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Phytate (*myo*-Inositol Hexaphosphate) and Risk Factors for Osteoporosis

A.A. López-González,[1] F. Grases,[2] P. Roca,[3] B. Mari,[4] M.T. Vicente-Herrero,[5] and A. Costa-Bauzá[2]

[1]*Servicio de Prevención de Riesgos Laborales, Gestión Sanitaria de Mallorca;*
[2]*Laboratory of Renal Lithiasis Research and* [3]*Departamento de Biologia Fonamental i Ciències de la Salut, Universitary Institute of Health Sciences Research, University of Balearic Islands;*
[4]*Servei de Medicina de l'Esport, Consell de Mallorca, Palma de Mallorca;*
and [5]*Correos de Valencia, Servicio Médico, Valencia, Spain*

ABSTRACT Several risk factors seem to play a role in the development of osteoporosis. Phytate is a naturally occurring compound that is ingested in significant amounts by those with diets rich in whole grains. The aim of this study was to evaluate phytate consumption as a risk factor in osteoporosis. In a first group of 1,473 volunteer subjects, bone mineral density was determined by means of dual radiological absorptiometry in the calcaneus. In a second group of 433 subjects (used for validation of results obtained for the first group), bone mineral density was determined in the lumbar column and the neck of the femur. Subjects were individually interviewed about selected osteoporosis risk factors. Dietary information related to phytate consumption was acquired by questionnaires conducted on two different occasions, the second between 2 and 3 months after performing the first one. One-way analysis of variance or Student's *t* test was used to determine statistical differences between groups. Bone mineral density increased with increasing phytate consumption. Multivariate linear regression analysis indicated that body weight and low phytate consumption were the risk factors with greatest influence on bone mineral density. Phytate consumption had a protective effect against osteoporosis, suggesting that low phytate consumption should be considered an osteoporosis risk factor.

KEY WORDS: • ***bone mineral density*** • ***inositol hexaphosphate*** • ***osteoporosis risk factors*** • ***phytate***

INTRODUCTION

OSTEOPOROSIS IS THE MOST PREVALENT bone metabolic disease of humans and has a worldwide distribution.[1] It is a systemic disorder characterized by low bone mass and microarchitectural deterioration of bone tissue. Individuals with osteoporosis have increased bone fragility and susceptibility to fracture, which is considered the most important clinical consequence of this disease. No single cause of osteoporosis has been identified, but several factors seem to play a role in its development. These are considered "risk factors" as each has an influence on the risk of individuals developing the disease. Among the major risk factors for osteoporosis are old age and estrogen deficiency, although a range of other factors, including genetic disposition[2] and those related to lifestyle[3] (including nutritional imbalance, inadequate exercise, and smoking), appear to be important.[4,5] Nevertheless, there is a lack of information in this area, and a search for new risk factors and global estimation of osteoporosis risk factors is necessary.[6]

Phytate (*myo*-inositol hexaphosphate) is a naturally occurring compound that is ingested in significant quantities by humans with diets rich in whole grains. In plant seeds, phytate is associated with calcium and magnesium ions as the salt phytin, where it acts as a phosphate store. Phytate is concentrated in the germ and aleuronic layers of the kernel and in the bran or hull.[7,8] For this reason large amounts of phytate are found in unrefined cereals and in other edible vegetable seeds such as legumes and nuts. However, because of cereal refinement processes, removal of seed bran and hulls, and consumption of low fiber foods, human diets are gradually becoming poorer in phytate. In 1949 Mellanby[9] demonstrated that dogs fed high-phytate diets (as the sodium salt) had reduced calcium absorption and increased incidence of rickets. Since that time a number of studies have attributed "anti-nutrient" properties to phytate,[10,11] and its capacity to induce osteoporosis has even been postulated.[12,13] However, recent studies indicate that dietary phytate (mainly as phytin) amounts to approximately 0.1% of a balanced diet and has no adverse effects on mineral bioavailability.[14–16] Studies in humans have indicated that a phytate intake of 2 g/day does not affect mineral balance when min-

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Address reprint requests to: Prof. Dr. F. Grases, Laboratory of Renal Lithiasis Research, Universitary Institute for Health Sciences Research, Ed. Mateu Orfila Rotger, University of Balearic Islands, 07122-Palma de Mallorca, Spain, E-mail: fgrases@uib.es

eral intake levels are adequate.[17,18] Interestingly, the so-called Mediterranean diet, known for its healthy properties, results in an intake of approximately 1 g of phytate/day. The aim of this study was to evaluate the influence of dietary phytate consumption as a risk factor in osteoporosis.

MATERIALS AND METHODS

Two transverse observational studies of workers belonging to different activity sectors on the Spanish island of Mallorca were carried out (study subject selection criteria are shown in Table 1). The first study involved 1,473 volunteer subjects for whom bone mineral density was determined by means of dual radiological absorptiometry of double energy in the calcaneus (Lunar PIXI dual energy X-ray absorptiometer, GE Medical Systems, Madison, WI) and expressed as *T*-score.

The second study, to validate the results of the first study, involved 433 workers selected randomly from the previous group. Bone mineral density was determined by means of dual radiological absorptiometry in the lumbar column and the neck of the femur (model XR-46 bone densitometer, Norland, White Plains, NY) and expressed as *T*-score. In both studies the measurements were carried out by the same skilled personnel to minimize interoperator variability.

To assess the occurrence of osteoporosis risk factors, subjects were interviewed individually, and answered a questionnaire specifically designed for the study (Table 2). The questionnaire was answered under the supervision of specially trained personnel.

The anthropometric parameters were determined with a height rod and using a homologated and calibrated scale.

Information on the dietary phytate consumption of study subjects was obtained by questionnaire (see Table 2) on two different occasions, the second between 2 and 3 months after performing the first one, to ensure the validity of obtained data.

To establish a subject's phytate consumption, the sum of servings consumed per week of the main food groups that contain phytate (legumes, nuts, and whole grain food including wholemeal bread) was assessed and used to classify the subject as a low phytate consumer (consumption of less than three servings per week) or a normal phytate consumer (consumption of three or more servings per week).

The study protocol was approved by the relevant institutional review boards. Written informed consent was obtained from all patients.

Statistics

Statistical analysis was performed using SPSS version 14.0 (SPSS Inc., Chicago, IL). Data are presented as mean ± SEM values. One-way analysis of variance or Student's *t* test was used to determine the statistical differences between groups. Statistical significance was set at $P < .05$. The relationships between risk factors and osteoporosis were examined by multivariate linear regression analyses, using a stepwise procedure.

RESULTS

The agreement between the two observational studies was very high, since the Cohen's kappa coefficient value was 0.8397 between the calcaneus and the lumbar column and 0.8204 between the calcaneus and the femur neck.

The agreement between the data on phytate consumption from the two questionnaires was also satisfactory (Cohen's kappa coefficient = 0.9351).

The influence of low or normal phytate consumption on the *T*-score values is shown in Figure 1. The *T*-score were significantly higher for subjects who consumed normal amounts of phytate, and the differences were statistically significant in all three cases ($P = .0000$ for the calcaneus, $P = .0006$ for the lumbar column, and $P = .0001$ for the femur neck).

The relationship between phytate consumption and other osteoporosis risk factors was also investigated (Tables 3 and 4). In all cases normal phytate consumption correlated with higher mineral bone density.

To determine which of the studied risk factors influenced bone mineral density levels and to what extent, a multivariate linear regression analysis using a stepwise method was

Table 1. Criteria for Selection of Study Subjects

Inclusion criteria	*Exclusion criteria*
Worker 18–65 years old	Younger than 18 or older than 65 years
Signing the informed consent form	Prosthesis or other artifacts in the measurement locations
Answering the questionnaire concerning social and demographic characteristics and osteoporosis risk factors	Pregnant
	Lesions in the measurement locations (*e.g.,* calcification or fractures)
	Diseases affecting bones (such as imperfect osteogenesis)
	Significant scoliosis with morphological vertebra alterations or a rotational component
	Foot malformation hindering appropriate heel rest on the densitometer

Table 2. Osteoporosis Risk Factor Questionnaire

Age (years)
Gender
Male
Female
Weight
Height
Body mass index
Exercise
Sedentary
Not sedentary
Tobacco
Usual consumption (quantity and history)
No consumption
Alcohol
Usual consumption (quantity and history)
No consumption
Consumption of drugs causing low bone density
Yes
No
Diseases related to bone density loss
Yes
No
Family history of osteoporosis
Yes
No
Calcium consumption
Adequate[a]
Not adequate[a]
Phytate consumption (number of servings per week)
Legumes
Nuts
Whole grain food
Menarche
Normal (≤15 years)
Delayed (>15 years)
Menopause
Yes
No
Pregnancy
Yes
No
On oral contraceptives
Yes
No

[a]Based on recommended consumption as a function of age and gender.

performed. Ten of the 16 risk factors studied had some influence on bone mineral density levels, with body weight and low phytate consumption having the greatest effect (Table 5).

DISCUSSION

The consumption of normal amounts of phytate-rich foods (legumes, nuts, whole grains) on at least three separate days each week constitutes the minimum amount required to attain adequate blood and tissue levels of phytate.[19–21] Therefore, subjects who consumed phytate-rich foods on less than three days per week were considered low phytate consumers.

The results indicate that dietary phytate consumption had protective effects against osteoporosis and that low phytate consumption should be considered an osteoporosis risk factor. These data are consistent with reports that phytate can inhibit hydroxyapatite dissolution in a concentration-dependent manner, similar to alendronate and to a greater extent than etidronate (F. Grases et al., unpublished data).[22] An important effect of phytate is as a crystallization inhibitor of calcium salts in urine[23,24] and soft tissues.[25] Crystallization inhibitors bind to crystal nuclei or crystal faces and disturb crystal development. The adsorption of such compounds to crystal faces can also inhibit crystal dissolution. Bisphosphonates, a group of polyphosphates that include phytate, have been found to have a high affinity for hydroxyapatite and to prevent calcification *in vitro*, and *in vivo* in animals even when administered orally.[26] The observations that bisphosphonates inhibit hydroxyapatite crystal dissolution[27,28] and can be administered orally led to studies that examined their potential use as inhibitors of bone resorption.[27–29] Many studies involving experimental systems and clinical trials have shown that a variety of bisphosphonates can inhibit osteoclast-mediated bone resorption.[29–31]

In contrast to synthetic bisphosphonates, phytate is a natural product found in mammal tissues and organs at levels dependent on dietary intake, but above a maximum intake level no further increase in absorption occurs. This was found to be 20.9 mg/kg/day for Wistar rats.[32] When extrapolated to a 70 kg weight for humans, the minimum intake to obtain maximum absorption is 1.463 g of phytate/day, which corresponds to the phytate consumption typical of the so-called "Mediterranean diet" (1 g of phytate/day). When phytate is eliminated from the diet its levels in fluids and organs notably decrease.[21,33] Consequently, regular consumption of phytate-rich foods is necessary to maintain elevated tissue values.

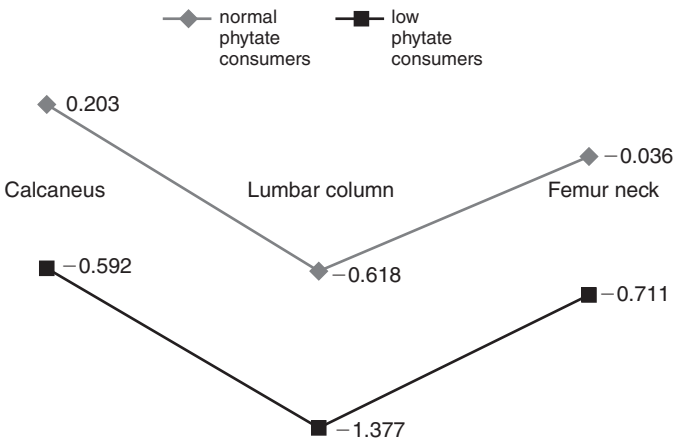

FIG. 1. Mean *T*-score values for the calcaneus, the lumbar column, and the femur neck when considering normal phytate consumers and low phytate consumers.

Table 3. Mean Calcaneus *T*-Score Levels for the Risk Factors Studied Among Normal Phytate Consumers and Low Phytate Consumers

	Calcaneus				
	Normal phytate consumers		*Low phytate consumers*		
Osteoporosis risk factor	*Mean (SEM)* T-*score*	n[a]	*Mean (SEM)* T-*score*	n[a]	P[b]
Age (>45 years)	0.130 (0.057)	480	−0.741 (0.116)	93	.0008
Gender (woman)	0.220 (0.039)	802	−0.472 (0.077)	181	.0005
Low weight	−0.212 (0.064)	276	−0.863 (0.097)	91	.0003
Low body mass index	−0.534 (0.136)	38	−1.220 (0.258)	20	.012
Exercise	0.123 (0.047)	574	−0.632 (0.081)	168	.0005
Tobacco	0.118 (0.054)	442	−0.414 (0.092)	139	.0002
Alcohol	0.115 (0.122)	92	−0.773 (0.168)	44	.0005
Drugs	0.126 (0.089)	156	−0.819 (0.217)	37	.0001
Diseases	0.138 (0.099)	144	−0.820 (0.214)	35	.0004
Family history	0.110 (0.061)	351	−0.637 (0.132)	78	.0003
Calcium	0.055 (0.092)	161	−0.699 (0.114)	85	.0001
Menarche delayed	0.130 (0.220)	20	0.380 (0.421)	5	.5996
Menopause	0.047 (0.073)	211	−0.440 (0.059)	35	.0162
Oral contraceptive	0.228 (0.061)	349	−0.362 (0.122)	86	.0002
Pregnancy	0.243 (0.049)	533	−0.537 (0.106)	106	.0002

A normal phytate consumer meant consumption of three or more servings of phytate-containing food per week. A low phytate consumer meant consumption of less than three servings of phytate-containing food per week.

[a]*n* = number of individuals.

[b]*P* = statistical significance between normal phytate consumers and low phytate consumers.

Table 4. Mean Lumbar Column and Femur Neck *T*-Score Levels for the Risk Factors Studied Among Normal Phytate Consumers and Low Phytate Consumers

	Lumbar column					*Femur neck*				
	Normal phytate consumers		*Low phytate consumers*			*Normal phytate consumers*		*Low phytate consumers*		
Osteoporosis risk factor	*Mean (SEM)* T-*score*	n[a]	*Mean (SEM)* T-*score*	n[a]	P[b]	*Mean (SEM)* T-*score*	n[a]	*Mean (SEM)* T-*score*	n[a]	P[b]
Age (>45 years)	−1.110 (0.112)	124	−2.024 (0.204)	46	.0006	−0.221 (0.098)	124	−0.901 (0.152)	46	.0009
Gender (woman)	−0.675 (0.096)	193	−1.559 (0.129)	93	.0002	0.141 (0.085)	193	−0.593 (0.102)	93	.0015
Low weight	−1.090 (0.165)	61	−1.758 (0.141)	62	.0026	−0.212 (0.140)	61	−0.891 (0.144)	62	.001
Low body mass index	−1.224 (0.377)	8	−2.047 (0.231)	23	.0799	−0.179 (0.328)	8	−1.040 (0.261)	23	.0868
Exercise	−0.844 (0.096)	147	−1.555 (0.123)	96	.0008	−0.151 (0.103)	147	−0.785 (0.104)	96	.0004
Tobacco	−0.734 (0.139)	85	−1.785 (0.161)	52	.0004	0.149 (0.127)	85	−0.945 (0.148)	52	.0002
Alcohol	−1.193 (0.219)	16	−0.846 (0.432)	10	.436	−0.542 (0.171)	16	−0.674 (0.400)	10	.7317
Drugs	−0.553 (0.123)	61	−2.116 (0.247)	33	.0009	0.295 (0.150)	61	−1.246 (0.203)	33	.0002
Diseases	−0.666 (0.203)	33	−1.240 (0.210)	32	.1247	0.344 (0.258)	33	−0.672 (0.143)	32	.0011
Family history	−0.470 (0.131)	104	−1.199 (0.172)	46	.0017	0.034 (0.126)	104	−0.565 (0.120)	46	.004
Calcium	−0.376 (0.177)	52	−1.499 (0.193)	45	.0004	−0.014 (0.169)	52	−0.858 (0.154)	45	.0004
Menarche delayed	−1.046 (0.290)	5	−1.700 (0.070)	2	.2362	0.062 (0.593)	5	0.220 (0.080)	2	.88
Menopause	−1.150 (0.160)	82	−2.778 (0.222)	22	.0003	−0.105 (0.134)	82	−1.182 (0.224)	22	.0003
Oral contraceptive	−0.852 (0.121)	97	−1.376 (0.203)	37	.0004	−0.123 (0.107)	97	−0.636 (0.119)	37	.0075
Pregnancy	−0.642 (0.117)	142	−1.801 (0.132)	72	.0005	0.183 (0.101)	142	−0.663 (0.122)	72	.0008

A normal phytate consumer meant consumption of three or more servings of phytate-containing food per week. A low phytate consumer meant consumption of less than three servings of phytate-containing food per week.

[a]*n* = number of individuals.

[b]*P* = statistical significance between normal phytate consumers and low phytate consumers.

Table 5. Influence of Risk Factors on Bone Mineral Density in Different Groups (Men and Women or Only Women) and Bone Locations

	Total sample (men + women)			*Women*		
Risk factor	*Calcaneus*	*Lumbar column*	*Femur neck*	*Calcaneus*	*Lumbar column*	*Femur neck*
Low phytate consumption	6.1	10.5	9.1	4.2	3.9	3.6
Age (>45 years)	2.8	8.0	2.4	1.4	2.2	0
Gender (female)	1.6	2.2	2.5			
Low weight (<57 kg)	2.2	2.8	4.4	11.5	14.9	12.9
Exercise (sedentary)	0.6	5.2	3.0	0.4	1.5	
Family history	0.3	0	0	0.5	0	0
Low body mass index (<19 kg/m^2)	8.2	0	0	0.8	0	0
Alcohol consumption	0	1.3	2.6	0	0	0
Menopause				0	11.7	3.4
Pregnancy				0	0	0

Values were calculated as R^2 and expressed as a percentage of the explained bone mineral density for each risk factor.

In conclusion, phytate is a natural product that occurs (as a calcium-magnesium salt) in significant concentrations in some common foods, including legumes, whole cereals, and nuts, and consequently is readily accessible to people consuming a balanced diet. The possibility that phytate consumption may reduce bone mineral density loss suggests that this compound may be used in the primary prevention of osteoporosis. Larger studies will be necessary to confirm these findings.

AUTHOR DISCLOSURE STATEMENT

No competing financial interests exist.

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