PAPERS AND SHORT REPORTS

Parathyroid hormone and 25-hydroxyvitamin D concentrations in sick and normal elderly people

M M PETERSEN, R S BRIGGS, M A ASHBY, R I REID, M R HALL, P J WOOD, B E CLAYTON

Abstract

Serum 25-hydroxyvitamin D and immunoreactive parathyroid hormone concentrations were measured in normal elderly subjects living at home and in sick elderly patients in hospital. Normal old people tended to have high 25-hydroxyvitamin D and low parathyroid hormone concentrations; in the sick elderly this pattern was reversed. The raised serum parathyroid hormone concentrations in the sick elderly were not due to poor renal function and may have been a response to vitamin D deficiency.

A high serum parathyroid hormone concentration in an elderly patient must be interpreted in the light of the patient's general health and nutritional state. Caution is needed in diagnosing primary hyperparathyroidism in this age group.

Introduction

Primary hyperparathyroidism is now more commonly diagnosed than previously, particularly in the elderly, because of biochemical screening.¹ Many patients in whom this diagnosis is made, however, have no symptoms, and questions arise whether their biochemical abnormalities matter clinically and whether they should be treated.²⁻³ Usually after biochemical screening has suggested the diagnosis of primary hyperparathyroidism the

concentration of immunoreactive parathyroid hormone is measured, but, although most patients diagnosed as having primary hyperparathyroidism are over 60, there are few published data on "normal" ranges of immunoreactive parathyroid hormone concentrations in this age group.

Serum concentrations of 25-hydroxyvitamin D are low in patients admitted to geriatric wards⁴ and in patients in long stay geriatric wards.⁵ "Vitamin D deficiency" in its various forms is the commonest cause of secondary hyperparathyroidism.⁶ Sick old people might, therefore, be expected to maintain serum calcium concentrations in the face of vitamin D depletion by increased secretion of parathyroid hormone. We have examined the relation between immunoreactive parathyroid hormone and 25-hydroxyvitamin D concentrations in healthy old people living at home and in patients in geriatric hospitals.

Subjects and methods

Twenty three men aged 69-86 and 11 women aged 66-81, all healthy volunteers, took part in the study. All were mobile and lived independently at home, and none had biochemical evidence of important renal impairment.

Eighty five patients in geriatric wards (40 men aged 76-92 and 45 women aged 63-95) were also studied. Patients with overt Paget's disease of bone or malignant disease and one woman with previously diagnosed hyperparathyroidism were excluded. The patients were divided on the basis of blood urea and serum creatinine concentrations into those with normal and those with impaired renal function. The upper limits for normal renal function were a urea concentration of 10 mmol/l (60 mg/100 ml) or a creatinine concentration of 150 μ mol/l (1.7 mg/100 ml); these were derived from data obtained in 335 independent elderly subjects living at home. Nine (22%) of the men and 12 (27%) of the women in the geriatric wards had renal impairment by these criteria.

The patients had been admitted with illnesses that made them unable to cope at home. Most had more than one diagnosis (mean 3.2, range 1-7): 36 (42%) had neurological disorders, mostly stroke or Parkinson's disease; and 20 (23%) suffered from arthritic conditions, contributing to immobility, falls, and inability to look after themselves. Cardiopulmonary (36 (42%)) and gastrointestinal (18 (21%)) diseases were often present. The patients had been in hospital for a mean of 5.3 weeks (range 1-58) before the study, although 61 (72%) had been admitted less than one month previously. It is important to note that elderly patients with chronic disability such as those we

Geriatric Medicine, Faculty of Medicine, Southampton General Hospital, Southampton SO9 4XY

M M PETERSEN, BSC, biochemist

R S BRIGGS, MSc, MRCP, senior lecturer

M A ASHBY, MB, MRCP, senior house officer

R I REID, MB, MRCP, consultant

M R HALL, MA, FRCP, professor

Chemical Pathology and Human Metabolism, Faculty of Medicine, Southampton General Hospital, Southampton SO9 4XY

P J WOOD, PhD, principal biochemist

B E CLAYTON, MD, FRCPATH, professor

Correspondence and reprint requests to: Dr R S Briggs.

studied are often housebound and living in poor circumstances before admission to hospital.

The patients were taking a mean of 3.1 drugs each (range 0-10). Some drugs may perturb calcium metabolism—notably thiazide and loop diuretics, which were taken by 36 (42%). Six patients were taking cimetidine, five steroids, and three anticonvulsants (phenobarbitone or phenytoin); only two were receiving calcium and vitamin D supplements. We did not exclude patients because of their treatment for two reasons. Firstly, we wished our findings to be relevant to routine geriatric practice, in which multiple drug use is common. Secondly, such treatment should not have obscured the hypothesis we wished to test—namely, that a disturbance in calcium or vitamin D metabolism might be countered by a change in parathyroid hormone secretion.

Correlation of serum 25-hydroxyvitamin D and immunoreactive parathyroid hormone concentrations (log transformed) in elderly subjects. $R=0.51$, $p<0.001$.

Conversion: SI to traditional units—25-Hydroxyvitamin D: 1 nmol/l $\approx$ 0.4 ng/ml.

Biochemical screening—The subjects did not have to fast before blood samples were taken. Routine biochemical tests were carried out using standard methods and either Vickers M 300 or SP 120 auto-analysers. Serum albumin concentration was estimated by the bromocresol green dye binding method.⁷ Calcium concentration (mmol/l) was corrected for albumin concentration (g/l) by the formula: corrected serum calcium = estimated serum calcium + 0.02 (40—serum albumin).

Parathyroid hormone—Radioimmunoassay of immunoreactive parathyroid hormone was carried out using Medical Research Council antiserum AS 211/32 at a final dilution of one in 400 000. Bovine parathyroid hormone was used as the standard and produced parallel dilution curves with human parathyroid hormone. The limit of detection of the assay was 100 ng/l; intra-assay and interassay coefficients of variation were 25% and 35% respectively. The assay is primarily directed to the N terminal.⁸

25-Hydroxyvitamin D—Serum concentrations of 25-hydroxyvitamin D were measured by a competitive protein binding assay.⁹ The limit of detection was 1.0 nmol/l (0.4 ng/ml). Intra-assay and interassay coefficients of variation were 5% and 16% respectively.

Statistical analyses—Group means were compared using both Student's unpaired *t* test and the Mann-Whitney U test. Distributions of serum alkaline phosphatase activity on concentrations of 25-hydroxyvitamin D and immunoreactive parathyroid hormone were appreciably skewed and therefore log transformed.

Results

The patients were older than the normal subjects, though in both the mean age was over 75 (table I). The mean uncorrected serum calcium concentration was lower in the patients than in the normal subjects, but this difference was accounted for by the lower serum albumin concentrations in the patients. The patients with impaired renal function retained phosphate, the patients with normal renal function having a significantly lower mean serum phosphate con-

TABLE I—Mean (SD) clinical and biochemical variables in elderly patients

	Normal elderly subjects (group A)	Elderly patients	
		Normal renal function (group B)	Impaired renal function (group C)
No of subjects	34	64	21
Age (years)	75.1 (5.0)*	80.9 (6.8)	83.3 (7.5)
Estimated serum calcium (mmol/l)	2.32 (0.07)*	2.21 (0.17)	2.29 (0.15)
Corrected serum calcium (mmol/l)	2.29 (0.06)	2.25 (0.15)	2.28 (0.11)
Serum albumin (g/l)	41.4 (2.3)*	37.8 (3.8)	40.1 (4.3)
Inorganic phosphate (mmol/l)	1.04 (0.14)*	0.87 (0.15)	1.08 (0.18)†
Blood urea (mmol/l)	6.3 (1.5)	7.6 (2.4)	14.3 (6.2)‡
Serum creatinine (μmol/l)	108 (18)	93 (22)	157 (86)†

Significance of differences between groups: * $p<0.001$, group A v group B; † $p<0.01$, ‡ $p<0.001$, group B v group C.

Conversion: SI to traditional units—Serum calcium: 1 mmol/l $\approx$ 4 mg/100 ml. Inorganic phosphate: 1 mmol/l $\approx$ 3.1 mg/100 ml. Urea: 1 mmol/l $\approx$ 6 mg/100 ml. Creatinine: 1 μmol/l $\approx$ 11.3 μg/100 ml.

centration; although blood samples were not taken when the subjects were fasting and the serum albumin concentration was also reduced, this finding is consistent with high prevalence of secondary hyperparathyroidism or osteomalacia in this group.

The patients had higher serum alkaline phosphatase activities than the normal subjects (table II): alkaline phosphatase activities tend to rise with age, which is probably due to occult disease affecting bone or liver rather than a genuine change with age.¹⁰ The range for normal adults in our laboratory is 50-300 IU/l.

There were no significant differences in mean serum alkaline phosphatase activity or 25-hydroxyvitamin D or immunoreactive parathyroid hormone concentrations between patients with normal and impaired renal function. There were, however, important differences between the healthy subjects and the patients. Both serum alkaline phosphatase activities and immunoreactive parathyroid hormone concentrations were higher in the patients, while 25-hydroxyvitamin D concentrations were reduced (table II).

TABLE II—Log transformed data for serum alkaline phosphatase activity and 25-hydroxyvitamin D and immunoreactive parathyroid hormone concentrations in elderly subjects (values expressed as means and 95% confidence intervals)

	Normal elderly subjects (group A)	Elderly patients	
		Normal renal function (group B)	Impaired renal function (group C)
No of subjects	34	64	21
Serum alkaline phosphatase (IU/l)	176 (83-373)*	274 (136-551)	291 (133-639)
25-Hydroxyvitamin D (nmol/l)	39 (2-788)*	8 (<1-102)	8 (<1-87)
Immunoreactive parathyroid hormone (ng/l)	200 (<100-590)*	1280 (336-2040)	1166 (297-2470)

Significance of differences between groups: * $p<0.001$, group A v groups B and C; no significant differences between groups B and C.

Conversion: SI to traditional units—25-Hydroxyvitamin D: 1 nmol/l $\approx$ 0.4 ng/ml.

There was no significant correlation between 25-hydroxyvitamin D concentrations and age, and age accounted for little of the variance in immunoreactive parathyroid hormone concentrations ($R^2=11\%$). There was, however, a significant correlation between immunoreactive parathyroid hormone and 25-hydroxyvitamin D concentrations ($p<0.001$, figure) when pooled data from all groups were used.

Discussion

The data that we obtained from routine biochemical screening are comparable with those found in previous studies.^{10 11} Sick elderly patients may be expected to have lower serum albumin concentrations and higher serum alkaline phosphatase activities than their normal counterparts, but serum calcium concentrations were normal in our population. It has been postulated that senile osteoporosis may in part be due to secondary hyperparathyroidism consequent on renal failure.¹² We found no difference in serum immunoreactive parathyroid hormone concentrations between those patients with impaired renal function and those with "normal" renal function. Blood urea concentration is a

more useful criterion of renal function in old people than serum creatinine concentration because creatinine concentration varies with body weight.¹⁰

Previous studies of immunoreactive parathyroid hormone concentrations in elderly subjects have produced conflicting results. Roof *et al* found the highest concentrations in the fifth or sixth decade of life and a fall during senescence.¹³ Two studies in the USA reported rises in immunoreactive parathyroid hormone concentrations with age; one study, however, included only 12 elderly volunteers,¹⁴ and the other obtained elderly subjects from old peoples' homes,¹⁵ a population that cannot be considered normal. (All three studies¹³⁻¹⁵ measured immunoreactive parathyroid hormone concentrations by a radio-immunoassay primarily directed to the biologically inactive carboxyterminal portion of the molecule, which is cleared from the circulation by glomerular filtration.) A range of immunoreactive parathyroid hormone concentration in young adults obtained with our assay was 250-450 (mean 380) ng/l.¹⁶ If we had compared the results in our "normal elderly" group with this mean our results would have suggested a decline in immunoreactive parathyroid hormone concentrations with age, whereas the data from patients in geriatric wards would have led to the opposite interpretation.

The mean 25-hydroxyvitamin D concentration was low in our patients, in accord with previous reports.^{4 5 17} Although 25-hydroxyvitamin D is an inactive metabolite and its measurement is not discriminant in diagnosing osteomalacia in individual cases,¹⁸ in group studies there is a highly significant correlation between concentrations of 25-hydroxyvitamin D and the derived effector hormone 1,25-dihydroxyvitamin D.⁶ There is evidence in Asian immigrants that serum immunoreactive parathyroid hormone concentrations are higher in subjects with low serum 25-hydroxyvitamin D concentrations (below 12.5 nmol/l (5 ng/ml)) than in controls with adequate vitamin D⁶ raised immunoreactive parathyroid hormone concentrations may be an adaptive response to developing vitamin D deficiency.⁶ Primary hyperparathyroidism is being diagnosed more commonly in elderly patients,¹⁻³ a group who are at high risk of vitamin D deficiency because of both poor diet and lack of sunlight.⁴ Excessive reliance should not be placed on serum immunoreactive parathyroid hormone concentrations in diagnosing primary hyperparathyroidism in old people.

We thank Schwarzhaupt of Cologne for financial support. We are grateful to Dr Carmel Hillyard, Royal Postgraduate Medical School, and Mrs Doreen Jackson, Hospital for Sick Children, London, for help with the parathyroid hormone assay, for which reagents were kindly donated by the National Biological Standards Board. We are

grateful to Dr M J Nicholls, Dr A M Plumtre, Dr S Bradberry, Dr D H White, Dr G B Salmon, and Dr M S Fisher for allowing us to study patients in their general practice. We also thank Mrs Hazel Killham for typing the paper.

References

- Heath H, Hodgson SF, Kennedy MA. Primary hyperparathyroidism: incidence, morbidity and potential economic impact on a community. *N Engl J Med* 1980;**302**:189-93.
- Mundy GR, Cove DH, Fiskin R. Primary hyperparathyroidism: changes in the pattern of clinical presentation. *Lancet* 1980;i:1317-20.
- Heath DA, Barnes AD, Wright AP, Oates GD, Dorricott NJ. Surgical treatment of primary hyperparathyroidism in the elderly. *Br Med J* 1980;**280**:1406-8.
- Nayal AS, MacLennan WJ, Hamilton JC, Rose P, Kong M. 25-hydroxyvitamin D, diet and sunlight exposure in patients admitted to a geriatric unit. *Gerontology* 1978;**24**:117-22.
- Corless D, Gupta SP, Sattar DA, Switala S, Boucher BJ. Vitamin D status of residents of an old people's home and long-stay patients. *Gerontology* 1979;**25**:350-5.
- Stanbury SW. Vitamin D and hyperparathyroidism. *J R Coll Phys Lond* 1981;**15**:205-17.
- Spencer K, Price CP. Influence of reagent quality and reaction conditions on the determination of serum albumin by the bromocresol green dye-binding method. *Ann Clin Biochem* 1977;**14**:105-15.
- Mallette LE. Sensitivity of the antiovine parathyroid hormone serum 211/32 to synthetic fragments of human parathyroid hormone. *J Clin Endocrinol Metab* 1980;**50**:201-3.
- Hamilton JC. A rapid simplified method for plasma 25-hydroxyvitamin D estimation. *J Clin Pathol* 1980;**33**:197-9.
- Hodkinson HM. *Biochemical diagnosis of the elderly*. London: Chapman and Hall, 1977:53-66.
- Leask RGS, Andrews GR, Caird FI. Normal values of sixteen blood constituents in the elderly. *Age Ageing* 1973;**2**:14-23.
- Berlyne GM, Ben Ari J, Kushelevsky A. The aetiology of senile osteoporosis: secondary hyperparathyroidism due to renal failure. *Q J Med* 1975;**44**:505-21.
- Roof BS, Piel CF, Hansen J, Fudenberg HH. Serum parathyroid hormone levels and serum calcium levels from birth to senescence. *Mech Ageing Dev* 1976;**5**:289-304.
- Insogna KL, Lewis MM, Lipinski BA, Bryant C, Baran DT. Effect of age on serum immunoreactive parathyroid hormone and its biological effects. *J Clin Endocrinol Metab* 1981;**53**:1072-5.
- Wiske PS, Epstein S, Bell NH, Queener SF, Edmondson J, Johnston CC. Increases in immunoreactive parathyroid hormone with age. *N Engl J Med* 1979;**300**:1419-21.
- Clayton BE, Jenkins P, Round JM. *Paediatric chemical pathology: clinical tests and reference ranges*. Oxford: Blackwell Scientific, 1980:122-3.
- Corless D, Beer M, Boucher BJ, Gupta SP, Cohen RD. Vitamin D status in long-stay geriatric patients. *Lancet* 1975;ii:1404-6.
- Kafetz K, Hodkinson HM. Osteomalacia in presence of "normal" serum 25-hydroxycholecalciferol concentration. *Br Med J* 1981;**283**:1437.

(Accepted 14 June 1983)

PURGING MEDICINES—Much jarring hath been amongst physicians about purging medicines, namely, whether they draw the humours to them by a hidden quality, which in plain English is, they know not how; or whether they perform their office by manifest quality, viz by heat, dryness, coldness, or moisture: it is not my present scope to enter the lists of a dispute about the business, neither seem it such an hidden thing to me that every like should draw its like. . . . First consider diligently, and be exceeding cautious in it too, what the matter offending is, what part of the body is afflicted by it, and which is the best way to bring it out. Only here, by the way, first, have a care of giving vomits, for they usually work more violently, and afflict the body more than purges do, therefore are not fit for weak bodies; be sure the matter offending lie in the tunicle of the stomach, else is a vomit given in vain. Vomits are more dangerous for women than men, especially such as are either with child, or subject to the fits of the mother. What medicine is appropriated to the purging of such a humour, for seeing the offending matter is not alike in all, the purging medicine ought not to be the same to all. I shall speak more of this anon. As also of the divers ways whereby medicines draw out or cast out humours, viz by lenifying, cleansing, provoking nature to expulsion, and (which is stranger than the

doctor's *hidden quality*) some purge by binding, but indeed, and in truth, such as are properly called purging medicines, which, besides these faculties, have gotten another, by which they draw or call out the humours from the most remote parts of the body, whether these do it by heat or by an hidden quality, physicians are scarce able to determine, it being very well known to modern physicians, though the ancients denied it, that many cold medicines purge. There is this faculty in all the purges of *Galen's* model, (because he gives the whole *simple* which must needs consist of divers qualities, because the creation is made up of and consists by an harmony of contraries) there is (I say) this faculty in all purges of that nature, that they contain in them a substance which is inimical both to the stomach and bowels, and some are of opinion this doth good, namely, provokes nature the more to expulsion; the reason might be good if the foundation of it were so, for by this reason nature herself should purge, not the medicine, and a physician should help nature in her business and not hinder her. But to forbear being critical, this substance which I told you was inimical to the stomach, must be corrected in every purge. (Nicholas Culpeper (1616-54) *The Complete Herbal*, 1850.)