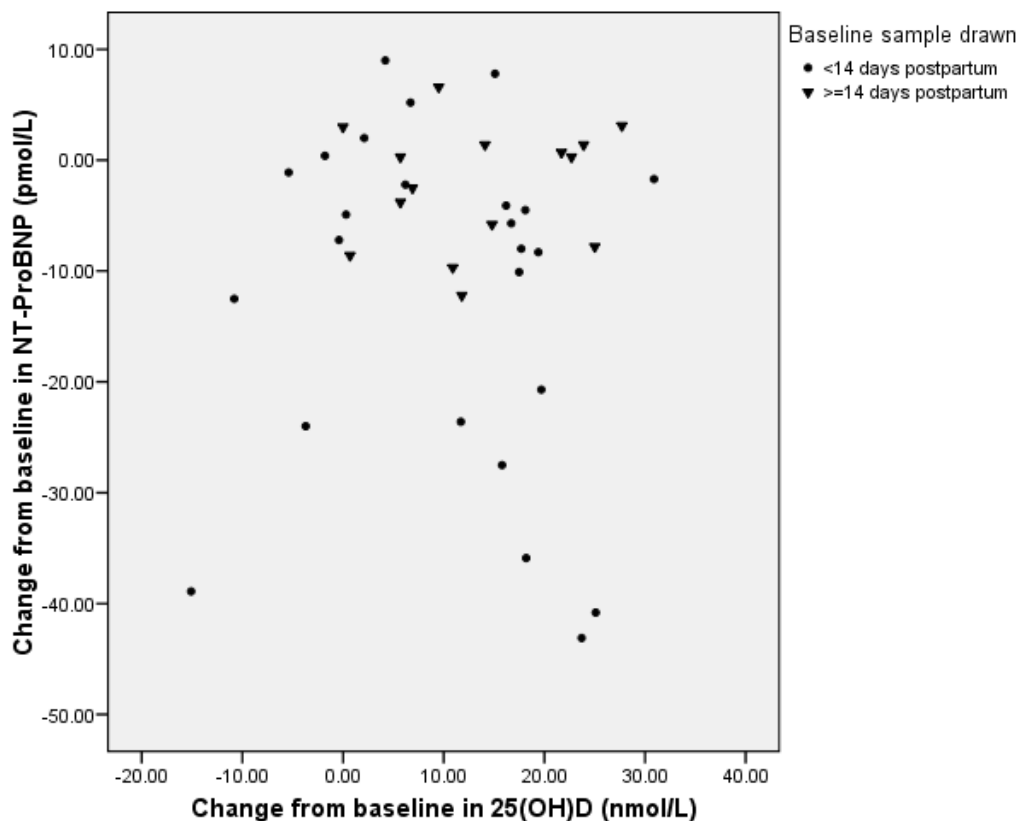
**Table 3: Change from baseline in biochemical and clinical variables of lactating women by type of vitamin D supplementation regimen<sup>1</sup>**

Variable	Daily regimen		Monthly regimen		Total	
	Change	p value	Change	p value	Change	p value <sup>2</sup>
25OHD (nmol/L)	13.9 ± 2.6	<0.001	10.9 ± 1.8	<0.001	12.3 ± 1.6	<0.001
PTH (pmol/L)	0.1 ± 0.4	0.9	-1.0 ± 0.7	0.2	-0.4 ± 0.4	0.3
Calcium mmol/L	-0.09 ± 0.04	0.04	-0.001 ± 0.03	1.0	-0.04 ± 0.02	0.1
NTproBNp (pmol/L)	-10.0 ± 3.0	0.003	-8.2 ± 3.0	0.008	-9.1 ± 2.0	<0.001
PRA (nmol/L/hr)	-0.4 ± 0.2	0.1	-0.2 ± 0.2	0.4	-0.3 ± 0.2	0.06
SBP (mm Hg)	-3.5 ± 2.6	0.2	-0.6 ± 1.8	0.7	-2.0 ± 1.5	0.2
DBP (mm Hg)	-4.4 ± 1.4	0.005	1.0 ± 1.9	0.6	-1.6 ± 1.2	0.2
Weight (kg)	-0.2 ± 0.6	0.7	-0.4 ± 0.6	0.5	-0.3 ± 0.4	0.5

<sup>1</sup> Mean ± SEM;

<sup>2</sup> P value by paired two-tailed t-tests.

25(OH)D, 25-hydroxyvitamin D; PTH, parathyroid hormone; NT-proBNP, N-terminal pro B-type natriuretic peptide; PRA, plasma rennin activity; SBP systolic blood pressure; DBP, diastolic blood pressure.



**Figure 2**  
Correlation between the changes from baseline in 25(OH)D and NT-proBNP by day of collected baseline sample (<14 or  $\geq$ 14 days postpartum).

trations or PTH with the change from baseline in NT-proBNP and PRA levels following vitamin D administration over a 2-month period. Further information is required to clarify the effects of vitamin D administration on cardiac structure and function and prevention of cardiovascular disease.

### Competing interests

The authors declare that they have no competing interests.

### Authors' contributions

HS was responsible for overall design, administration and coordination of the project, analysis of results, and writing the manuscript. MGN organised measurements of NT-proBNP and PRA, and participated in analysis of results and writing the manuscript. CF performed the statistical analysis and participated in analysis of results and writing the manuscript. SB and JY were responsible for sample preparation and biochemical analyses. All authors read and approved the final manuscript.

### Acknowledgements

This work is supported by a research grant from Sheikh Hamdan Bin Rashid Al Maktoum Award for Medical Sciences. We are grateful to Barbara Griffin for expert secretarial assistance.

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### Pre-publication history

The pre-publication history for this paper can be accessed here:

<http://www.biomedcentral.com/1472-6823/9/4/prepub>

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