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Unexplained musculoskeletal pain in people of South Asian ethnic group referred to a rheumatology clinic – relationship to biochemical osteomalacia, persistence over time and response to treatment with calcium and vitamin D

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ABSTRACT

Background. *Hypovitaminosis D continues to be a problem for South Asian people living in the UK. This study investigates the association between widespread unexplained pain and biochemical osteomalacia in this group of people.*

Methods. *All South Asian patients attending with unexplained widespread pain (CWP) over a two-year period had biochemical tests for osteomalacia: calcium, phosphate, alkaline phosphatase, vitamin D (25OHD), and parathyroid hormone (PtH). For comparison, a control group consisted of patients in whom a specific rheumatic diagnosis (SRD) had been made. A follow up questionnaire was sent enquiring about pain, disability and dietary habits. A small proportion of the responders attended for a further set of biochemical tests for osteomalacia.*

Results. *The majority of patients in both groups had a raised PtH (124/220, 57%) and a low 25OHD (117/160, 73%). Where data on both PtH and 25OHD were available, 47% (64/137) had a combination of reduced 25OHD and raised PtH. Few of these patients had abnormal calcium, phosphate or alkaline phosphates.*

From the postal questionnaire the prevalence of disability and continuing pain was high in both groups, with the majority of respondents complaining of difficulty with activities and nearly half needing help. Pain was widespread, the same or worse and graded above 7/10 for 69% and 78% of respondents in the CWP and SRD groups respectively. Overall, sixty one percent of respondents thought their gait pattern had changed in the last year. No significant differences were seen between respondents based on diagnosis (CWP or SRD), initial or subsequent PtH levels, or current calcium and vitamin D consumption.

At the time of the second blood test, 52% of those with an elevated PtH on the first test now had a normal PtH value but 31% of those with a normal PtH first time had an elevated PtH.

Conclusions. *This observational study conducted in a rheumatology clinic in the north of England has shown high levels of biochemical osteomalacia in people of South Asian origin and high levels of persistent pain and disability, unrelated to diagnosis, biochemical status or treatment with calcium and vitamin D.*

Introduction

The UK now has a South Asian population of approximately 1.5 million with a well-maintained cultural and ethnic identity. In Bradford, UK 18% of the 486,000 community is from Pakistan, mostly from a small area to the North West called Miapur (URL: http://www.bradford.gov.uk). Generalised musculosketetal complaints are more common in South Asian females living in the UK than North Europeans (1). Chronic widespread pain may be secondary to a wide variety of conditions including endocrine diseases such as hypothyroidism and vitamin D deficiency disorders such as osteomalacia. Vitamin D deficiency and osteomalacia have been a persistent problem in people of South Asian ethnic background living in the UK. This problem has been known for at least 40 years and continues despite awareness in the medical and dietetics community (2-4). The UK government, also aware of this problem, has opted for increasing awareness and education of target groups rather than instituting a program fortifying staple foods (5). The relationship between chronic widespread pain and hypovitaminosis D in this group of people has not previously been explored although musculoskeletal pain is a well recognised feature of vitamin D deficiency (6, 7).

This study was undertaken to:

- relate unexplained chronic widespread pain to biochemical osteomalacia (defined as a raised parathyroid hormone with normal or low calcium levels) in people of South Asian ethnic origin
- determine changes in pain with time
- assess the response to treatment with calcium and vitamin D supplements.

Methods

Full informed consent was obtained and appropriate ethical committee approval obtained for this study. The design of the study is outlined in the Figure. Between August 2000 and August 2002, 494 requests for biochemical tests to exclude osteomalacia were

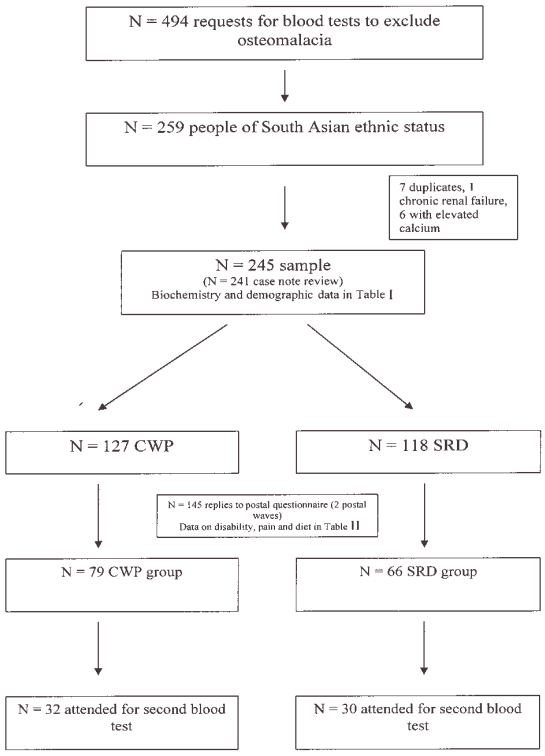

Fig. 1. Study design in diagrammatic form (CWP = chronic widespread pain. SRD = specific rheumatic diagnosis).

made by the Dept. of Rheumatology, St Lukes Hospital, Bradford. Biochemical tests included parathyroid hormone (PtH), 25-hydroxy vitamin D (25OHD), adjusted calcium, phosphate, alkaline phosphatase and creatinine. These tests were requested for unexplained widespread pain on new referrals from primary care and, in some cases, as part of the panel of biochemical tests requested in existing patients with a known rheumatic diagnosis.

From this group, all patients with a South Asian name were selected. Bradford has a population of 18% of people of South Asian ethnic origin, 85% of whom are, or are related to, people originating from a relatively small area of North West Pakistan and are, therefore, a relatively homogenous group who are readily identified by name.

Of this group of 259 people, 14 were excluded from the study: 7 had duplicate blood tests, 6 had hypercalcaemia, and 1 had chronic renal failure with a creatinine over 400 μmol/litre. There were no exclusions because of malabsorption, gastric or small bowel resection or hepatobiliary disease. Of the remaining 245 patients, the case notes were reviewed for 241 patients and data on reason for referral, hospital diagnosis, tests requested and treatment given were recorded. All 245 patients were sent a questionnaire through the post in early (February to March) 2003. The questionnaire asked about demographic details, continuing symptoms, diet and current medication. The questionnaire also asked if the respondent would be willing to attend for a further blood test. Sixty-two people subsequently attended for this between March and July 2003. The same biochemical measurements were made on the second blood sample.

Statistics

Most of the data in this survey were non-parametric so that appropriate tests, chi-squared and Mann Whitney, were used for 2x2 and continuous data comparisons respectively.

Results

Demographic details, biochemistry and rheumatic diagnoses

Patients were divided into two groups according to their diagnostic status: unexplained chronic widespread pain (defined as pain for at least 3 months in 4 body areas), fibromyalgia and patients with a definite diagnosis of osteomalacia were grouped together (CWP) and compared with patients having a specific rheumatic diagnosis (SRD). Demographic details, biochemistry, and hospital diagnoses for these two groups are given in Table I. Apart from age, no differences were observed between the two groups for any of the variables. Across both groups the majority of patients tested had a raised PtH (124/220, 57%) and a low 25OHD (117/160, 73%). Where data on both PtH and 25OHD were available, 47% (64/137) had a combination of reduced 25OHD and raised PtH. Conversely, 38 patients (28%) had a low 25OHD level with normal PtH levels. Patients with a combination of raised PtH, low 25OHD, and low calcium numbered 12 (9%). The combination of raised PtH, low 25OHD, and low calcium and raised alkaline phosphatase was uncommon with only 4 patients (3%).

Postal questionnaire

One hundred and forty-five valid responses were obtained, 110 females 35 males, median age 43.6y (range 18 – 79y). Of the respondents, 84 (59%) had been born in Pakistan although 54% had been in the UK for over 25 years. When outside the home, most of the females (78%) covered all areas but face and hands: only a minority (12%) covering all areas in the traditional manner. Responses to the pain and disability aspects of the questionnaire, divided by group (CWP and SRD) are tabulated in Table II.

The prevalence of disability and continuing pain was high, with the majority of respondents complaining of difficulty with activities and nearly half needing help with certain activities. Pain was widespread, the same or worse and graded above 7/10 for the majority of respondents. Fifty-one (65%) of respondents in the CWP group thought their gait pattern had changed in the last year, compared to 38 (59%) of the SRD group.

Dietary habits were recorded. The following figures are the number (%) of people never consuming the food: eggs 27 (19), milk 15 (11), cheese 70 (51), yoghurt 29 (20), fish 30 (21) and chappati 5 (4). Eight people admitted to being vegetarian and 11 to being vegans. Since a high prevalence of lactose intolerance has been reported in Pakistanis (8) respondents were asked if dairy products upset their stomachs: 33

(23%) responded in the affirmative. None of these figures was different between the two comparison groups.
Current medication was recorded. Thirty-four people (43%) in the CWP group reported taking simple analgesics either on a regular or intermittent basis compared to 34 (52%) in the SRD group. The comparable figures for NSAIDs were 31 (40%) and 28 (43%) for CWP and SRD groups respectively. Calcium and vitamin D tablets were identified as current medication by 26 (33%) of the CWP group and 20 (31%) of the SRD group.
To examine the effect of a raised initial PtH on the persistence of pain and disability a comparison of groups based on initial PtH value (normal or elevated) was carried out – the only significant difference between the groups was in calcium and vitamin D consumption (12 people in the 'normal' group, 30 people in the 'elevated' group, chi-squared 4.8, p = 0.03). Analysing the group on the basis of current calcium and vitamin D consumption similarly did not reveal any significant differences in pain and disability.

Second blood test
Respondents to the postal questionnaire were asked to attend for a second blood test and 62 complied. Overall there was a wide difference between the first and the second PtH levels with a range of -160 to +385 ng/L. At the time of the second blood test 52% of those with an elevated PtH on the first test now had a normal PtH value but 31% of those with a normal PtH first time now had an elevated PtH. There was no significant difference between the CWP and SRD groups in the second PtH level (CWP: raised PtH 12/32, SRD rasied PtH 14/30). Overall for people reporting taking calcium and vitamin D, 45% still had abnormal PtH levels, compared to 41% of people not taking calcium and vitamin D. No differences in pain severity or pain persistence were found between two groups defined on the basis of the result of the second PtH level.

Table 1. Demographic, biochemistry and initial hospital diagnosis in 245 patients of South Asian ethnic origin. CWP = chronic widespread pain group; SRD = specific rheumatic diagnosis group.

Variable (normal range in brackets)	CWP group	SRD group
N	127	118
Age (years)*	40.2, 16.4 – 79.1	46.4, 17.3 – 92.1
Gender	28 male; 99 female	22 male, 96 female
Parathyroid hormone ng/L (less than 54)	58, 14 - 953	63, 16 - 695
Parathyroid hormone – N (%) above upper limit of normal	39 (55)	36 (60)
Adjusted calcium mmol/L (2.15 – 2.55)	2.24, 1.73 – 2.54	2.28, 2.03 – 2.53
Phosphate mmol/L (0.8 – 1.31)	1.08, 0.67 – 1.51	1.12, 0.65 – 1.69
Alkaline phosphatase IU/L (50 – 270)	191, 98 -1387	208, 94 -835
Creatinine mol/L (55 – 110)	81, 57 - 137	84, 59 - 154
Vitamin D µg/L (more than 10)	6.9, 1.5 -26.9	6.7, 2.3 - 29.1
Hospital diagnoses	**N (% within group)**	**N (% of total group)**
Chronic widespread pain	103 (81)	
Fibromyalgia	18 (14)	
Osteomalacia	6 (5)	
Regional pain syndrome		26 (22)
Osteoarthritis		23 (19)
Rheumatoid arthritis		21 (18)
Connective tissue disorder		18 (15)
Seronegative spondyloarthropathy		11 (10)
Others (crystal disease, polymyalgia rheumatica, hypermobility syndrome, unclassified polyarthritis.		19 (16)
Treatment with calcium and vitamin D	**N (% within group)**	**N (% within group)**
Given prescription in clinic	29 (23)	43 (36)
Recommended by letter to patient and GP	57 (45)	54 (46)

* significant difference between CWP and SRD at p = 0.01

Discussion

This observational study conducted in a rheumatology clinic in the north of England has shown high levels of biochemical osteomalacia in people of South Asian origin and high levels of persistent pain and disability, unrelated to diagnosis, biochemical status or treatment with calcium and vitamin D.
Low levels of 25OHD may have adverse health effects independent of their effects on calcium metabolism including susceptibility to infection, cardiovascular disease and diabetes mellitus (9). More importantly, hypovitaminosis D can lead to defective calcium absorption, hypocalcaemia and, subsequently, a raised PtH level. However, low vitamin D is a poor predictor of osteomalacia (10). A persistently low 25OHD will result in compensatory raised PtH levels and this secondary hyperparathyroidism will lead to decalcification of the skeleton and the formation of uncalcified osteoid tissue. The poor quality bone may fracture, manifested by the presence of Looser's zones. Muscle weakness, myalgia and bone pain can occur and support the diagnosis, although the definitive method for diagnosing osteomalacia is by bone biopsy. In the early stages of osteomalacia the biochemical abnormalities (calcium, phosphate and alkaline phosphatase) resulting from a low 25OHD level may be absent due to compensatory changes but the PtH may be elevated.
In this study, it is perhaps not surprising that the continuing pain and disability were unrelated to PtH levels nor to reported oral intake of vitamin D and calcium. However, it is worth noting that treatment with calcium and vitamin D failed to correct the biochemical abnormalities in half the patients and 32% of those with a normal PtH level on their first clinic visit subsequently had a raised value. The relationship between pain, disability, low vitamin D level and raised PtH therefore remains unanswered.

Table II. Respondents to postal questionnaire (n = 145). Figures refer to N responses with percentage of responders in brackets. No differences were found between the two groups for any of the comparisons.

Variable (normal range in brackets)	CWP N (%)	SRD N (%)
N	79	66
Gender	19 M 60 F	16 M, 50 F
Disability*:		
- getting up and down stairs	55 (70)	47 (72)
- getting up from a chair or the toilet	43 (54)	39 (60)
- putting on shoes, socks or stockings	38 (48)	38 (59)
- standing or walking	59 (75)	51 (79)
Help+:		
- dressing and/or undressing	31 (34)	30 (46)
- getting in or out of bed	34 (43)	34 (52)
- getting in and out of the house	29 (37)	26 (40)
Pain		
- 4 or 5 areas#	51 (71)	36 (62)
- pain continued since attending clinic	74 (95)	57 (95)
- same or worse	63 (80)	49 (79)
- severity equal to or greater than 7$	51 (69)	45 (78)

* Respondents were asked: 'In the last 3 months have you had any difficulties with any of the following activities because of health problems or disabilities?'.
+ Respondents were asked: 'In the last 3 months have you needed any help with any of the following?'
# Respondents marked the site of their pain on a manikin which was then divided into 5 areas: each limb and head/spine.
$ Respondents were asked: 'During the past 12 months what is the most pain you have felt? A 10 point Likert scale anchored with the descriptors 'No pain at all' and 'Worst pain imaginable' was provided.

Chronic widespread pain is more common in people of South Asian origin living in the UK (1). It has been our perception that this was due to subclinical osteomalacia but there may be other explanations such as a high rate of somatisation, reflecting distress, in this ethnic group (11). Further studies will be required to examine the contribution of psychological distress to chronic pain in this group but it is worth noting the high levels of distress found in patients with fibromyalgia (12, 13).

What are the likely consequences of a persistently raised PtH level in the absence of other biochemical abnormalities and in the absence of overt osteomalacia? An unpublished study from Bradford has found lower bone mineral density in a group of unselected South Asian females matched for age and socio-economic status with a group of North European females (Armes, F, Devlin J, Rajaratnam *et al*. Personal communication). The latter study specifically excluded patients with a low 25(OH) 25OHD and a raised PtH. A study of people of Gujarati origin living in Leicester also failed to link low bone mineral density scores with vitamin D status (14). However, Serhan and Holland, found significant decreases in bone mineral density in South Asians with hypovitaminosis D and secondary hyperparathyroidism (15). It is possible we have yet to see the consequences of this as many South Asians immigrated in the 60s and are only now entering their 6th decade.

The lack of response, both biochemically and symptomatically, to treatment is disappointing and may reflect poor compliance or insufficient therapy. The dose of vitamin D in most commercial preparations is 10 mcg so that taking two of these should provide sufficient to meet daily requirements. It is possible a larger dose of vitamin D is required for people who already have deficiency of this vitamin - as much as 40mcg has been suggested (9). It is our practice to give vitamin D by intramuscular injection annually if there are doubts about compliance or if overt osteomalacia, particularly with bone disease, is found. It is salutary to note that despite 40 years of awareness of this problem vitamin D deficiency is still a widespread problem in the adult South Asian community in Bradford.

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