# Lactose intolerance and bone mass in postmenopausal Italian women

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**Previous studies on the role of lactose malabsorption in the pathogenesis of postmenopausal osteoporosis have yielded conflicting results and further information is needed. To date, all studies have been carried out on populations with a low prevalence of lactose malabsorption and the lactose intestinal absorptive capacity was tested using a non-physiological dose of lactose. In fifty-eight Italian postmenopausal women (mean age 57 (SD 7) years), bone mineral density (BMD) at lumbar spine, $H_2$ breath response after ingestion of 20 g lactose, intensity of symptoms of intolerance after a lactose load and daily Ca intake were evaluated. No differences were found between women with or without a positive $H_2$ breath test with regard to BMD (−1·2 (SD 0·9) *v.* −0·9 (SD 0·8)) and Ca intake (509 (SD 266) *v.* 511 (SD 313) mg/d). On the contrary, both BMD and Ca intake were significantly lower in women with lactose malabsorption and symptoms of intolerance (−1·5 (SD 0·7) and 378 (SD 220) mg/d) than in those with malabsorption without symptoms (−0·9 (SD 0·9) and 624 (SD 254) mg/d). Moreover, in lactose malabsorbers Ca intake was correlated inversely with symptom score ($r_s$ −0·31, $P < 0·05$) and positively with BMD ($r_s$ 0·42, $P < 0·005$). Our results show that in Italian postmenopausal women Ca intake and BMD are not influenced directly by lactose malabsorption; the appearance of symptoms of intolerance seems to influence BMD unfavourably through a reduced Ca intake.**

**Calcium: $H_2$ breath test: Lactose: Osteoporosis: Postmenopausal women**

Osteoporosis is extremely common among postmenopausal women. Its aetiology is multifactorial (Dempster & Lindsay, 1993) and, although the reduction in plasma levels of oestrogens represents the main pathogenetic factor (Richelson *et al.* 1984), not all menopausal women develop osteoporosis (Riggs & Melton, 1990). This implies that other factors are involved, and amongst these the importance of dietary Ca intake has been emphasized (Dawson-Hughes *et al.* 1987; Andon *et al.* 1991).

Lactose malabsorption, caused by primary late-onset lactase (*EC* 3.2.1.23) deficiency, may lead to the onset of abdominal symptoms and consequently induce the avoidance of milk and milk products from the diet (Birge *et al.* 1967; Newcomer *et al.* 1978*a*). Since these foodstuffs provide about two-thirds of the dietary requirement of Ca (Birge *et al.* 1967; Newcomer *et al.* 1978*a*) lactose malabsorption has been suggested as a predisposing factor to osteoporosis (Birge *et al.* 1967; Newcomer *et al.* 1978*a*; Finkenstedt *et al.* 1986; Horowitz *et al.* 1987; Vigorita *et al.* 1987). However, other studies have failed to show a clear relationship between these two conditions (Alhava *et al.* 1987; Jodry *et al.* 1987; Härmä & Alhava, 1988; Slemenda *et al.* 1991). These discrepancies could depend on the different

methods used to evaluate lactose malabsorption and osteoporosis and the different criteria used to recruit the patients.

All these studies were carried out in populations with a low prevalence of lactose malabsorption (Scrimshaw & Murray, 1988) and their results may not be applicable, therefore, to populations with a higher prevalence of lactose malabsorption, such as the Italian population (Burgio *et al.* 1984; Bozzani *et al.* 1986). Moreover, since all studies were performed with a non-physiological dose of lactose (50 g or more; Bayless, 1981; Rosado & Solomons, 1983; Smith *et al.* 1985), their findings need to be confirmed by testing the intestinal absorptive capacity with a more physiological dose of this carbohydrate.

## PATIENTS AND METHODS

### *Patients*

Eighty-three consecutive postmenopausal women (mean age 57 (SD 7) years) suspected of having osteoporosis because of back pain, all Caucasian from the Bologna area, were recruited. Twenty-five patients were excluded from the study for the following reasons: ovariectomy (*n* 6), oestrogen replacement therapy (*n* 6), Ca supplementation (*n* 5), gastrointestinal diseases (*n* 4), recent treatment with antibiotics or drugs which could modify the intestinal flora (*n* 4). The fifty-eight women included in the study were free of diseases known to influence Ca and bone metabolism.

Informed consent was obtained from all the subjects taking part in the study.

### *Bone mass measurement*

Bone mineral density (BMD) was measured in each patient at the lumbar spine region (L2-L4) by dual-photon absorptiometry (Norland DBD 2600, Norland Co., WI, USA), and BMD values were expressed as Z-scores, which indicate the deviation from the average expected sex- and age-matched BMD value in SD units, and normalize the raw data for sex- and age-dependent variation in BMD (Seeman *et al.* 1982). Since the relative risk of fracture in women increases by a factor of about 2 for each SD decrease in BMD (Johnston *et al.* 1989), diagnosis of osteoporosis was made in those women whose BMD was 1 SD below the mean values for healthy female control subjects.

### *Diet history*

All patients were asked about their awareness of a relationship between the onset of abdominal symptoms, such as meteorism, flatulence, abdominal pain, diarrhoea and the intake of milk, ice cream, cheese and yoghurt.

Daily Ca intake was evaluated in each patient by completing a dietary diary for three consecutive days (two weekdays and one weekend day) listing all the food eaten and the respective quantities, evaluated on the basis of usual portion sizes (Hankin, 1989). The diaries were then checked by one of the authors who was unaware of the clinical details of the patients and analysed on the basis of food-composition tables provided by the Italian National Institute of Nutrition (Istituto Italiano della Nutrizione, 1983).

### *Hydrogen breath testing*

Alveolar breath samples were collected before and every 30 min for 4 h after the ingestion of a 100 ml solution containing 20 g lactose (Corazza *et al.* 1990). To minimize basal $H_2$ excretion, all the subjects taking part in the study ate a meal of rice and meat the evening before the test (Kotler *et al.* 1982) and then fasted for the next 12 h. End-alveolar breath samples were collected using a commercial device (AlveoSampler; Quintron Instruments, Milwaukee, WI, USA). Measurement of $H_2$ concentration was performed using a

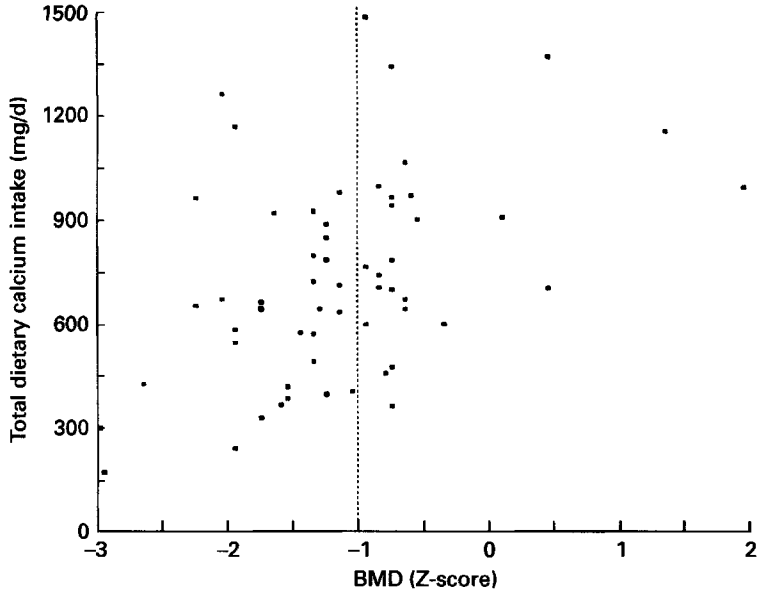


Fig. 1. Correlation between total dietary calcium intake and bone mineral density (BMD) in fifty-eight Italian postmenopausal women. (---), Separates women with osteoporosis (left) from those without osteoporosis (right). For details of subjects and procedures, see pp. 480–481. $r_s$ 0·40, $P < 0·002$.

Microlyzer 12 gas–liquid chromatograph (Quintron Instruments). The chromatograph was calibrated with a standard gas mixture containing 102 $\mu$l $H_2$/l. An increase in breath $H_2$ concentration $\geqslant$ 20 ppm above the baseline value was considered indicative of lactose malabsorption (Kotler *et al.* 1982; Corazza *et al.* 1990). During the 8 h after lactose ingestion, patients were asked to record the appearance of symptoms of intolerance (meteorism, flatulence, abdominal pain, diarrhoea) in a personal diary, indicating the intensity of each symptom with the following scores: absent 0, mild 1, moderate 2, severe 3; diarrhoea was always scored as 3 (Rosado *et al.* 1984). Each diary was examined blindly by a physician who, on the basis of the partial scores, calculated a cumulative index.

### *Statistical analysis*

Data were expressed as means and standard deviations and statistical comparisons were performed using Spearman's rank correlation coefficient, Mann Whitney U test, and Fisher's exact probability test.

## RESULTS

Fig. 1 shows total dietary Ca intake and BMD for the fifty-eight postmenopausal women studied. A significant ($P < 0·002$) positive correlation between these two variables is evident. Thirty-three of the fifty-eight women (57%) studied had a BMD 1 SD below the mean values for healthy female control subjects and, therefore, were considered to have osteoporosis. The mean age of women with osteoporosis (58 (SD 7) years) was not significantly different from that of the women without osteoporosis (57 (SD 7) years).

The prevalence of women aware of being intolerant to milk and milk products in the osteoporotic group (58%) was not significantly different from that of the non-osteoporotic group (40%). Fig. 2 shows that no significant differences were found, with respect to BMD and Ca intake from milk and milk products, between women unaware of being intolerant

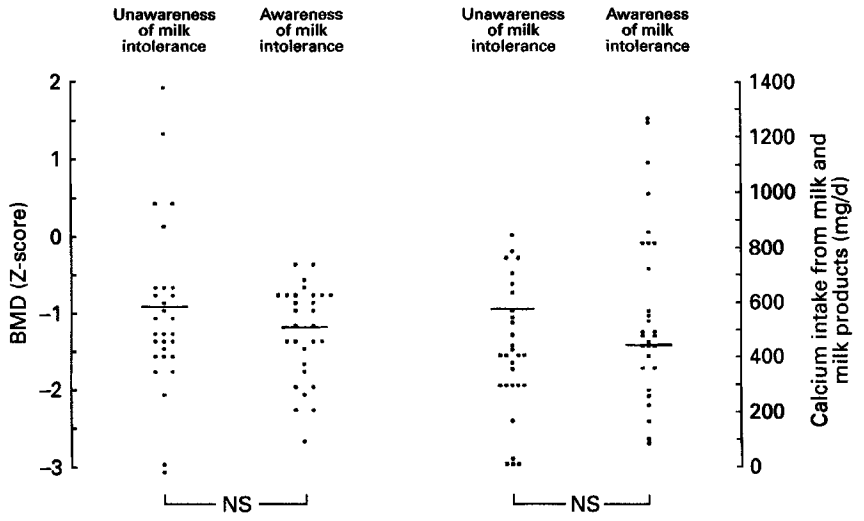


Fig. 2. Bone mineral density (BMD) and calcium intake from milk and milk products in fifty-eight Italian postmenopausal women who were unaware and aware of being intolerant to milk and milk products. For details of subjects and procedures, see pp. 480–481. NS, not significant.

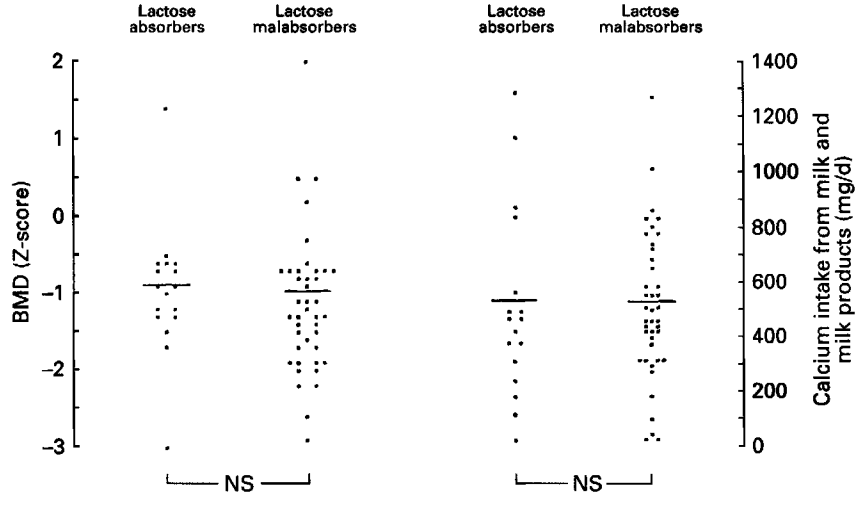


Fig. 3. Bone mineral density (BMD) and calcium intake from milk and milk products in fifty-eight Italian post menopausal women who were lactose absorbers and malabsorbers. For details of subjects and procedures, see pp. 480–481. NS, not significant.

to milk and milk products (−1·2 (SD 0·6) and 579 (SD 319) mg/d respectively) and women aware of being intolerant (−0·9 (SD 1·1) and 441 (SD 238) mg/d respectively).

Measurement of $H_2$ response after the ingestion of 20 g lactose showed that 76% of the osteoporotic women and 64% of the non-osteoporotic women were lactose malabsorbers; there was no significant difference between these two values. Fig. 3 shows that there were no differences with respect to BMD and Ca intake from milk and milk products between lactose absorbers (−0·9 (SD 0·8) and 511 (SD 313) mg/d respectively) and malabsorbers (−1·2 (SD 0·9) and 509 (SD 266) mg/d respectively).

The prevalence of lactose malabsorbers with symptoms of intolerance in the 8 h

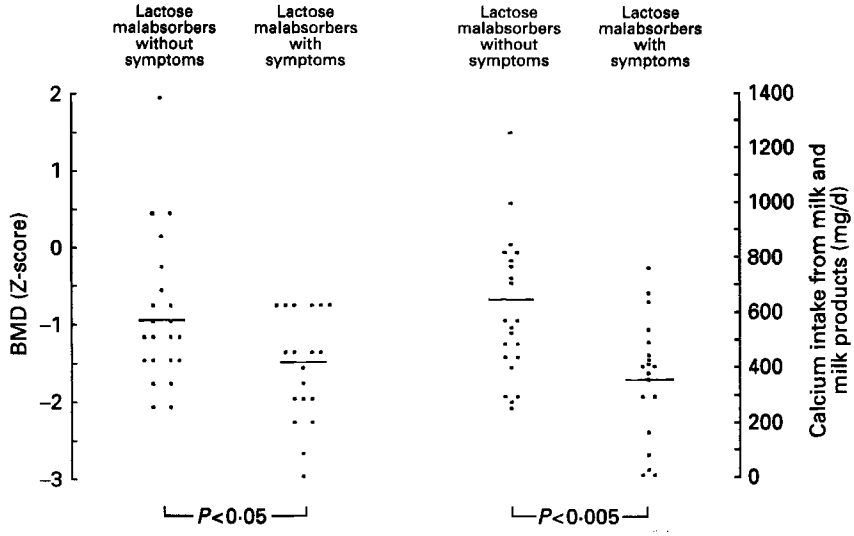


Fig. 4. Bone mineral density (BMD) and calcium intake from milk and milk products in fifty-eight Italian postmenopausal women who were lactose malabsorbers without and with symptoms of intolerance in the 8 h after lactose ingestion. For details of subjects and procedures, see pp. 480–481.

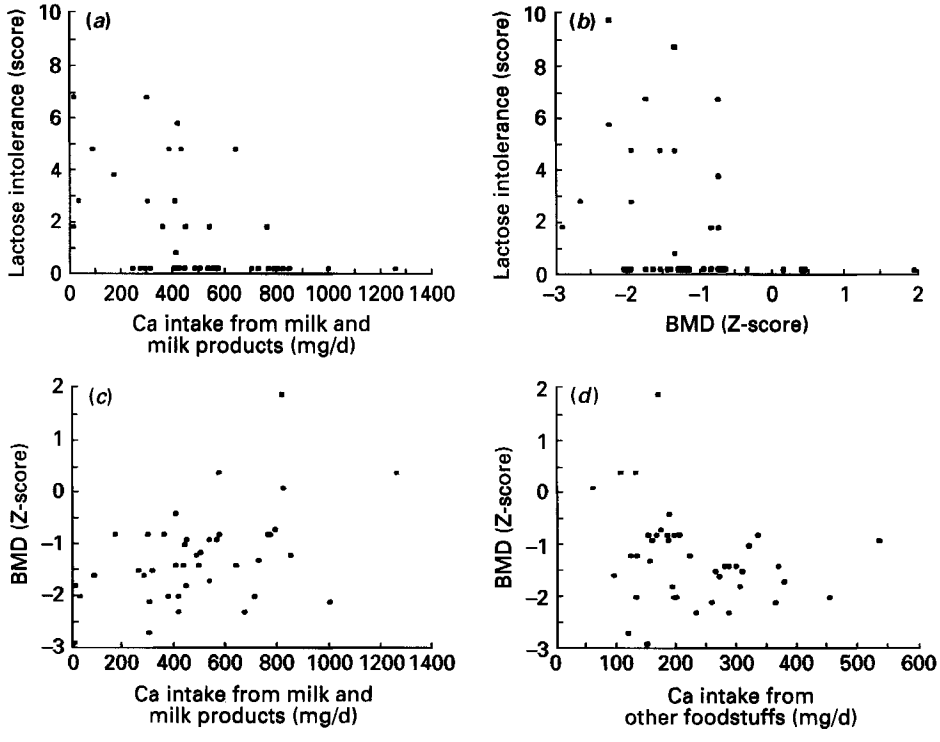


Fig. 5. Correlations between symptom score of intolerance and (a) calcium intake from milk and milk products ($r_s$ −0·31, $P < 0·05$) and (b) bone mineral density (BMD; $r_s$ −0·16, not significant), and between BMD and Ca intake from (c) milk and milk products $r_s$ 0·42, $P < 0·005$ and (d) from other foodstuffs ($r_s$ 0·23, not significant) in Italian postmenopausal women who were lactose malabsorbers. For details of subjects and procedures, see pp. 480–481.

following carbohydrate ingestion did not differ significantly between osteoporotic (39%) and non-osteoporotic women (24%). Fig. 4 shows that in lactose malabsorbers with symptoms of intolerance both BMD and Ca intake from milk and milk products (−1·5 (SD 0·7) and 378 (SD 220) mg/d respectively) were significantly lower ($P < 0·05$ and $P < 0·005$ respectively) than those in malabsorbers without symptoms (−0·9 (SD 0·9) and 624 (SD 254) mg/d respectively).

Fig. 5 shows that in women with a positive $H_2$ breath test for lactose malabsorption the symptom score of intolerance correlated negatively with Ca intake from milk and milk products ($P < 0·05$) but did not correlate with BMD. BMD, in turn, was correlated positively with Ca intake from milk and milk products ($P < 0·005$) but not with Ca intake from other foodstuffs.

## DISCUSSION

It is well known that in postmenopausal women an adequate Ca intake causes a positive shift in Ca balance (Heaney *et al.* 1978) and suppresses biochemical indices of bone resorption (Horowitz *et al.* 1984). Moreover, inadequate Ca intake might be associated with low BMD, although this relationship has been confirmed by some authors (Dawson-Hughes *et al.* 1987; Andon *et al.* 1991) but not by others (Riggs *et al.* 1987; Angus *et al.* 1988). The reasons for these discrepancies could depend on the different methods used to evaluate the dietary intake of Ca. We used a 3 d diet record (Hankin, 1989), with similar precision to that of a 7 d diet record (Payette & Gray-Donald, 1991), which is considered the 'gold standard' in evaluating Ca intake (Cummings *et al.* 1987). In a vast group of menopausal women this method confirmed that a highly significant correlation exists between total Ca intake and BMD.

Since lactose malabsorption might cause a marked reduction in milk and milk-product consumption (Bayless, 1981), which together provide most of the Ca in the diet (Birge *et al.* 1967; Newcomer *et al.* 1978*a*), the relationship between lactose malabsorption and postmenopausal osteoporosis has been extensively studied (Birge *et al.* 1967; Alhava *et al.* 1977; Newcomer *et al.* 1978*a*; Finkenstedt *et al.* 1986; Horowitz *et al.* 1987; Jodry *et al.* 1987; Vigorita *et al.* 1987; Härmä & Alhava, 1988; Slemenda *et al.* 1991). In some of these studies (Newcomer *et al.* 1978*a*; Horowitz *et al.* 1987; Vigorita *et al.* 1987) this relationship was confirmed by the finding of a higher prevalence of lactose malabsorbers in osteoporotic than in non-osteoporotic women. In all previous studies prevalence of lactose malabsorbers range from 26% (Newcomer *et al.* 1978*a*) to 65% (Vigorita *et al.* 1987) in osteoporotic women and from 0% (Birge *et al.* 1967) to 20% (Härmä & Alhava, 1988) in non-osteoporotic women. Compared with these values our prevalence value was much higher both in osteoporotic (76%) and non-osteoporotic women (64%). This result confirms previous findings of a high prevalence of primary late-onset lactase deficiency in the Italian population (Burgio *et al.* 1984; Bozzani *et al.* 1986), and could explain the absence of a statistically significant difference between osteoporotic and non-osteoporotic women. In some of the previous studies (Newcomer *et al.* 1978*a*; Horowitz *et al.* 1987; Vigorita *et al.* 1987) the lower Ca intake found in lactose malabsorbers than in absorbers was attributed to the avoidance of milk and milk products due to lactose malabsorption. Unlike these studies (Newcomer *et al.* 1978*a*; Horowitz *et al.* 1987; Vigorita *et al.* 1987), but in agreement with others (Jodry *et al.* 1987; Härmä & Alhava, 1987; Slemenda *et al.* 1991), our results show that lactose malabsorption alone is not sufficient to induce a spontaneous avoidance of milk and milk products and, therefore, does not affect bone mass. It is clear that the true culprit for the avoidance of lactose-related foods from the diet is not malabsorption itself but intolerance due to malabsorption of this carbohydrate. Lactose malabsorption, in fact, does not always lead to intolerance (Newcomer, 1981; Rosado *et*

*al.* 1987; Johnson *et al.* 1993). There are various explanations for this discrepancy: the variability in the individual's perception of symptoms (Jones *et al.* 1976; Gudmand-Hoyer *et al.* 1977), the ability of the colon to absorb short-chain fatty acids derived from the bacterial fermentation of malabsorbed lactose (Bond *et al.* 1980), $H_2$ consumption by colonic methanogenic bacteria (Strocchi & Levitt, 1992) and/or reduced colonic pH (Perman *et al.* 1981) which could lead to a significant decrease in volume of colonic gas, and the possible induction of colonic bacterial lactase by lactose malabsorption (Saavedra & Perman, 1989).

Although some authors (Härmä & Alhava, 1988; Slemenda *et al.* 1991) had already reported the importance of relating osteoporosis to lactose intolerance, this relationship was never studied. It has been demonstrated that patients' awareness of a previous milk intolerance cannot predict either lactose absorptive status or the occurrence of symptoms after lactose load (Di Palma & Narvaez, 1988). In agreement with these results, we show that this awareness does not significantly affect either Ca intake from milk and milk products or BMD, confirming the unreliability of previous convictions of the patients in relation to their food–symptom relationship (Ferguson, 1990).

Since the appearance of symptoms of intolerance is related to the dose of lactose ingested (Newcomer *et al.* 1978*b*), we evaluated malabsorption and the occurrence of abdominal symptoms after administration of a watery solution containing 20 and not 50 g lactose. It is conceivable that malabsorption of 50 g lactose doses not permit compensation, by the above-mentioned mechanisms, sufficient to prevent the onset of intolerance symptoms. It can be presumed, therefore, that in those studies in which malabsorption alone was significantly associated with osteoporosis (Birge *et al.* 1967; Newcomer *et al.* 1978*a*; Finkenstedt *et al.* 1986; Horowitz *et al.* 1987; Vigorita *et al.* 1987), lactose malabsorption was more frequently accompanied by intolerance, specifically because of the doses of carbohydrate used. Their main pitfall, however, is the fact that their experimental conditions were far removed from what occurs in real life. In other words, we are not sure that these subjects would have really experienced symptoms of intolerance after a more physiological lactose dose and if, precisely for this reason, they did in fact tend to avoid lactose-containing products.

The low Ca intake found in women with a low BMD could be attributed to many other factors, and not to lactose intolerance only. However, we have shown that in lactose malabsorbers with symptoms, Ca intake from milk and milk products correlates inversely with the degree of intolerance and positively with BMD. These results, therefore, suggest that lactose malabsorption and intolerance do have a role in the pathogenesis of postmenopausal osteoporosis. Otherwise, it was expected that in such a typically multifactorial disease the extent of bone loss would not correlate with the degree of lactose intolerance: lactose intolerance would represent a cofactor and not 'the aetiological factor' of postmenopausal osteoporosis.

In the past the association between lactase deficiency and osteoporosis had been questioned because American blacks, in whom lactose malabsorption is common (Cuatrecasas *et al.* 1965), had a lower incidence of osteoporosis than whites (Cohn *et al.* 1977). This discrepancy could be explained not only by the differences in the initial bone mass (Cohn *et al.* 1977), or in other factors such as the resistance to the bone resorptive effects of parathyroid hormone and 1,25-dihydroxycholecaliferol (Bell *et al.* 1985) or the rate of bone remodelling (Weinstein & Bell, 1988) or, perhaps, physical activity, but also by a greater lactose tolerance of hypolactasic blacks (Cuatrecasas *et al.* 1965), and this is totally in accordance with our findings.

In conclusion, the present study shows that when lactose malabsorption is accompanied by symptoms of intolerance it represents a risk factor for postmenopausal osteoporosis.

From a practical point of view, when lactose malabsorption causes the onset of symptoms of intolerance, Ca intake must be supplemented either pharmacologically or with the intake of less-harmful milk products, such as yoghurt (Kolars *et al.* 1984), and/or with the addition to milk of exogenous lactases (Rosado *et al.* 1984; Corazza *et al.* 1992).

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