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Dietary calcium intake in a cohort of individuals evaluated for low bone mineral density: a multicentre Italian study

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Abstract: A low calcium intake is associated with an increased fracture risk. We assessed the dietary calcium intake in a cohort of Italian individuals evaluated for low bone mineral density (BMD).

A 7-day food-frequency questionnaire was administered to 1793 individuals consecutively referred at a Centre of the Italian Society for Osteoporosis, Mineral Metabolism and Skeletal Diseases for low BMD.

In 30.3% (544/1793) and 20.9% (374/1793) of subjects the calcium intake was inadequate (<700 mg/day) and adequate (>1200 mg/day), respectively. Patients with calcium intake <700 mg/day showed a higher prevalence of diabetes mellitus, idiopathic hypercalciuria and food allergy/intolerance (8.1%, 5.1%, 7.2%, respectively) than patients with calcium intake >700 mg/day (5.3%, 3.0%, 4.1%, respectively, p<0.04 for all comparisons), also after adjusting for age, gender and BMI. In 30.3% of fractured subjects the calcium intake was <700 mg/day.

In Italy, a low calcium intake is highly prevalent in individuals at risk for low BMD. Importantly, an inadequate calcium intake is highly prevalent even in patients with history of fragility fractures. Only about a fifth of patients at risk for low BMD reported an adequate calcium intake.

Keywords: dietary calcium intake, osteoporosis, fractures.

1. Introduction

Calcium intake is a well-known factor influencing the achievement of an adequate peak bone mass [1] and, subsequently, the maintenance of bone mass later in life. Indeed, in the presence of inadequate calcium intake a negative calcium balance can develop, frequently leading to metabolic alterations, such as secondary hyperparathyroidism, increased bone turnover and, eventually, increased fracture risk [2].

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The calcium intake largely differs among countries according to age, sex, ethnics, cultures and socioeconomic status [3] and the national recommendations on calcium intake vary worldwide. In the adult population, the Recommended Dietary Allowance (RDA) of calcium is between 1000 and 1300 mg/day according to the US National Institutes of Health [4] and between 700 and 1000 mg/day according to the UK National Osteoporosis Society [5]. Both the Italian Society for Osteoporosis, Mineral Metabolism and Skeletal Diseases (SIOMMMS) and the Italian Society of Human Nutrition recommends a calcium intake above 1200 mg/day in postmenopausal women not on hormone replacement therapy and in men older than 60-65 years of age [6,7].

The adequate daily calcium requirement is influenced by several other factors, such as age, comorbidities, and vitamin D levels, the latter being fundamental for a proper intestinal calcium absorption [8]. Finally, the use of calcium supplements is still a matter of debate [9].

Despite these differences and controversies, a recent systematic review found that dietary calcium intakes fall below the recommended levels in many areas of the world [10], including Italy [11]. This is a matter of concern for bone health, especially if already threatened as in a population at risk for low bone mineral density (BMD), in whom an adequate calcium intake represents one of the first non-pharmacological interventions [6].

This is a multicenter national observational study which was aimed to assess dietary calcium intake in a cohort of Italian individuals referred for evaluation of possible low BMD.

2. Materials and Methods

For this cross-sectional observational study, between November 2015 and June 2016, 1793 consecutive subjects referred in one SIOMMMS referral Centre for Osteoporosis and Metabolic Bone Diseases by their General Practitioners, that agreed in participating in this study, were recruited. We excluded subjects reporting the intake of calcium supplements and/or bone active drugs because these treatments inevitably imply some kind of previous medical counselling about osteoporosis and the related importance of an adequate calcium intake and then estimated dietary calcium intake would have not reflected their usual dietary habits.

In all individuals height and weight were measured and body mass index (BMI) was calculated.

The dietary calcium intake, expressed as mg/day, was assessed using a specific questionnaire. In particular, usual calcium intake coming from some selected calcium-rich foods was estimated by a 7-day food frequency questionnaire derived for the International Osteoporosis Foundation (IOF) Calcium Calculator [12] after simplification according to the ordinary Italian alimentary habits. Portion sizes were quantified by means of household measures (slices, cups, glasses).

The history of clinical fragility fractures (i.e. caused by low energy trauma, such as falling from a standing height or less) was investigated at consultation. Hip and vertebral fractures (major fragility fractures) were considered apart from the others (e.g. wrist, ribs and proximal humerus). In all patients, the presence of previous fragility fractures was ascertained by self-report and no additional validation of this information was conducted.

Information about bone mineral density (BMD), measured by performed Dual-energy X-ray Absorptiometry (DXA) using reliable densitometers at lumbar spine, total femur and femoral neck and expressed as standard deviation units in relation to the young (T-score) and age-matched (Z-score) reference healthy population, were collected. DXA scans had been carried out according to the Italian Ministry of Health recommendations [13]. Diagnosis of low BMD was made in the presence of T-score at any site ≤ -2.5 for postmenopausal women and men older than 50 [14] or in the presence of Z-score at any site < -2.0 for premenopausal women and men younger than 50 [15].

Demographic and clinical data were collected anonymously regarding the following comorbidities: diabetes mellitus, endogenous or iatrogenic hypercortisolism, rheumatoid arthritis (AR), idiopathic hypercalciuria, primary hyperparathyroidism (PHPT), nephrolithiasis, adverse reaction to food (including food allergy or intolerance) [16], inflammatory bowel diseases (IBD) and chronic obstructive pulmonary disease (COPD). Clinical data were confirmed by the review of medical reports. No blood or additional instrumental tests were performed.

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The protocol was approved (approval 1511/2015) by the Ethical Committee of each SIOMMMS centre and all subjects gave their written informed consent before participating in the study.

Statistical Analysis

Statistical analysis was performed by SPSS version 21.0 statistical package (SPSS Inc, Chicago, IL). In a previous study reporting the daily calcium intake in subjects with and without vertebral fracture [17] the response within each subject group was normally distributed (standard deviation 300) and the difference in daily calcium intake between fractured and not fractured patients was 60 mg/day. On the basis of these data we needed to include 329 fractured subjects and 1316 not fractured (power 90%, type I error 5%) for the study to be adequately powered.

For each continuous variables the normality of distribution was tested by the Kolmogorov–Smirnov test). Data were expressed as median (range) for non-normally distributed continuous variables or as mean±standard deviation for normally distributed variables, and as absolute and relative frequencies for categorical variables. Continuous variables were compared using one-way Student t test or Mann–Whitney U test, as appropriate. Categorical variables were compared using $\chi 2$ or Fisher's Exact test, as appropriate.

We arbitrarily decided to consider a daily calcium intake of 700 mg/day as the threshold below which the dietary calcium intake is clearly inadequate and a supplementation is generally considered mandatory [18]. Even if some enrolled individuals were men or premenopausal women, we decided to use the threshold of 1200 mg/day for defining an adequate calcium intake as suggested by SIOMMMS [6] in postmenopausal women not on hormone replacement therapy and in men older than 65 years of age. This decision has been taken for the sake of consistency in the data analysis since men and premenopausal females (n=119 and 88, respectively) represented a minority of the entire cohort and had been however referred for low BMD and/or fragility fracture.

The multivariate logistic regression analysis was performed in order to assess the association between inadequate or adequate calcium intake (categorical dependent variable) and relevant clinical characteristics (categorical independent variables), after adjusting for possible confounders. P-values <0.05 were considered significant.

3. Results

The clinical characteristics of the whole cohort and the comparisons among individuals grouped according tertiles of dietary calcium intake are reported in Table 1.

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Table 1	All subjects (n=1793)	I tertile (n=598)	II tertile (n=598)	III tertile (n=597)
Daily calcium intake (mg/day)	874.9	<723	723-1043	>1043
Sex (females)	1674 (93.4)	567 (94.8)	556 (93.0)	551 (92.3)
Premenopausal females	88 (5.3)	41 (7.2)˜	28 (5.0)	19 (3.4)
Age (years)	65.0 (25-97)	64.5 (25-97)˜	65.0 (28-90) ˜	66.0 (27-94)
BMI (kg/m²)	24.6 (14.2-48.6)	25.1 (14.3-48.6)	24.2 (14.2-43.9)	24.3 (15.1-44.9)
Low BMD	778 (43.4)	253 (42.3)˜	242 (40.5)˜	283 (47.3)
Prevalence of calcium intake <700 mg/day	544 (30.3)	544 (100)	0 (0.0)	0 (0.0)
Prevalence of calcium intake >1200 mg/day	374 (20.9)	0 (0.0)	0 (0.0)	374 (100)
Major fragility fractures	368 (20.5)	119 (19.9)˜	99 (16.6)*	150 (25.1)
Other fragility fractures	334 (18.6)	102 (17.1)	119 (19.9)	113 (18.9)
Low BMD and/or major fragility fractures	901 (503)	297 (49.7)˜	279 (46.7)*	325 (54.4)
Diabetes Mellitus	110 (6.1)	47 (7.9)	32 (5.4)	31 (5.2)
Hypercortisolism (endogenous or exogenous)	137 (7.6)	44 (7.3)	48 (8.0)	45 (7.5)
RA	269 (15.0)	87 (14.5)	93 (15.6)	89 (14.9)
Idiopathic hypercalciuria	65 (3.6)	31 (5.2)˜	18 (3.0)	16 (2.7)
PHPT	30 (1.7)	7 (1.2)	11 (1.8)	12 (2.0)
Nephrolitiasis	132 (7.4)	47 (7.9)	49 (8.2)	36 (6.0)
Adverse reaction to food	90 (5.0)	41 (6.9) ♀	25 (4.2)	24 (4.0)
IBD	65 (3.6)	27 (4.5)	16 (2.7)	22 (3.7)
COPD	71 (4.0)	22 (3.7)	24 (4.0)	25 (4.2)

Data are expressed as median values (range) or absolute number (percentage).; *p<0.005 vs tertile III; ˜p<0.05 vs tertile III; ♀p<0.05 vs tertile II. BMI: body mass index. RA: rheumatoid arthritis. PHPT: primary hyperparathyroidism. IBD: inflammatory bowel disease. COPD: chronic obstructive pulmonary disease. Low BMD: T-score at any site ≤−2.5 for postmenopausal women and men older than 50 or in the presence of Z-score at any site <−2.0 for premenopausal women and men <50 years.

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In the entire cohort the mean calcium intake was 874.9 mg/day, The 30.3% of the enrolled subjects showed a clearly inadequate calcium intake and in only 20.9% of subjects the calcium intake was adequate (Figure 1).

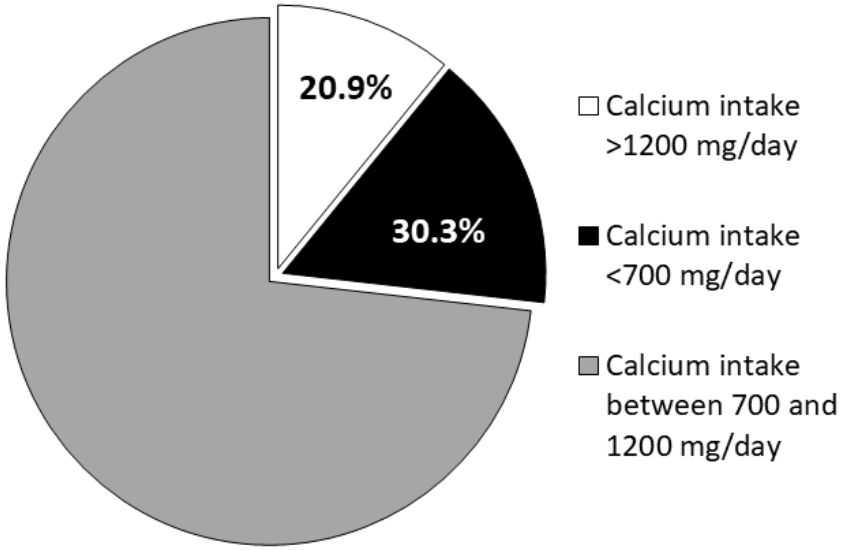

Figure 1. Prevalence of adequate, intermediate and definitely inadequate dietary dietary calcium intake (>1200 mg/day, 700-1200 mg/day and <700 mg/day, respectively), in 1793 individuals referred to outpatients clinics for osteoporosis of the Italian Society for Osteoporosis, Mineral Metabolism and Skeletal Diseases

Three hundred sixty-eight subjects reported a previous major fragility fracture, whereas the remaining 1425 did not, thus respecting the sample size calculation requested to guarantee the adequate power of the study. The enrolled subjects were mainly females and were comparable among the different tertiles as far as gender, BMI and prevalence of the main comorbidities. Subjects in the lowest and intermediate tertiles were younger and showed a lower prevalence of low BMD and major fragility fractures than those in the highest tertile. Moreover, the prevalence of premenopausal females, idiopathic hypercalciuria and adverse reaction to food was higher in subjects in the lowest tertile than in those in the highest tertile of daily dietary calcium intake.

The Table 2 illustrates the comparisons between subjects with calcium intake below and above 700 mg/day. The patients with calcium intake < 700 mg/day showed an increased prevalence of idiopathic hypercalciuria, diabetes mellitus and of a personal history of adverse reaction to food compared to patients with calcium intake >700 mg/day. Age, BMI, prevalence of low BMD, fragility fractures and other comorbidities (RA, endogenous or exogenous hypercortisolism, PHPT, nephrolithiasis, IBD and COPD) were comparable between the two groups.

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Table 2	Calcium intake <700 mg/day (n=544)	Calcium intake >700 mg/day (n=1249)	*p*
Sex (females)	517 (95)	1157 (92.6)	0.060
Age (years)	65 (25-97)	65 (27-94)	0.170
BMI (kg/m²)	25.0 (17.3-48.6)	24.4 (14.2-44.9)	0.190
Low BMD osteoporosis	236 (43.4)	542 (43.4)	0.990
Major fragility fractures	113 (20.8)	255 (20.4)	0.860
Other fragility fractures	92 (16.9)	242 (19.4)	0.220
Low BMD and/or major fragility fractures	274 (50.4)	627 (50.2)	0.948
Diabetes Mellitus	44 (8.1)	66 (5.3)	**0.020**
Hypercortisolism (endogenous or exogenous)	40 (7.4)	97 (7.7)	0.720
RA	76 (14.0)	193 (15.5)	0.420
Idiopathic hypercalciuria	28 (5.1)	37 (3.0)	**0.020**
PHPT	6 (1.1)	24 (1.9)	0.210
Nephrolithiasis	45 (8.3)	87 (7.0)	0.330
Adverse reaction to food	39 (7.2)	51 (4.1)	**0.006**
IBD	24 (4.4)	41 (3.3)	0.240
COPD	19 (3.5)	52 (4.2)	0.500

Data are expressed as median values (range) or absolute number (percentage). BMI: body mass index; RA: rheumatoid arthritis; PHPT: primary hyperparathyroidism; IBD: inflammatory bowel disease; COPD: chronic obstructive pulmonary disease. BMD: Bone mineral density. Low BMD: T-score at any site ≤−2.5 for postmenopausal women and men older than 50 or in the presence of Z-score at any site <−2.0 for premenopausal women and men younger than 50.

Interestingly, about one third of subjects with low BMD (236/778) and one third of subjects with fragility fractures (113/368) had a calcium intake below 700 mg/day (Figure 2).

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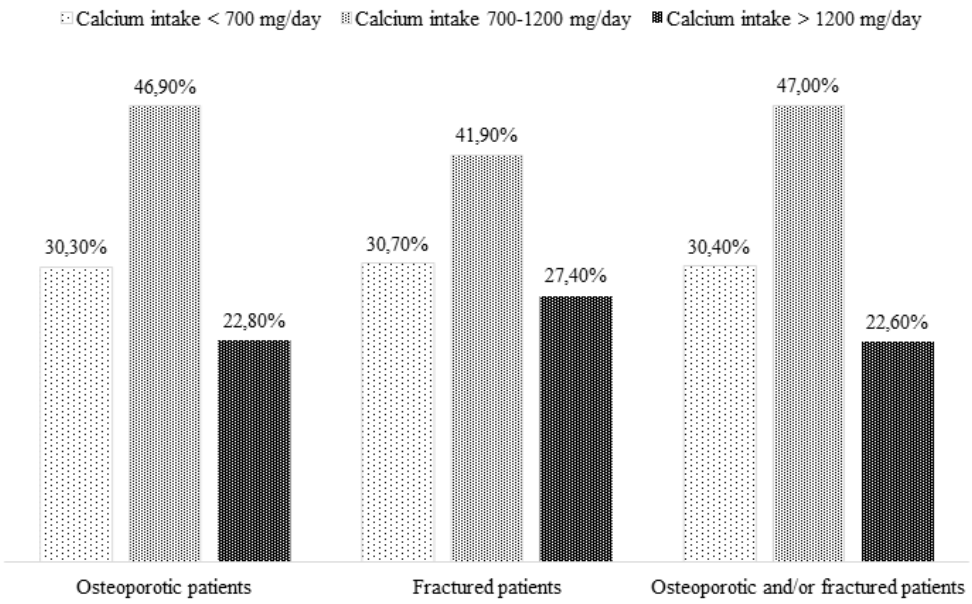

Figure 2: Prevalence of adequate, intermediate and definitely inadequate dietary dietary calcium intake (>1200 mg/day, 700-1200 mg/day and <700 mg/day, respectively), in 1793 individuals referred to outpatients clinics for osteoporosis of the Italian Society for Osteoporosis, Mineral Metabolism and Skeletal Diseases stratified on the basis of the presence of densitometric low bone mineral density (BMD) or fragility fractures or both

The Logistic regression analysis showed that a calcium intake below 700 mg/day was independently associated with the female gender (odds ratio [OR]: 1.58; 95% confidence interval [CI]: 1.01-2.47; p=0.047), a history of diabetes mellitus (OR: 1.61; 95%CI: 1.07-2.42; p=0.023), food intolerance/allergy (OR: 1.82; 95%CI: 1.18-2.82; p=0.007) or a previous diagnosis of idiopathic hypercalciuria (OR: 1.73; 95%CI: 1.04-2.89; p=0.035), regardless of age, BMI, the presence of low BMD and of major fragility fractures.

The comparison between individuals with calcium intake below or above 1200 mg/die is depicted in Table 3.

Table 3	**Calcium intake <1200 mg/day (n=1419)**	**Calcium intake >1200 mg/day (n=374)**	***p***
Sex (females)	1329 (93.7)	345 (92.2)	0.330
Age (years)	65 (25-97)	65 (37-94)	0.073
BMI (kg/m²)	24.7 (14.2-48.6)	24.2 (15.1-38.0)	0.063
Low BMD	601 (42.4)	177 (47.3)	0.080
Major fragility fractures	267 (18.8)	101 (27.0)	**0.001**
Other fragility fractures	268 (18.9)	66 (17.6)	0.580

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Low BMD and/or major fragility fractures	697 (49.1)	204 (54.5)	0.062
Diabetes Mellitus	94 (6.6)	16 (4.3)	0.090
Hypercortisolism (endogenous or exogenous)	105 (7.4)	32 (8.6)	0.520
RA	219 (15.4)	50 (13.4)	0.320
Idiopathic hypercalciuria	53 (3.7)	12 (3.2)	0.630
PHPT	19 (1.3)	11 (2.9)	**0.032**
Nephrolithiasis	114 (8.0)	18 (4.8)	**0.034**
Adverse reaction to food	78 (5.5)	12 (3.2)	0.070
IBD	56 (3.9%)	9 (2.4)	0.160
COPD	54 (3.8)	17 (4.5)	0.510

Data are expressed as median values (range) or absolute number (percentage).
BMI: body mass index. RA: rheumatoid arthritis. PHPT: primary hyperparathyroidism. IBD: inflammatory bowel disease. COPD: chronic obstructive pulmonary disease. BMD: bone mineral density. Low BMD: T-score at any site ≤−2.5 for postmenopausal women and men older than 50 or in the presence of Z-score at any site <−2.0 for premenopausal women and men younger than 50.

Patients with calcium intake above 1200 mg/day showed a lower prevalence of nephrolithiasis, but a higher prevalence of major fragility fractures and of history of previous PHPT compared to the patients with calcium intake below 1200 mg/day. Age, gender, BMI and prevalence of prior evidence of low BMD and other assessed comorbidities (RA, endogenous or exogenous hypercortisolism, IBD, food intolerance/allergy, COPD and diabetes) were comparable between the two groups. It is worth underlying that only 23% and 27% of low BMD and fractured subjects, respectively, had an adequate daily calcium intake (Figure 2). An adequate calcium intake was inversely associated with BMI (OR: 1.04; 95%CI: 1.01-1.06; p=0.016) and directly associated with a history of major fragility fractures (OR: 1.55; 95%CI: 1.16-2.07; p=0.003), a previous diagnosis of PHPT (OR: 2.66; 95%CI: 1.23-5.75; p=0.013) and the absence of nephrolithiasis (OR: 1.86; 95%CI: 1.10-3.14; p=0.020), regardless of age, gender and the presence of low BMD.

Individuals with low BMD and/or fractures showed a higher calcium intake (949.9±417.3 mg/day), were older (67.7±10.3 years) and less frequently premenopausal (1.9%) than those without low BMD and fractures (907.5±382.9 mg/day, p=0.025; 61.3±10.8 years, p<0.0001; 8.7%, p<0.0001, respectively). The logistic regression analysis showed that the presence of low BMD and/or fragility fractures was not associated with the daily calcium intake.

Finally, even excluding male patients and premenopausal females from the analyses, the results did not change (data not shown).

4. Discussion

The present study shows that the mean calcium intake in a cohort of Italian individuals referred for the evaluation of low BMD is lower than recommended. Recommended daily calcium intake in the general adult population varies across countries and according to the different guidelines.

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However, a daily calcium intake of at least 1000-1200 mg/day is usually considered adequate [4,6,7,19]. A quite recent systematic review shows that mean dietary calcium intakes fall below the recommended levels in many areas of the world [10], including Italy, where a survey on this topic performed in 2005-2006 reveals an average calcium intake in the adult population of 765 mg/day [11]. The mean daily calcium intake in the present study (about 875 mg) is better than before, but still insufficient, especially considering that these data were collected in a population at risk of low BMD. Indeed, it is well-established that an adequate calcium and vitamin D intake is essential for bone health and that a low calcium intake is associated with an increased fracture risk [20]. Our results are in agreement with those of previous studies showing a mean calcium intake lower than the recommended thresholds in osteoporotic populations, both in Europe [21] and in Italy [22].

It is worth noting that within our cohort almost one third of individuals with low BMD and/or fractures had an estimated calcium intake lower than 700 mg/day, the threshold below which the dietary calcium intake is considered to be associated with an increased risk of fracture and osteoporosis and below which a supplementation is considered mandatory [18] and less than a quarter of individuals with low BMD and/or fractures had an adequate daily calcium intake. Despite these findings, indicating an insufficient awareness of the importance of this nutritional issue for bone health, the prevalence of low BMD and previous major fragility fractures were higher in subjects of the third tertile than in those of the first and second tertiles of daily dietary calcium intake. This finding might be explained by the possibility that individuals with low BMD and/or fractures are more prone to increase the daily calcium intake. In keeping, individuals with low BMD and/or fractures were older than those without low BMD and/or fractures and the dietary calcium intake increased with age. Accordingly, premenopausal females were more represented in the lowest tertile of daily calcium intake. Therefore, even if entirely speculative, this may suggest that the awareness of a low BMD and/or of a fragility fracture could have positively influenced the nutritional habits.

Moreover, individuals in the lowest tertile of daily calcium intake showed a higher prevalence of idiopathic hypercalciuria and of adverse food reactions (mainly lactose intolerance, to a lesser extent food allergy or autoimmune intollerance) than patients in the highest tertile. This result was also confirmed when we compared patients with calcium intake below and above 700 mg/day and, in particular, these conditions were associated with an inadequate calcium intake independent of possible confounders, including the presence of low BMD and prevalent fragility fractures. These findings suggest that adverse food reactions and the presence of hypercalciuria may have contributed to decrease calcium intake. Indeed, despite the availability of lactose-reduced or lactose-free dairy products, lactose-intolerant individuals frequently avoid milk and derivatives which represent the main sources of dietary calcium and so are at risk of calcium inadequacy [23]. Likewise, hypercalciuric subjects, possibly not appropriately informed, could have been worried of worsening the urinary calcium excretion by assuming dairy products. Conversely, it is known that an adequate dietary calcium intake is important even in hypercalciuric individuals in order to counterbalance the increased urinary loss and avoid a negative calcium balance [24].

An inadequate calcium intake was also independently associated with the female gender and with the presence of diabetes mellitus. The first result, despite being consistent with previous data [10], acquires even more value considering that calcium requirements in women are generally higher than in men of the same age [19]. A history of diabetes mellitus could have negatively influenced calcium intake due to the need to follow not only a hypoglucidic but also a cholesterol-lowering diet, which is a known factor risk for reduced calcium intake and low BMD [25].

The comparison between patients with calcium intake below and above 1200 mg/day showed that an adequate daily calcium intake was associated with a lower prevalence of nephrolithiasis, and a higher history of major fragility fractures and a previous diagnosis of PHPT. The lower rate of nephrolithiasis in patients with adequate calcium intake is in keeping with the amount of data about the protective role against the lithogenic risk of the normocalcic diet [26]. In our opinion, the apparently unexpected findings of a higher history of major fragility fractures and a previous diagnosis of PHPT in subjects with adequate daily calcium intake have plausible explanations.

Indeed, as discussed above, a previous fragility fracture may have encouraged subjects to increase their daily calcium intake. Similarly, a past diagnosis of PHPT and the subsequent transient hypocalcemia may have contributed to increase the awareness of the importance of an adequate calcium intake.

Anyway, even though fractured patients have more likely an adequate calcium intake as compared to the not fractured ones, the proportion of fractured subjects with an adequate calcium intake does not exceed the 28%, thus indicating that over two-thirds of fractured patients had an inadequate calcium intake. Finally, the fact that hypercortisolism was not associated with a higher prevalence of adequate calcium intake confirms the still insufficient awareness in Italy of the importance of and adequate calcium intake for maintaining the skeletal health [27].

The current study has several limitations. Firstly, the cross-sectional design permits to find associations but not to demonstrate a link of causality. Indeed, the recruitment of patients in referral centres for osteoporosis can have introduced a selection bias. Indeed, in some individuals the calcium intake assessed in this study reflects the individual habits before the diagnosis of osteoporosis and/or the occurrence of a fragility fracture. However, many subjects have probably been referred to these centres after the diagnosis of osteoporosis was made by their General Practitioners. Thus, it is not possible to discriminate whether these data reflect the attitude of the Italian General Practitioners in suggesting an adequate calcium intake in patients with at risk for fractures or the individual dietary habits. Secondly, the questionnaire assessed the dietary calcium intake at the moment of the study enrolment, and, therefore, could not have been informative of the dietary calcium intake in the past. Finally, a limitation of the study is the lack of data on vitamin D status in our sample which could have been useful in the interpretation of the results.

Overall, despite these limitations, our data suggest that, to date, an inadequate calcium intake is still highly prevalent in a population with low BMD or at risk for this condition. Educational campaigns should be encouraged to correct the lack of knowledge about the safety and the benefits of an adequate calcium intake and, conversely, about the risks associated with a low calcium intake, particularly in osteoporotic or already fractured subjects

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