Journal of Steroid Biochemistry & Molecular Biology 121 (2010) 217–220

Contents lists available at ScienceDirect

Journal of Steroid Biochemistry and Molecular Biology

journal homepage: www.elsevier.com/locate/jsbmb

Interrelation of parathyroid hormone and vitamin D metabolites in adolescents from the UK and The Gambia☆

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ARTICLE INFO

Article history:
Received 5 November 2009
Received in revised form 15 February 2010
Accepted 1 March 2010

Keywords:
Parathyroid hormone
Vitamin D status
Vitamin D metabolites
Biomarkers

ABSTRACT

Parathyroid hormone (PTH) is used as a marker of vitamin D (VD) status. However, PTH depends on many other factors. The 24,25-dihydroxy VD (24,25VD) concentration may be a sensitive marker because its production is reduced in VD deficiency.

The relationship between VD metabolites, their ratio and PTH was investigated in adolescents from the UK and The Gambia with different calcium intakes and VD status. In the UK, there was a significant positive (+ve) association between 25VD and both 1,25-dihydroxy VD (1,25VD) and 24,25VD and a negative (−ve) association with PTH. The 24,25:25VD ratio was consistent across the 25VD concentration range. There was a +ve association between PTH and 1,25:25VD, (1,25 + 24,25):25VD or 1,25:24,25VD, a −ve association with 24,25VD and none with 1,25VD or 24,25:25VD. Using LnPTH and 1,25:25VD ratio (but not 1,25VD:24,25VD or 25VD:24,25VD) increased uniformity between groups and strength of relationships compared to PTH and 1,25 or 25VD alone. In The Gambia, there was a significant −ve relationship between 25VD and PTH and none with 1,25VD. There was a +ve association between 1,25VD or 1,25:25VD and PTH.

The more uniform prediction of PTH by the 1,25VD:25VD ratio may be because this better reflects the extent to which PTH-induced 1,25VD production can be met by VD supply. Further validation is needed.

1. Introduction

The plasma concentration of 25-hydroxy vitamin D (25VD) is the most commonly used biomarker for VD status because its half-life is relatively long and its concentration is not under tight homeostatic regulation. It therefore reflects VD supply and metabolism. However, it does not provide information about the extent to which the VD supply meets functional requirements [1]. Parathyroid hormone (PTH) has been proposed as functional marker of vitamin D (VD) status because an elevated plasma PTH is a risk factor for osteoporosis and VD can lower it [2]. An inverse relation between PTH and 25VD has been reported in many cross-sectional and intervention studies in different age groups [1]. However, PTH depends on many other factors than VD status and therefore varies widely within and among individuals at any given concentration of 25VD [3,4]. The plasma concentration of 1,25VD has proven to be of limited value as biomarker of VD function, because 25VD and 1,25VD correlate very little, if at all, except in cases of severe VD deficiency [1]. The plasma concentration of 24,25-dihydroxy VD (24,25VD) or its ratio to other VD metabolites may be a sensitive marker of VD status because its production is reduced in early stages of VD deficiency and may be increased when the VD supply is high, as the first step in the catabolic pathway of 25VD [5]. In addition, its production but not plasma half-live is regulated by PTH [6] and may be up-regulated by increasing 1,25VD concentrations as shown in vitro [7].

Here we report a secondary analysis of the relationship between VD metabolites, their ratios and PTH in adolescents from the UK and The Gambia, characterised by different calcium intakes and VD status.

2. Materials and methods

2.1. Subjects

Subjects differing in VD status, calcium intake and parathyroid hormone concentration (Table 1) were selected. Adolescents from the UK (n = 240; 17–19 years; n = 128M and 112F) participated in a randomised placebo controlled calcium supplementation study for 15 months [8]. The samples included in this study were obtained non-fasting in winter at the end of the supplementation period.

☆ Special issue selected article from the 14th Vitamin D Workshop held at Brugge, Belgium on October 4–8, 2009.

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doi:10.1016/j.jsbmb.2010.03.012

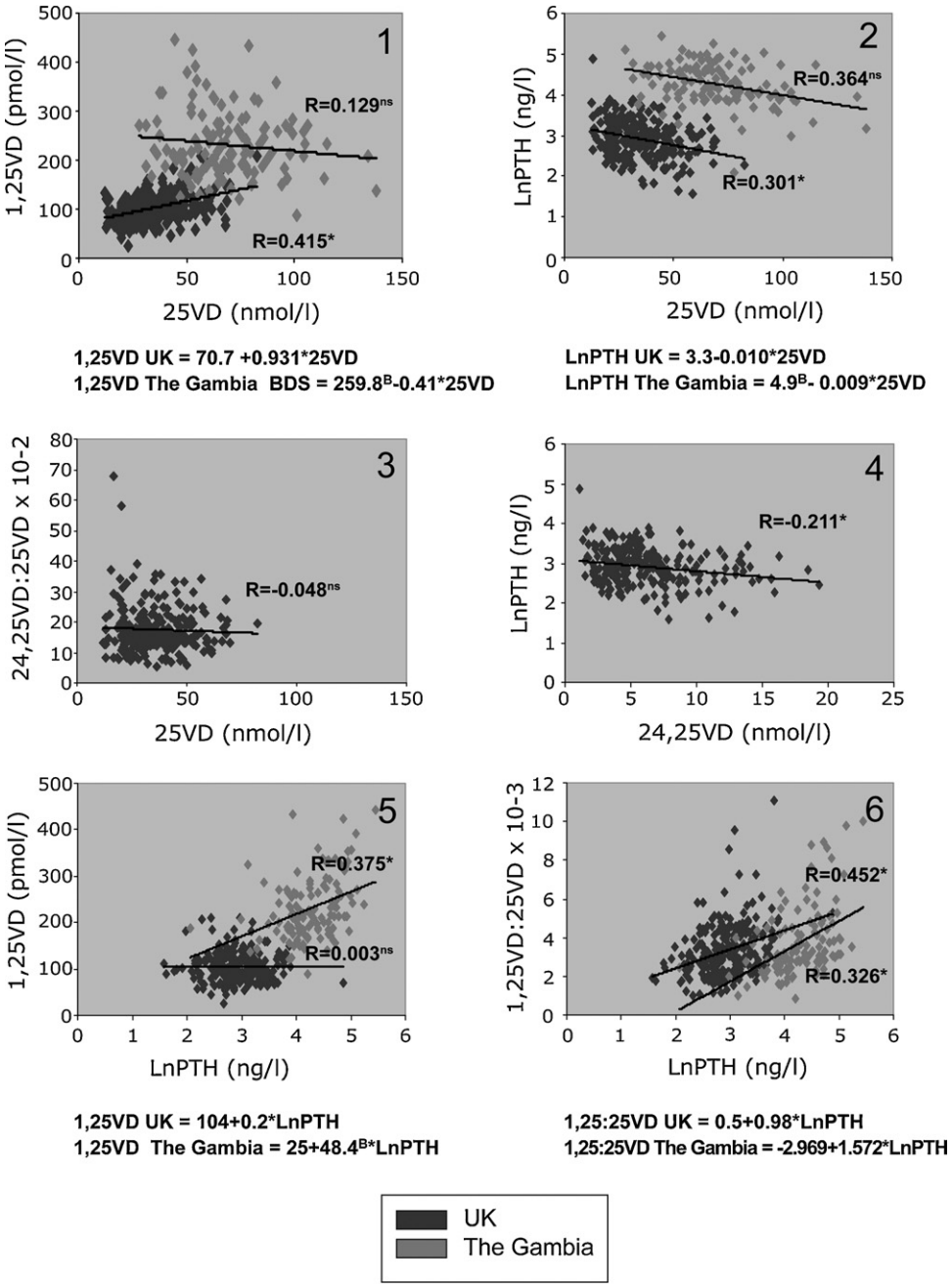
Table 1
Plasma concentrations of calcium, phosphate and calciotropic hormones and calcium intakes.

	UK	The Gambia
Ca (mmol/l)	2.47 (0.01)	2.21 (0.01)^{B}
*p*P (mmol/l)	1.19 (0.01)	1.43 (0.02)^{B}
25VD (nmol/l)	35.5 (0.9)	68.6 (1.7)^{B}
24,25VD (nmol/l)	6.2 (0.2)	–
1,25VD (pmol/l)	103.6 (2.0)	231.3 (5.9)^{B}
PTH (ng/l)	18.4 (17.3, 19.4)	67.2 (66.2, 68.3)^{B}
Calcium intake (g/d)	1.4 (0.5)	0.3 (0.2)^{B}

Values are expressed as mean (SE), except for PTH (geometric mean (95CI)). Values within a row with superscript are significantly different from subjects from the UK (B), as tested by *t*-test ($P \leq 0.05$).

Subjects from The Gambia ($n = 127$; 17–21 years; $n = 74$M and 53F) were participants in a follow-up of a randomised, double blind 1-year calcium supplementation study for 12 months [9]. The samples used for this study were collected from fasting subjects 8.0 years after supplementation had stopped.

Exclusion criteria included any medical problem, a history of eating disorders or medication known to alter calcium or bone metabolism. Approval of the studies was given by the Ethical Committee of the Dunn Nutrition Unit (of which the Nutrition and Bone Health Group of MRC Human Nutrition Research was formerly part) and by the MRC/Gambian Government Ethics Committee. Written consent was obtained from all subjects and/or their parents or guardians as appropriate.



Figs. 1–6. Relation between vitamin D (VD) metabolites, their ratios and parathyroid hormone (PTH) in adolescents from the UK and The Gambia. Footnote to Figs. 1–6: correlation coefficient: *R*; significance of correlation coefficient at $P < 0.05$:* or non-significant at $P > 0.05$:ns. *B*: significantly different form the UK at $P < 0.05$;

2.2. Laboratory and data analyses

Plasma calcium (Ca) and phosphate (P) were measured by colorimetric methods, intact PTH, 25-hydroxy VD (25VD) and 1,25-dihydroxy VD (1,25VD) were by immunoradiometric assay (RIA; Diasorin and IDS, USA). The RIA for 25VD has a 100% cross-reactivity for 24,25VD and therefore reports the sum of the two metabolites. The plasma concentration of 24,25VD was measured by ELISA (IDS, UK) after C18 and silica column extraction [10] in subjects for the UK but not from The Gambian because of intermittence of availability of the method. Analysis of 24,25VD by IDS was cross-calibrated against RIA (Diasorin).

Calcium intake in the UK was assessed by a diet and supplement diary and Calquest [8] and in The Gambia by a 2d weighed record [9].

Group differences in summary statistics were tested with Student's *t*-tests. Group effects were analysed using multiple regression analyses with exploration of potential group interactions with the interrelationship between variables by including group × variable in the model. Values were converted to natural logarithms (Ln) for non-normally distributed data and models were run for both unconverted and Ln converted data. The ratio between VD metabolites was calculated to explore proportional relationships. Probability plots were used to identify outliers. Data for each group were analysed with gender combined because there were no sex effects.

3. Results

3.1. UK

There was a significant positive (+ve) association between 25VD and 1,25VD (Fig. 1) and a negative (−ve) association with LnPTH (Fig. 2). There was a strong positive linear relationship ($R = 0.684$; $P < 0.0001$) between 25VD and 24,25VD and the 24,25:25VD ratio was consistent across the 25VD concentration range (15–100 nmol/l) (Fig. 3).

There was no significant association between LnPTH and 1,25VD (Fig. 5) with a −ve association with 24,25VD, which parallels the association with 25VD (Fig. 4). There was a +ve association between LnPTH and 1,25:25VD (Fig. 6), (1,25 + 24,25):25VD ($P < 0.0001$) and 1,25:24,25VD ($P < 0.0001$) ratio. Using LnPTH and 1,25:25VD ratio increased the strength of the found relationships compared to PTH and 1,25VD or 25VD alone, respectively.

Using the 1,25VD or 25VD ratio to 24,25VD did not increase the significance of associations. Also, correction of 25VD concentrations for the corresponding 24,25VD concentration did not increase the significance of associations.

3.2. The Gambia

There was a significant −ve relationship between 25VD and PTH and none with 1,25VD. There was a +ve association between LnPTH and 1,25VD or 1,25:25VD.

3.3. UK versus The Gambia

There were some significant differences in the constant and β coefficient of the regression equations between cohorts (Figs. 1–6). However, a similar slope for the 25VD–LnPTH relationship was found, indicating a similar increment in PTH in response to a decrement in 25VD.

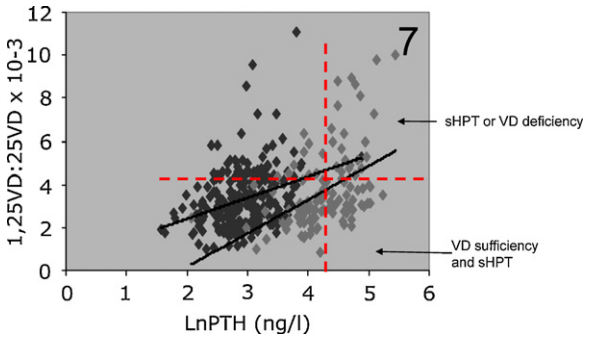


Fig. 7. Relation between 1,25:25VD ratio and PTH in adolescents from the UK and The Gambia. The sectors reflect different physiological states, affecting this relationship. The cut-off values were arbitrarily based on reference values given for the methodology used (110 pmol/l for 1,25VD; 25 mmol/l for 25OHVD and 69 ng/l for PTH). These values were based on the analyses of samples obtained from healthy Caucasian adults and may not be appropriate in other age and ethnic groups. Footnote to Fig. 7: sHPT: secondary hyperparathyroidism.

4. Discussion

Contrary to expectations, the 24,25:25VD ratio in the UK cohort was independent of 25VD throughout its concentration range of 15–100 nmol/l. This was consistent with the findings of Wagner, presented at this meeting [11]. Due to the strong linear relationship between 24,25VD and 25VD, correction of the 25VD concentration for 24,25VD and/or expressing 1,25 or 25VD as a ratio to 24,25VD did not contribute to the refinement of a VD status marker.

Similar slopes for the 25VD–LnPTH and 1,25VD:25VD–LnPTH relationships were found for subjects from the UK and The Gambia, despite very different levels of PTH. This indicates that the 25VD–PTH–1,25VD axis responds similarly in these cohorts. Thus, the higher levels of PTH in the Gambian subjects may therefore be ascribed predominantly to their low calcium intakes. Another explanation may be differences in skeletal maturation between groups due to a slower linear growth trajectories and bone mineral accrual in Gambian children [12]. Calcium accretion, which is paralleled by an elevation in plasma PTH and 1,25VD may therefore still be high in Gambian subjects of this age [13]. Failure to recognise group differences such as those seen in this study could lead to artificial relationships due to data clustering and may be of particular importance when subjects with different calcium intakes or kidney function are investigated [14,15].

The more uniform and slightly better prediction of PTH by the ratio of 1,25VD to 25VD may be because this ratio takes the interdependency of the plasma concentrations of 1,25VD and 25VD into account and may therefore better reflect the extent to which PTH induced 1,25VD production can be met by the VD supply. Interpretation of this relationship should be made in the context of the PTH–1,25VD and 25VD–1,25VD relationship. Sectors reflecting different physiological states could be proposed on the basis of this relationship, as indicated in Fig. 7 and should be set specifically in relation to the population under investigation. Further refinement and validation of this marker is needed.

Acknowledgements

The study in the UK was funded by the Medical Research Council as an addition to work supported by awards from the Department of Health/Medical Research Council Nutrition Research Initiative, the Mead Johnson Research Fund and the National Osteoporosis Society. The study in The Gambia was funded by the Medical Research Council. We are indebted to the staff in Cambridge and in Keneba for their assistance in the field and laboratory studies.

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