Quarterly Journal of Medicine, New Series 76, No. 281, pp. 923–933, September 1990

Asian Osteomalacia is Determined by Dietary Factors when Exposure to Ultraviolet Radiation is Restricted: a Risk Factor Model

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Accepted 7 November 1989

SUMMARY

Twenty-seven previously osteomalacic and 77 normal Asian women participated in a seven-day survey of dietary intake and daylight outdoor exposure. Individual levels of daylight outdoor exposure discriminated poorly between normal and osteomalacic women. The presence of osteomalacia was strongly related to varying degrees of vegetarianism. Lactovegetarianism (no meat, fish or egg consumption) was associated with significantly greater osteomalacic risk than ovolactovegetarianism (no meat or fish consumption). Unlike Asian rickets, high-extraction wheat cereal as chapatti was not a significant risk factor for osteomalacia in Asian women and dietary fibre was a less important risk factor than absent dietary meat, fish or egg. When exposure to ultraviolet radiation is limited, Asian osteomalacia (and Asian rickets) are determined by dietary factors.

INTRODUCTION

Vitamin D deficiency was first described in the British Asian community in 1962 [1] and may lead to congenital [2], infantile [3] and late rickets [4] in children and adolescents and to osteomalacia [5, 6] in adults (defined in the present communication as women > 16 years of age). The reasons for this state of affairs are disputed [7–12].

A risk factor model derived from a previous case-control study showed that severe Asian rickets was significantly related to high chapatti and low meat intakes when exposure to ultraviolet radiation was limited [13]; no other food classes were significantly associated with rachitic risk. The present case-control study examined the relationships of daylight outdoor exposure and dietary factors to the presence of osteomalacia in Asian women. A brief account of this study has been published [13].

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SURVEYS OF DIET AND OUTDOOR EXPOSURE

SUBJECTS AND METHODS

Subjects

There are approximately 10 000 Asians in Glasgow, who originate from the Punjab province of India and Pakistan and the Mirpur district of Kashmir. The community is ethnically homogeneous and the men are mainly self-employed in small shops, businesses and restaurants. In 1987, the parents of 81 per cent of Glasgow Asian schoolchildren gave their birthplace as Pakistan; these families are predominantly Muslim. The parents of the remaining 19 per cent gave their birth place as India; these families are mainly Sikh and Hindu (Glasgow Education Department; personal communication). Between 1972–1984, 37 Asian women, aged 17–66 years, were discharged from all Glasgow hospitals with the diagnosis of privational osteomalacia. Fifteen women could not be contacted; the remaining 22 agreed to take part in a survey of diet and outdoor exposure. Twelve of the 22 women showed radiographic evidence of disease (Looser zones) and had experienced severe symptoms (bone pain and muscle weakness) before treatment. In the remaining 10 radiographically negative patients symptoms were milder, although sufficiently severe to merit hospital admission.

An additional 82 Asian women were recruited as controls for the study. They formed part of a larger random sample of Asian women drawn from the age-sex registers of three inner-city general practices who participated in a survey of the prevalence of Asian osteomalacia in Glasgow during 1982–1983 [14]. The Asian sub-sample recruited for the survey of diet and outdoor exposure comprised all the available women in the general practice survey who had not taken vitamin D supplements in the previous five years and who were not pregnant. Five of the 82 women showed biochemical evidence of osteomalacia (see below) but were radiographically negative. These women were treated, re-classified as cases, and included in the hospital osteomalacia group. Thus, the case control study carried out between 1982 and 1985 comprised 27 previously osteomalacic women and 77 normal women.

Biochemical Methods

A blood sample had been taken from the 82 participants in the previous general practice [14] survey for the estimation of serum calcium, inorganic phosphorus, alkaline phosphatase and 25-hydroxycholecalciferol (25-OHD). The biochemical methods employed in the analysis have been published [14, 15]. A blood sample had been taken after admission from the 22 hospital patients for the estimation of serum calcium, phosphorus and alkaline phosphatase and, in a few cases, 25-OHD. The hospital and general practice patients were classified into osteomalacic and normal groups by the presence or absence at diagnosis of a low corrected serum calcium (<2.20 mmol/l) inorganic phosphorus (<0.8 mmol/l) or elevated serum alkaline phosphatase (>115 IU/l). As noted, serum 25-OHD concentrations were not available for most previously treated hospital patients and were not employed in classification. A note on the biochemical diagnosis of osteomalacia is given in Appendix A.

Dietary Survey

Seven-day weighed dietary intakes were recorded, as described by Marr [16], by 91 of the 104 Asian women (19 osteomalacic; 72 normal); records were checked daily by JBH. Recall records of dietary pattern were obtained from the remaining 13 women who were unable to complete a weighed survey (eight osteomalacic; five normal). A pre-treatment recall dietary history was also obtained from the 22 patients discharged from hospital with a diagnosis of privational osteomalacia. Nutrient intakes were calculated from the computerized food tables of Paul and Southgate [17] and the Nutritive Values of Indian Foods [18].

Daylight Outdoor Exposure Survey

Ninety-nine of the 104 women who participated in the dietary survey also completed satisfactory seven-day records of daylight outdoor exposure. Records were checked daily by JBH. Twenty-two women recorded 'summer' daylight outdoor exposures in the months of July and August and 77 recorded exposures in the remaining non-summer months of the year. Fifty-two of the latter subsequently recorded 'summer' daylight outdoor exposure in the following months of July and August.

Statistical Methods

The significance of univariate osteomalacic–normal differences was derived by considering each factor singly in a logistic regression model. Stepwise analysis then identified the independent contributions of significant variables to multivariate statistical models of osteomalacic risk [19–21]. The discriminating power of each model was expressed by calculating a relative risk from individual model-derived probabilities of osteomalacia for osteomalacic and normal subjects. This was termed the 'model relative risk'. Fuller details of the statistical methods employed are given in Appendix B.

RESULTS

Daylight Outdoor Exposure Survey (Table 1)

This comprised 74 weeks of 'summer' exposure and 77 weeks of 'non-summer' exposure. Daylight outdoor exposure recorded in July and August ('summer') was significantly greater than that recorded in the remaining 'non-summer' months of the year (analysis of variance; $p<0.05$). Daylight outdoor exposures for 'non-summer' months showed no significant between-month variation. The analysis therefore considered 'summer' and 'non-summer' values separately.

'Non-summer' daylight outdoor exposure levels of osteomalacic women were significantly lower than those of normal women; between-group discrimination was poor as reflected in the relatively low model relative risk (Table 1). 'Summer' daylight outdoor exposure levels of osteomalacic and normal women were not significantly different and the model relative risk was low.

The inclusion of food classes and nutrients in the 'summer' and 'non-summer' daylight outdoor exposure models resulted in the elimination of daylight outdoor exposure from both models in favour of dietary factors. Daylight outdoor exposure was therefore eliminated from the final food class and nutrient models described below.

Dietary Survey

The food class intakes of osteomalacic women showed a significantly more lactovegetarian dietary pattern than those of normal women (Table 2). Nutrient intakes reflected these

TABLE 1. *Significance of 'summer' and 'non-summer' daylight outdoor exposure as a negative (protective) risk-factor for osteomalacia in osteomalacic and normal Asian women*

Logistic model (samples)	Median exposure (min/day)	Risk (±)	p*	Model Relative Risk (95% C.I.)†	p
'Summer' daylight outdoor exposure					
(O = 15 women)‡	O = 51			1.7	
(N = 59 women)	N = 69	(−)	0.10	(0.5–6.4)	0.28
'Non-summer' daylight outdoor exposure					
(O = 22 women)‡	O = 25			3.0	
(N = 55 women)	N = 44	(−)	0.04	(1.1–9.4	0.04

* Significance of the regression coefficient
† C.I. = confidence interval
‡ O = Osteomalacia, N = Normal

TABLE 2. *Median daily food class intakes during the Asian women's weighed dietary survey*

Variable	Median intakes (g/day)	
	Osteomalacia ($n=19$)	Normal ($n=72$)
Chapatti	160	155
Pulses	120***	51
Vegetables	167**	130
Meat	0**	49
Fish	0	10
Eggs	11	21
Milk	420*	318
Butter[a]	11*	6
Margarine	0*	3

[a] Spread butter only; does not include butter used in cooking.

Logistic regression osteomalacia: normal; *$p<0.05$ **$p<0.01$ ***$p<0.001$

TABLE 3. *Median daily nutrient intakes during the Asian women's weighed dietary survey*

Variable	Median intakes	
Variable	Osteomalacia ($n=19$)	Normal ($n=72$)
Energy (kJ/day)	6827	6215
Protein (g/day)	53	52
Fat (g/day)	72	64
Carbohydrate (g/day)	208	192
Fibre (g/day)	27**	22
Calcium (mg/day)	958*	760
Phosphorus (mg/day)	1058	892
Phytate (mg/day)	160	142
Vitamin D (μg/day)	1.0	1.4
Age (years)	40	35

Logistic regression osteomalacia:normal; $*p<0.05$; $**p<0.01$.

changes (Table 3). The difference in median dietary vitamin D intakes between osteomalacic and normal women was small (0.4 μg; 16 IU) and statistically insignificant.

A dietary pattern analysis showed that the occurrence and severity of osteomalacia were significantly associated with varying degrees of vegetarianism. Low or absent egg consumption *per se* was not significantly associated with osteomalacia but osteomalacic risk associated with absent meat, fish and egg consumption (lactovegetarianism) was reduced by the consumption of eggs (ovolactovegetarianism; Table 4). The religious composition of the osteomalacic and normal groups reflects the association of strict lactovegetarianism with the

TABLE 4. *Prevalence of lactovegetarianism (LV), ovolactovegetarianism (OLV) and non-vegetarianism (Non-V) in 104 osteomalacic and normal Asian women*

Group	Osteomalacia		Normal	Osteomalacia: normal
	X-ray +ve[a]	X-ray −ve		p*
	($n=12$)	($n=15$)	($n=77$)	
Group	(%)	(%)	(%)	
LV	10 (83)	4 (27)	1 (1.3)	<0.001
OLV	2 (17)	2 (13)	5 (6.5)	<0.04
Non-V	0 (0)	9 (60)	71 (92)	<0.001

* χ^2 test

[a] Looser zones

Sikh and Hindu religions. Fifty-two (68 per cent) of the normal group were Muslim and 25 (32 per cent) Sikh and Hindu, reflecting the preponderance of Muslims in the Glasgow Asian community (see above). In contrast, only eight (30 per cent) of the osteomalacic group were Muslim and the remaining 19 (70 per cent) were Sikh or Hindu. Moreover, only one (8 per cent) of the 12 most severe, radiographically positive osteomalacic patients was Muslim and the remaining 11 (92 per cent) were Sikh or Hindu. The Muslim patient had been a strict lactovegetarian from choice from childhood.

Nutrient Model (*Table 5*)

Dietary fibre and phytate were highly correlated ($r=0.88$; $P<0.001$); phytate was consequently not considered in the final food component model. In decreasing order of significance, dietary fibre, age and dietary vitamin D were the most important variables in the model contributing as positive (fibre, age) and negative (vitamin D) risk factors for osteomalacia.

As indicated by the model relative risk, between-group discrimination was poor, being only slightly greater than in the 'non-summer' daylight outdoor exposure model.

Food Class Model (*Table 5*)

In decreasing order of significance, lactovegetarianism, ovolactovegetarianism and vegetables formed the most significant positive risk factors for osteomalacia. The food class

TABLE 5. *Significant negative (protective) and positive risk-factors for osteomalacia in two logistic models derived from the age and dietary intake (food classes and nutrients) of 91 osteomalacic and normal Asian women*

Logistic models (samples)	Variables	Risk(±)	p*	Model relative risk (95% C.I.)†	p*
Nutrients[a]	Fibre	(+)	0.01		
(O = 19 women)‡	Age	(+)	0.06	3.9	0.01
(N = 72 women)	Vitamin D	(−)	0.09	(1.2–15.2)	
Food classes[a,b]	Lactovegetarianism	(+)	<0.001		
(O = 19 women)	Ovolactovegetarianism	(+)	0.03	13.4	<0.001
(N = 72 women)	Vegetables	(+)	0.05	(2.8–124.7)	

* Significance of the regression coefficient.

† C.I. = Confidence interval.

‡ O = Osteomalacia, N = Normal.

[a] Stepwise logistic regression excluded the following insignificant variables from: (1) nutrients: energy, protein, fat, carbohydrate, calcium, phosphorus. (2) food classes: age, chapatti, pulses, milk, butter, cheese, margarine, meat, eggs and fish.

[b] Significance of improved goodness of fit between models: nutrients-food classes; $p<0.001$.

model provided significantly better goodness of fit than the nutrient model ($p < 0.001$). As expressed by the higher model relative risk, between-group discrimination considerably exceeded that found in the daylight outdoor exposure and nutrient models.

DISCUSSION

We agree with Dent that the epidemiology of osteomalacia is the study of 'cases', [22]. The present case-control study comprised subjects defined as cases or normal subjects on clinical, radiological and biochemical criteria. Cases or controls formed the dependent variables in a statistical evaluation of the relationship of all possible risk factors to the disease or 'case'. Previous studies of the relationship of diet and outdoor exposure to the aetiology of Asian rickets and osteomalacia have been reviewed [13]. The present investigation and our companion study of Asian rickets [13] are the only case control studies which have examined this problem in the British Asian population.

Cases and controls were predominantly derived from the main inner-city areas of Asian residence in Glasgow and were comparable in respect of ethnic origin and social class (see above). The religious composition of the control group reflects the predominantly Muslim composition of the Glasgow Asian population. The predominantly Sikh and Hindu composition of the cases reflects the strong association of these religions with lactovegetarianism. Measurements of individual daylight outdoor exposure over a total of 151 person–weeks discriminated poorly between osteomalacic and normal women and there were no differences in skin pigmentation or mode of dress between normal and osteomalacic women. Asian women 'cover up' more than their white counterparts and sunbathing is rare. The cases and controls were thus comparable in all major respects except that of diet (and of religion related to dietary practices). The role of age in the nutrient model is unclear; its relatively weak significance suggests that it is of minor importance.

Glasgow Asian women consume diets which range from strict lactovegetarianism to highly adapted 'western' diets containing only occasional Asian foods (in second generation younger women). Careful enquiry was made regarding possible changes in dietary pattern after the diagnosis and treatment of osteomalacia. One woman had changed from a vegetarian to a non-vegetarian Asian diet; her pre-treatment diet was utilized as a recall record of dietary pattern only. None of the other women had altered their dietary intake; of the four women whose time from diagnosis to survey exceeded five years, three Sikh and Hindu women were life-long lactovegetarians and the remaining woman consumed a traditional Muslim diet which was not altered by the treatment of her osteomalacia.

The occurrence of privational osteomalacia was significantly related to varying degrees of vegetarianism and to intakes of certain food classes and nutrients (meat, white fish, eggs, vegetables, fibre and vitamin D). The results reinforce the findings of our previous case-control study of Asian rickets [13], but the relative importance of the food classes associated with osteomalacic and rachitic risk differ. Rachitic risk associated with decreasing meat intake was distributed continuously; osteomalacic risk appeared only with absent meat and fish consumption (i.e. lactovegetarianism). Rachitic but not osteomalacic risk was positively associated with chapatti consumption; discrimination provided by fibre consumption was correspondingly less in the osteomalacic compared with the rachitic nutrient model. The more stringent dietary requirements for the reduction of osteomalacic bone disease may reflect the absence of growth-related demand for vitamin D.

The role of eggs in reducing osteomalacic risk (Table 4) may be attributed to their known vitamin D content. Current analyses suggest that meat, meat fat and the small quantities of white fish consumed by non-vegetarian Asian women and children contain only 'traces' of vitamin D [17] (oily fish, liver and cheese are rarely consumed). These estimates are based on a relatively insensitive rachitic rat bioassay [16].

In the course of his classical experiments on rachitic puppies [23, 24] which led to the discovery of the 'accessory factor' (later identified by McCollum [25] as vitamin D), Mellanby observed that lean meat and suet (meat fat) were strongly anti-rachitic. Recent estimates of the vitamin D storage capacity of rat and human adipose tissue using high pressure liquid chromatography indicate that concentrations of the order of 100 ng vitamin D_3/g may be attained in both species [26]. If such concentrations are present in meat fat, additional unmeasured vitamin D of the order of 1 μg (40 IU) may have been present in the relatively small quantity of meat consumed daily by our normal group of Asian women. Higher concentrations of vitamin D may be present in some meat samples due to over-fortification of animal feeding stuffs [27]. As an alternative hypothesis, Dollery *et al.* [28] observed that meat-eating subjects have a higher drug-oxidation rate than vegetarian subjects and suggested that reduced 25-OHD_3 formation may result from lack of stimulation of the hepatic mixed-function oxidase system by the traditional vegetarian diet.

The contribution of dietary fibre to osteomalacic risk was less than that of strict lactovegetarianism. Diet-induced hypocalcaemia in the rat increases the clearance and inactivation of serum 25-OHD [29]; this may be accomplished by high fibre diets in man [30]. Interruption of the enterohepatic circulation of vitamin D by dietary fibre seems less likely to be of biological significance than when first suggested [31, 32].

The occurrence of privational rickets and osteomalacia in the Glasgow Asian community has permitted a reappraisal of the epidemiology of these diseases. The risk factor models presented previously [13] and in the present communication suggest that when ultraviolet radiation is limited by high latitude (Glasgow is 55°52′ N), urbanization, social custom and skin pigmentation, the occurrence of 'cases' of privational rickets and osteomalacia is determined by dietary factors. In these circumstances animal foods (predominantly meat, fish and eggs) appear to increase and fibre-containing foods (predominantly high extraction/wholemeal cereal) to decrease the supply or metabolism of a limited quantity of endogenously synthesized vitamin D. Unless dietary calcium intakes are very low [33], dietary factors do not appear to induce privational rickets or osteomalacia in the vitamin D replete state. The latter may result from the higher levels of ultraviolet radiation exposure associated with lower, sunnier latitudes or from the replacement of deficient ultraviolet radiation by adequate dietary vitamin D supplementation.

ACKNOWLEDGEMENTS

We are indebted to the Asian women who participated in the surveys of diet and outdoor exposure and to Mrs. Margaret Sloan who organized the surveys. We are most grateful to Ruby Bedi, Tara Bashir, Heema Mehta, Razia Akhtar and Munju Mohindra for valuable interpreting services which were funded by the Manpower Services Commission. The study was made possible by grants from the Biomedical Research Committee of the Scottish Home & Health Department and from the Research Support Group, Greater Glasgow Health Board.

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APPENDIX A: THE BIOCHEMICAL DIAGNOSIS OF OSTEOMALACIA

Comparison of serum calcium, phosphate and serum alkaline phosphatase in patients with histologically proven osteomalacia and controls showed serum alkaline phosphatase to be the best single routine biochemical screening test for osteomalacia [34]. Serum alkaline phosphatase was also the best predictor of radiographic evidence of rickets in Asian schoolchildren [15]. Serum 25-OHD was a poor predictor of radiographic evidence of rickets in this study [15].

None of the osteomalacic patients in the present study had renal or hepatic disease and Paget's disease is uncommon in women aged less than 60 years. For these reasons, we regard serum alkaline phosphatase as the best single marker of osteomalacic bone disease in the British Asian population. Serum 25-OHD is a good indicator of the vitamin D status of population samples but a poor predictor of rachitic or osteomalacic bone disease in individual patients.

APPENDIX B: STATISTICAL METHODS

MULTIVARIATE ANALYSIS

Examination of univariate differences between osteomalacic and normal women does not indicate the extent, if any, of the independence of 'overlap' of their contributions (in statistical terms) to osteomalacic risk. To resolve this problem, multivariate analysis is required. In this study, stepwise logistic regression analysis identified the independent contributions of significant variables to explanatory statistical models of osteomalacic risk [19–21]. This technique has the particular advantage over multivariate discriminant analysis that both dichotomous variables (e.g. vegetarianism) and non-normally distributed continuous variables (e.g. age and many food class and nutrient variables) can be considered in the analysis. Daylight outdoor exposure, and food class and nutrient models were considered in succession. In principle, the method involves the computation of a χ^2 statistic as each variable is entered in stepwise fashion in the statistical model. Variables producing the most significant improvement in goodness of fit as measured by the log likelihood statistic are identified. Where variables are highly correlated, the variable providing the largest improvement in goodness of fit is retained. The final model contains the best combination of variables or risk factors which are important in the prediction of rachitic risk and measures their independent contributions to that risk.

The relative importance of the significant variables in each logistic model is indicated by the significance of their standardized regression coefficients (Tables 1 and 5). The significance of improvements in goodness of fit between nutrient and food class models derived from changes in the log likelihood statistic is also shown (Table 5).

DISCRIMINATING POWER OF LOGISTIC MODELS

A statistical probability of osteomalacia was computed from the structure of the variables in each logistic model for each osteomalacic and normal woman in the sample. This is equivalent to allocating a risk score for osteomalacia to each woman which measured the osteomalacic potential of her model variables. The extent to which these probabilities distinguish between osteomalacic and normal groups measures the discriminating power of the model.

In the study this discrimination is expressed as a single relative risk for each model.

Individual probabilities above and below the common median for each osteomalacic and normal group were designated as 'high' or 'low' respectively. The relative risk of osteomalacia associated with 'high' probabilities in each logistic model was derived from the proportion of 'high' probabilities in the osteomalacic group compared with the normal group in the conventional way. This is shown as the model relative risk (Tables 1 and 5).

Further information on the statistical methods used is available from the authors.