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ORIGINAL ARTICLE

**Jane Zochling · Jian Sheng Chen · Markus Seibel
Jennifer Schwarz · Ian D. Cameron
Robert G. Cumming · Lyn March · Philip N. Sambrook**

Calcium metabolism in the frail elderly

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Abstract Elderly residents of aged care facilities are usually considered at high risk of osteoporosis not only due to their age, but also due to nutritional factors, poor sunlight exposure and renal insufficiency. This study aimed to describe calcium metabolism and related hormones in this high-risk population. A total of 1280 elderly residents of hostels and nursing homes in the northern Sydney area (aged 65 years or over) had serum analysis for clinical chemistry including serum 25-hydroxy vitamin D (25OHD) and parathyroid hormone (PTH). Moderate renal impairment (creatinine clearance 30–60 ml/min) was common (62%), but hypocalcaemia was uncommon (7.0%). Mild hypoalbuminaemia was common (34% below 40 g/l, but only 3.2% below 35 g/l); 77.5% of the cohort had low serum 25OHD levels (<39 nmol/l) and 41.7% had elevated PTH levels (>66 pg/ml). Independent predictors of low serum 25OHD levels included gender, age, serum PTH, season, mobility and creatinine clearance. Use of vitamin D supplementation conferred modestly higher serum 25OHD levels (45.5 vs 27.1 nmol/l in non-supplemented residents, $p<0.0001$) and lower PTH levels (50.0 vs 78.1 pg/ml, $p<0.0001$). Despite adequate overall nutrition, vitamin D deficiency is present in the majority of this population. Vitamin D deficiency remains a significant public health problem in the institutionalized frail elderly. Currently available supplements are not adequate or utilized frequently enough to address this problem.

Keywords Calcium · Creatinine · Parathyroid hormone · Vitamin D

J. Zochling · J. S. Chen
Institute of Bone and Joint Research, University of Sydney, Sydney, Australia

M. Seibel
Anzac Research Institute, University of Sydney, Sydney, Australia

J. Schwarz
Department of Rheumatology, Royal North Shore Hospital, St Leonards, 2065, Australia

I. D. Cameron
Department of Rehabilitation Medicine, University of Sydney, Sydney, Australia

R. G. Cumming
School of Public Health and Centre for Education and Research on Ageing, University of Sydney, Sydney, Australia

L. March
Institute of Bone and Joint Research, Royal North Shore Hospital, St Leonards, 2065, Australia

P. N. Sambrook (✉)
Institute of Bone and Joint Research, Royal North Shore Hospital, University of Sydney, St Leonards, 2065, Australia
E-mail: sambrook@med.usyd.edu.au
Tel.: +61-2-99267281
Fax: +61-2-99061859

Introduction

Elderly patients in residential care are considered at high risk of poor nutrition, vitamin D deficiency and osteoporosis. Indeed vitamin D deficiency is a silent epidemic, affecting men and women around the globe [1–5]. Its prevalence increases in older populations as mobility and general health decline [6–8], related to inadequate sunlight exposure, poor nutrition and increasing renal insufficiency leading to secondary hyperparathyroidism [9, 10]. Institutionalized elderly persons appear at particular risk for low vitamin D levels [11–15], but there is less known about their overall calcium metabolism and the relationship between vitamin D, parathyroid hormone (PTH), gender, season, and biochemical measures of calcium homeostasis in the frail elderly.

The aim of this study was to characterize the clinical chemistry and determinants of serum 25-hydroxy vitamin D (25OHD) and PTH levels in an elderly population living in aged care facilities. The prevalence of vitamin D supplementation and its association with serum 25OHD levels in this frail elderly cohort was also examined.

Methods

Subjects

Study participants were drawn from the ongoing Fracture Risk Epidemiology in the Frail Elderly (FREE) Study in Northern Sydney [16]. Not all residents were able to or gave consent for venesection but all who had blood collected as a part of the FREE study were included in this analysis. Carer consent was obtained for venesection where appropriate. Current medications were recorded from interview and verified by medical records and medication charts, including prescription drugs and over-the-counter vitamin preparations. Vitamin D and PTH levels were measured in 1280 subjects and other clinical chemistry in 551 subjects. There were 22 individuals with biochemical primary hyperparathyroidism (elevated PTH and associated hypercalcaemia) who were excluded from further analyses, resulting in a final study population of 1258 subjects.

Biochemical measurements

Serum 25OHD, intact PTH, calcium (adjusted for circulating albumin levels), creatinine and inorganic phosphorus levels were measured. Serum 25OHD was measured using a DiaSorin radioimmunoassay kit (DiaSorin Inc., Stillwater, Minn., USA). Sensitivity was measured at 4 nmol/l, intra-assay precision 7.6% and inter-assay precision 9.0%, with a "normal" laboratory range of 39–140 nmol/l.

Serum levels of intact PTH were determined by two-site chemiluminescent enzyme-linked immunometric assay on a DPC Immulite 1000 analyzer (Diagnostic Products Corp., Los Angeles, Calif., USA). The assay has an intra-assay precision of 5.5%, an inter-assay precision of 7.9% and the laboratory reference range is 23.7–66.2 pg/ml (2.5–7.0 pmol/l).

Clinical chemistry was analyzed on a Hitachi 917 analyzer (Hitachi Ltd., Tokyo, Japan) in a single laboratory. Serum calcium was measured by colorimetric assay (Roche Diagnostics, Indianapolis, Ind., USA) using *p*-cresolphthalein and adjusted for circulating albumin levels, with a normal range of 2.15–2.55 mmol/l, manufacturer's within-run coefficient of variance (CV) of 0.9% and between-run CV of 1.5%, and measured inter-assay CV in this laboratory of 2.1%. A modified Jaffé (picric acid) kinetic colorimetric assay was used to measure serum creatinine with a normal range in males of 70–110 mol/l and in females of 50–90 mol/l, manufacturer's precision of 0.7% intra-assay and 2.3% inter-assay and a measured inter-assay CV of 3.0%. Creatinine clearance was calculated using the Cockcroft-Gault formula [17]. Inorganic phosphorus levels were measured by an endpoint method with sample blanking, based on the formation of ammonium phosphomolybdate complex. The normal range in this laboratory is 0.6–1.3 mmol/l and inter-assay precision 2.5%; manufacturer's within-run CV is 0.9% and between-run CV is 1.4%. Serum albumin was measured by bacillus Calmette-Guérin (BCG) colorimetric assay (Roche Diagnostics, Indianapolis, Ind., USA), with a normal range of 40–50 g/l. The within-run precision (CV) given by the manufacturer was 0.4% and the between-run CV was 1.7%. Inter-assay precision in this laboratory has been calculated as 2.0%.

Statistical analysis

Analyses were carried out using the SPSS 11.0 statistical software package. Independent sample Student's *t*-test was used to compare means between continuous variables (log transformed if required to confer normality) and Pearson's chi-squared statistic calculated to test differences between proportions. Vitamin D levels were treated both as a continuous variable and divided into categories to define "hypovitaminosis D". One-way analysis of variance (ANOVA) was used to evaluate univariate associations for continuous variables. Logistic and multiple linear regression analyses were performed using a stepwise backward method.

Results

Baseline demographics

Total recruitment for the FREE study comprised 2005 subjects of whom venesection was possible in 1280. Twenty-two individuals (1.7%) exhibited biochemical primary hyperparathyroidism and were excluded from further analysis. The median serum PTH in this group was 100 pg/ml and the median corrected calcium level was 2.68 mmol/l. Demographics of the remaining 1258 subjects are shown in Table 1. The women were on average 3.6 years older than the men ($p < 0.0001$) and were more likely to require a walking aid (usually a frame).

Clinical chemistry

Descriptive statistics for clinical chemistry variables are shown in Table 2. Hypocalcaemia (< 2.15 mmol/l) was present in 37 residents (7.0%). Inorganic phosphorus was elevated (1.33 mmol/l) in 113 (21.2%) individuals. Using the laboratory range, albumin was low (< 40 g/l) in 183 (34.3%) subjects, although very low albumin values were uncommon (only 3.2% < 35 g/l and 0.4% < 30g/l). Serum creatinine was elevated in 34.3% of males (i.e. > 110 mol/l) and 42.1% of females (i.e. > 90 mol/l). However, 67.4% of males and 60.5% of females had moderately reduced creatinine clearance (30–60 ml/min). Severely reduced creatinine clearance values (< 30ml/min) were present in 5.4% of males and 29.9% of females.

Table 1 Demographics of institutionalized elderly cohort with biochemical measures

	All	Gender		Significance[a]
		Male	Female	
Age (mean)	86.0	83.1	86.7	$p < 0.0001$
Institution				
Intermed. care	267 (56.0%)	137 (51.3%)	567 (57.2%)	$p = 0.09$
Nursing home	991 (44.0%)	130 (48.7%)	424 (42.8%)	
Mobility				
Walks unaided	397 (30.4%)	93 (35.1%)	286 (29.1%)	$p = 0.007$
Uses a stick	285 (22.9%)	68 (25.7%)	217 (22.1%)	
Uses a frame	391 (31.4%)	60 (22.6%)	331 (33.7%)	
Wheelchair	192 (15.4%)	44 (16.6%)	148 (15.1%)	
On vitamin D supplements		16 (6.0%)	113 (11.4%)	$p = 0.01$

[a]Males vs females

Nine hundred and seventy-five residents (77.5%) had low serum 25OHD levels when compared to the laboratory normal range (39–140 nmol/l). The prevalence of "hypovitaminosis D" was 51.2% with a cut-off value of 25 nmol/l, 63.0% with a cut-off of 30 nmol/l and 88.7% with a cut-off level of 50 nmol/l. Serum PTH was elevated in 524 individuals (41.7%) (normal range: 23.7–66.2 pg/ml).

Males had significantly higher creatinine clearance and lower PTH and phosphate levels than women ($p < 0.05$), independent of aged care institution. There was no statistically significant difference in PTH levels between institution type in either gender. Serum albumin was lower in nursing homes than in intermediate care facilities (hostels) in both males and females ($p < 0.01$), and phosphate levels were higher in hostels than nursing homes in females ($p = 0.02$) but not significantly different between institutions in males. Creatinine clearance was not significantly different between institutions in either males ($p = 0.4$) or females ($p = 0.9$). Albumin decreased with increasing age in both males and females ($p < 0.05$), and PTH increased with age ($p < 0.005$). Creatinine clearance decreased with age in both males and females ($p < 0.0001$), but calcium and phosphate were not related to age in either gender.

Serum 25OHD decreased with increasing age in the total cohort ($p = 0.035$), but did not reach statistical significance in either males or females alone. Serum 25OHD levels were higher in intermediate care (hostel) accommodation than in nursing home residents in both males (mean difference 6.1 nmol/l, $p = 0.005$) and females (mean difference 4.1 nmol/l, $p < 0.0001$). Males had significantly higher 25OHD levels than women ($p < 0.05$), independent of institution. Serum 25OHD levels were significantly associated with the use of a walking aid ($p < 0.0001$), being highest in those residents able to walk independently or with a stick, and lowest in those who used a wheelchair.

Table 2 Biochemical measures grouped by gender and institution, given as mean ± standard error of the mean (range), median

	Intermediate care facility		Nursing home	
	Male	Female	Male	Female
Corr. calcium (mmol/l)	2.33 ± 0.015 (1.96–2.55), 2.33	2.35 ± 0.008 (1.87–2.63), 2.35	2.34 ± 0.018 (2.01–2.60), 2.36	2.36 ± 0.010 (1.86–2.67), 2.37
Inorg. phosphorus (mmol/l)	1.15 ± 0.021 (0.75–1.66), 1.14	1.26 ± 0.012 (0.77 – 2.11), 1.26	1.13 ± 0.020 (0.76–1.67), 1.11	1.20 ± 0.012 (0.59–1.77), 1.21
Albumin (g/l)	42.0 ± 0.38 (32–49), 42.0	41.7 ± 0.23 (30–58), 42.0	40.1 ± 0.43 (32–50), 40.0	39.4 ± 0.22 (26–47), 39
Creatinine (μmol/l)	106.7 ± 4.2 (53–311), 95.5	95.0 ± 2.4 (45–306), 88.5	103.1 ± 4.1 (53–205), 98.0	90.8 ± 2.9 (32–513), 80.0
Creatinine clearance (ml/min)	53.1 ± 2.27 (19.2–115.9), 50.8	39.2 ± 1.15 (10.4–124.5), 36.3	50.2 ± 2.54 (20.2–109.9), 47.7	39.0 ± 1.15 (10.4–130.2), 35.9
25-OH-vitamin D (nmol/l)	35.5 ± 1.46 (5–92), 34.0	29.9 ± 0.64 (2–104), 27.0	29.5 ± 1.59 (5–103), 25.5	25.7 ± 0.79 (2–101), 21.0
PTH (pg/ml)	60.4 ± 3.98 (12.6–238.0), 46.9	78.5 ± 2.98 (4.6–886.0), 62.1	68.8 ± 4.46 (12.2–440.0), 58.0	77.5 ± 3.51 (5.6–663.0), 56.0

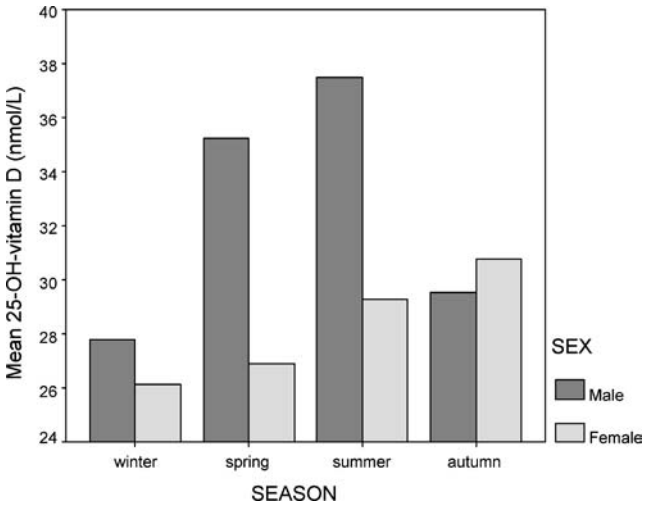

Fig. 1 Changes in 25OHD levels with season in males and females

When those individuals taking vitamin D supplements are excluded from the analysis ($n = 129$), 25OHD levels were significantly associated with season in both males ($p = 0.003$) and females ($p < 0.0001$). Levels were lowest in winter in both sexes, but males had an earlier peak in spring/summer compared to an autumn peak in women (Fig. 1).

When serum 25OHD levels were divided into quintiles, mean PTH levels were observed to rise between the third and fourth quintiles (Fig. 2), representing a mean vitamin D level of 29 nmol/l, consistent with 30 nmol/l as an appropriate cut-off for defining hypovitaminosis D in this frail elderly population.

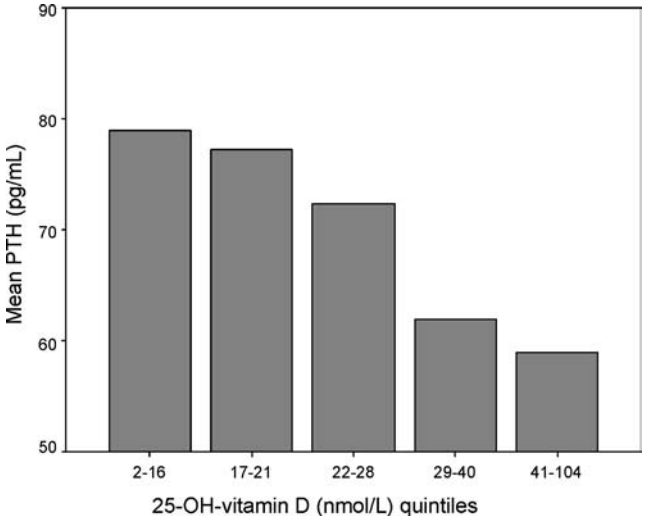

Fig. 2 Mean PTH values relating to 25OHD quintiles

Independent predictors of 25OHD

Univariate analysis corrected for age showed 25OHD levels to be significantly and inversely associated with PTH in men ($p < 0.0001$) and in women ($p < 0.0001$). In females, 25OHD was associated with creatinine clearance ($p = 0.004$) and with albumin ($p = 0.016$) but there was no association observed in the smaller sample of males ($p > 0.2$). Serum 25OHD was not associated with calcium or phosphate in either gender ($p > 0.15$).

All significant univariate parameters were included in multiple regression models for men and women separately, and for the entire cohort (Table 3). Female gender, reduced mobility, higher PTH, increasing age, cooler season and creatinine clearance were independently related to lower 25OHD levels.

Vitamin D supplementation

The prevalence of use of vitamin D supplementation and other bone-active medications was low overall in this population (Table 4). There was no statistically significant difference between men and women in the use of mixed vitamin supplements containing either vitamin D or calcium; however, the use of specific bone-targeted compounds including calcium alone, vitamin D analogues (calcitriol) and bisphosphonates was more frequently seen in females than males. A small number of individuals were taking both vitamin D supplements and analogues.

Residents taking vitamin D preparations were much more likely to be taking concomitant calcium supplements ($p < 0.0001$). Mean vitamin D levels were 45.5 nmol/l in those taking any form of vitamin D supplementation, which was significantly higher than 27.1 nmol/l for the group without supplementation (mean difference 18.4 nmol/l, $p < 0.0001$). This significant difference was maintained in men and women. Residents taking either ergocalciferol or cholecalciferol had significantly higher mean 25OHD levels (55.9 and 56.1 nmol/l, respectively) than residents not taking supplements ($p < 0.001$). However, there was no significant increase in those residents using vitamin D analogues (calcitriol) whose mean 25OHD levels were 29.3 nmol/l. Mean PTH levels were significantly lower in the supplementation group, 50.0 pg/ml compared to 78.1 pg/ml in those not receiving supplements, mean difference 28.1 pg/ml ($p < 0.0001$).

Discussion

These data provide information on the prevalence of various biochemical abnormalities relevant to calcium metabolism in a frail elderly population. A high prevalence of renal impairment and hypovitaminosis D was observed. Hypocalcaemia was uncommon given the high prevalence of renal impairment and hypovitaminosis D;

Table 3 Independent determinants of serum 25OHD

	Variable[a]	*B*	SE	*t*	Significance
Males ($R^2 = 0.14$)	(Constant)	4.264	0.217	19.653	< 0.0001
	Ln PTH	−0.178	0.053	−3.331	0.001
	Walking aid	−0.116	0.029	−3.951	< 0.0001
Females ($R^2 = 0.06$)	(Constant)	5.112	0.545	9.381	< 0.0001
	Age	−0.011	0.005	−2.056	0.04
	Ln PTH	−0.149	0.053	−2.812	0.005
	Cr. clearance	−0.007	0.002	−3.261	< 0.0001
	Walking aid	−0.086	0.028	−3.045	0.003
Entire cohort ($R^2 = 0.10$)	(Constant)	5.090	0.479	10.625	< 0.0001
	Age	−0.009	0.005	−2.000	0.046
	Gender	−0.151	0.064	−2.367	0.018
	Ln PTH	−0.141	0.046	−3.064	0.002
	Cr. clearance	−0.006	0.002	−3.386	0.001
	Walking aid	−0.100	0.024	−4.158	< 0.0001
	Season	0.052	0.024	2.205	0.028

[a]Excluded variables: in males, season, age; in females, season, institution, albumin; in total cohort, institution, albumin

Table 4 Frequency of "bone-active" medication use among men and women living in aged care facilities

Medication	All	Male	Female	Significance
Vitamin D analogue	50 (4.0%)	3 (1.1%)	47 (4.7%)	$p < 0.007$
Ergocalciferol (D2)	47 (3.7%)	5 (1.9%)	42 (4.2%)	$p = 0.07$
Cholecalciferol (D3)	86 (6.8%)	12 (4.5%)	74 (7.5%)	$p = 0.09$
Any vitamin D preparation[a]	129 (10.3%)	16 (6.0%)	113 (11.4%)	$p = 0.01$
Calcium alone	107 (8.5%)	13 (4.9%)	94 (9.6%)	$p = 0.018$
Other vitamin supplements with calcium	138 (11.1%)	21 (8.0%)	117 (12.0%)	$p = 0.077$
Hormone therapy	34 (2.8%)	1 (0.4%)	33 (3.4%)	$p = 0.005$
Bisphosphonates	60 (4.8%)	3 (1.1%)	57 (5.8%)	$p = 0.001$

[a]Some subjects were taking multiple supplements

however, the first change in mineral metabolism with renal impairment is generally an increase in phosphate, before a fall in serum calcium and our data reflect this pattern. Hypoalbuminaemia was also relatively uncommon suggesting overall adequate nutrition in this population. Indeed, albumin values were normal in approximately two-thirds of all residents in the study. The prevalence of renal impairment in our population was substantially higher than in other population studies [18–21], but our population represents a frailer older cohort than the ones investigated in these studies. Using estimated creatinine clearance in older people derived from equations based on serum creatinine, weight, age and sex may underestimate actual creatinine clearance [22]; however, it would be impractical to directly measure creatinine clearance in a frail elderly population with a high prevalence of incontinence. It is likely our subjects have both reduced muscle mass (sarcopenia) and impaired renal function, which may explain the discordance between the prevalence of elevated serum creatinine values vs reduced creatinine clearance.

Vitamin D is added to some foods in the United States of America but not in Europe or Australia. Vitamin D_3 is generally found in small quantities in foods but richer sources are fish, especially high-fat fish such as salmon, herring and mackerel. Other sources of importance are meat and eggs and fortified foods such as margarine. Sydney is situated at 33°55 min south of the Equator and at this latitude, there is sufficient sunlight to provide adequate UV exposure for vitamin D synthesis in the skin of healthy younger individuals all year round [23]; however, cutaneous vitamin D production is known to be diminished in the elderly [24]. Indeed, serum 25OHD levels were generally low in this cohort of frail elderly people living in residential aged care facilities in northern Sydney. A cross-sectional study of 99 elderly men and women conducted in Melbourne 6 years earlier [12] showed that 52% of residents of the aged care facilities studied had 25OHD levels below the normal range. Similarly low levels of 25OHD in aged care facilities have been described elsewhere [11, 14, 15], suggesting that elderly persons living in such facilities do not get sufficient sunlight exposure to maintain their vitamin D levels.

Males had higher 25OHD levels than women independent of season or institution, as has been reported previously [25]. Residents in intermediate care accommodation had higher 25OHD and higher albumin levels than their counterparts in nursing homes. If one considers that serum albumin is a reasonable measure of general nutrition and morbidity [26–28], it seems likely that these differences in vitamin D status between

institutions reflect the poorer mobility and general health of nursing home residents.

Sunlight exposure is important for maintaining adequate vitamin D levels. Melin et al. [29] showed in a prospective study that seasonal variation of 25OHD levels requires three or more hours per week of sunlight exposure during summer months in Scandinavia and that 25OHD levels measured in autumn reflect this exposure during summer. Individuals living in aged care facilities are less mobile than those living independently, and therefore less likely to get outdoors, contributing to an increased prevalence in hypovitaminosis D [11, 14] which may not be compensated by dietary intake [15]. As well, there are strong public health warnings about sunlight exposure and risk of skin cancer in Australia. It has previously been shown that seasonal variation in 25OHD levels is less marked in residents of aged care facilities than in independently living elderly people [13, 30]. We observed a modest seasonal variation of 25OHD in this institutionalized group, with lowest levels occurring in winter as has been shown in previous cross-sectional [31–35] and longitudinal studies [36] in independently living elderly populations. Serum 25OHD peaked during the spring/summer in men and in autumn in women; this difference might be explained by poorer mobility of the female group, resulting in a slower accumulation of sunlight exposure over the warmer months. Mobility, as measured by the use of a walking aid, was also an independent predictor of 25OHD; residents who were independently mobile or used a stick had higher 25OHD levels than those using a walking frame or wheelchair, presumably due to increased sunlight exposure.

There has been considerable debate about the appropriate definition of hypovitaminosis D, with cut-off values previously ranging from as low as 8–10 nmol/l [36] up to 50–80 nmol/l [1, 10, 37, 38, 39]. Differences in 25OHD assays might account for some of this variability [40], and so associating low 25OHD levels with other parameters such as PTH is important to assess clinical significance. One of the most commonly used cut-off values is below 30 nmol/l [2, 6, 23, 41–43], on the basis that at this level of 25OHD a mild increase in serum PTH is seen and so has clinical significance. Our findings are not inconsistent with the use of 30 nmol/l as a cut-off for defining hypovitaminosis D in the frail elderly living in aged care facilities, based upon the PTH rise in subjects with values below 29 nmol/l.

Despite taking a wide variety of preparations and doses, the overall rate of vitamin D supplementation seen in this frail elderly population was disappointing with only 10.3% of residents ($n = 129$) receiving vitamin D supplementation or vitamin D analogues. Of interest, the DiaSorin assay did not suggest any difference in response of serum 25OHD according to whether supplementation was with either ergocalciferol or cholecalciferol. Vitamin D supplementation was associated with increased serum 25OHD levels in this elderly group, with a mean difference in levels between residents on supplements and those not taking vitamin D supplements of 18 mnol/l, bringing those individuals on treatment to a mean level of 45 nmol/l. However, it has been suggested that the elderly require higher doses of vitamin D to overcome hyperparathyroidism related to increasing creatinine levels [43] and it has been argued that 50 nmol/l is a more appropriate cut-off for ''bone health''. Few of the supplemented individuals in our study had 25OHD values above 50 nmol/l, suggesting currently available low-dose daily vitamin D supplements are relatively inadequate for this population, probably due to both poor compliance with a daily therapy and cost. Higher dose, less frequent inexpensive vitamin D supplements are available in other countries with good safety experience and may be more appropriate for institutionalized subjects.

Elderly institutionalized men and women have a high prevalence of hypovitaminosis D despite overall adequate nutrition, which is not currently adequately addressed by appropriate replacement therapy, and is likely to have important public health implications for bone and muscle health.

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