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ORIGINAL CONTRIBUTION

Protective effect of myo-inositol hexaphosphate (phytate) on bone mass loss in postmenopausal women

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Abstract
Introduction The objective of this paper was to evaluate the relationship between urinary concentrations of Ins*P*6, bone mass loss and risk fracture in postmenopausal women.
Materials and methods A total of 157 postmenopausal women were included in the study: 70 had low ($\leq$0.76 μM), 42 intermediate (0.76–1.42 μM) and 45 high ($\geq$1.42 μM) urinary phytate concentrations. Densitometry values for neck were measured at enrollment and after 12 months (lumbar spine and femoral neck), and 10-year risk fracture was calculated using the tool FRAX®.
Results Individuals with low Ins*P*6 levels had significantly greater bone mass loss in the lumbar spine (3.08 ± 0.65 % vs. 0.43 ± 0.55 %) than did those with high phytate levels. Moreover, a significantly greater percentage of women with low than with high Ins*P*6 levels showed more than 2 % of bone mass loss in the lumbar spine (55.6 vs. 20.7 %). The 10-year fracture probability was also significantly higher in the low-phytate group compared to the high-phytate group, both in hip (0.37 ± 0.06 % vs 0.18 ± 0.04 %) and major osteoporotic fracture (2.45 ± 0.24 % vs 1.83 ± 0.11 %).
Discussion It can be concluded that high urinary phytate concentrations are correlated with reduced bone mass loss in lumbar spine over 12 months and with reduced 10-year probability of hip and major osteoporotic fracture, indicating that increased phytate consumption can prevent development of osteoporosis.

Keywords Bone mass loss · Bone mineral density · Osteoporosis · Phytate · Risk of fracture

Abbreviations

SERMs	Selective estrogen receptor modulators
FDA	US food and drug administration
RANKL	Receptor activator for nuclear factor κ B ligand
HRT	Hormone replacement therapy
Ins*P*6	Myo-inositol hexaphosphate, phytate
HAP	Hydroxyapatite
BMD	Bone mineral density

Introduction

The most common systemic skeletal disease known is osteoporosis, which is characterized by low bone mineral density and microarchitectural deterioration of bone tissue with a consequent increase in bone fragility. Early osteoporosis (also known as osteopenia) is not usually diagnosed and remains asymptomatic; the condition does not become

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clinically evident until fractures occur. Loss of bone density and fracture rates increase markedly with age, resulting in significant morbidity and some mortality.

Osteoporosis is an established, well-defined disease, affecting more than 75 million people in Europe, Asia and the USA and causing more than 2.3 million fractures annually in Europe and the USA [1]. Osteoporosis is threefold more common in women than in men, partly because women have a lower peak bone mass and partly because of hormonal changes that occur at menopause. In addition, women live longer than do men and therefore show a greater reduction in bone mass. Because of increases in longevity in many parts of the world, women now live more than one-third of their lives after menopause; moreover, the number of postmenopausal women is increasing (http://www.iofbonehealth.org/, consulted September 2011).

Loss of skeletal tissue function is a major cause of hospitalization in elderly individuals. For example, it has been estimated that around 90 % of Europeans will, at some time during their lives, experience hard-tissue-related conditions that require treatment. This figure is expected to increase, as the proportion of individuals aged over 80 years is raising in many populations. The costs of hard-tissue treatment are substantial; treatment in Europe of orofacial hard tissues is estimated to cost about 25 billion € annually, whereas revision surgery for failing hip implants costs 5,000 million €.

Until recently, osteoporosis was an under-recognized disease and was considered to be an inevitable consequence of aging. However, perceptions have changed, as epidemiological studies have highlighted the high burden of this disease and the associated costs to society and healthcare systems [2]. As a result of osteoporotic fractures, healthcare costs from osteoporosis exceed 15 billion US dollars annually in USA and 30 billion Euros in Europe.

The combination of clinical risk factors that could lead to fracture with the measure of bone mineral density is the most effective method to evaluate the risk of fracture. Kanis et al recently presented the FRAX® [3] model to estimate the 10-year fracture risk, which includes the main clinical risk factors to be considered together with the femoral neck bone mineral density. The FRAX® model is based on data obtained from 9 large population cohorts from around the world and has been validated in 11 population cohort studies.

The FRAX® is a tool to estimate the fracture risk for men and women aged between 40 and 90. The algorithms of this model, by means of specific software, allow calculating the 10-year probability of a major osteoporotic fracture (clinical spine, forearm, hip or shoulder fracture) and specifically the 10-year probability of hip fracture. There are 14 specific versions of the model, which consider the Caucasian, Afro-American, Latino and Asiatic ethnic origin, for the following countries: Austria, China, France, Germany, Italy, Japan, Spain, Sweden, Switzerland, Turkey, UK and USA.

Both non-pharmacological and pharmacological methods are available to prevent and treat osteoporosis [4]. Many pharmaceutical agents are currently available to treat the condition, including substances that prevent bone resorption and those that stimulate bone formation. Anti-resorptive agents include calcium and vitamin D (usually combined with other anti-resorptive agents), calcitonin, bisphosphonates and SERMs (selective estrogen receptor modulators), such as raloxifene [4]. Bisphosphonates have been associated with various side effects, mostly related to the digestive system [5]. Moreover, although bisphosphonates are effective agents for reducing fracture risk, their long-term administration has raised some concerns regarding their long-term safety, such as increasing fragility, and may even cause osteonecrosis of the jaw [6]. The FDA recently approved denosumab, a fully human monoclonal antibody that binds to RANKL [7], for the treatment of postmenopausal women who have a high risk of osteoporotic fractures. The agents that stimulate bone formation include fluoride [8, 9] and teriparatide [10–12]. In postmenopausal women, hormone replacement therapy (HRT), consisting of estrogens and progestin, may be used although the balance of risks and benefits in healthy postmenopausal women remains uncertain [13]. Other therapies, such as strontium ranelate, have a dual mechanism of action, first stimulating new bone formation and subsequently decreasing resorption. Sodium ranelate treatment of women with postmenopausal osteoporosis has been found to increase bone mass density and to lower the risk of fracture [14].

Myo-inositol hexaphosphate (Ins*P*6), also termed phytic acid or phytate, is a molecule abundant in vegetable seeds and legumes. Ins*P*6 constitutes 1.5–6.4 % of the dry weight of grains and is mostly bound to calcium and magnesium ions. Ins*P*6 is also present in all organs and tissues of animals, in ionized form [15–17]. Ins*P*6 has various biological functions [18]; the substance is a potent inhibitor of calcium salt crystallization [19] and an antioxidant (an inhibitor of hydroxyl radical formation) [20]. In addition, Ins*P*6 has been found to inhibit tumor formation in the colon [20].

The in vivo effects of Ins*P*6 intake on osteoporosis have been studied by evaluating the properties of bone in ovariectomized Wistar rats, an animal model of postmenopausal osteoporosis. Ins*P*6 consumption was found to reduce the loss of bone mineral density caused by estrogen deficiency [21]. Indeed, a retrospective clinical study on 1,500 volunteers showed that low Ins*P*6 intake could be

considered a risk factor for osteoporosis, because such reduced consumption was associated with a decline in bone mineral density in the vertebrae and the femurs [22]. A descriptive clinical trial in 180 volunteers confirmed these observations, by measuring urinary phytate concentrations [23].

We hypothesized that phytate consumption levels and bone mineral density would be associated, based on studies showing that phytate inhibits bone resorption, a process mediated by osteoclasts [24]. These effects resemble those exhibited by some bisphosphonates, which are chemically similar to phytate; phosphate and phosphonate groups have a high affinity for calcium crystal surfaces, thereby promoting self-adsorption. Since our previous work did not evaluate the evolution of bone mineral density values with time depending on phytate physiological levels, we therefore evaluated the relationship between urinary phytate concentration and bone mass loss in the lumbar spine and femoral neck over 12 months and the effect of phytate physiological levels on the risk fracture valuated through FRAX.

Materials and methods

Participants

A descriptive cross-sectional clinical trial was performed on 157 postmenopausal women from Mallorca (in the Balearic Islands). All subjects provided written informed consent and satisfied the inclusion criteria outlined in Table 1. Moreover, no subject fulfilled any exclusion criterion (Table 1), as determined by in-depth clinical interview. Weights were measured using standardized scales. Prior to enrollment in the study, a clinical interview was conducted to determine which women had entered menopause. In instances of doubt, hormone concentrations were measured. Personal and clinical data were collected by the Servicio de Prevención de Riesgos Laborales (GESMA, Palma de Mallorca, Spain). The study protocol was approved by the Balearic Research Ethics Board (Protocol # IB 1027/08 PI).

Urine samples and phytate analysis

After discarding the first urine of the morning, a fasting urine sample was collected 2 h later from each volunteer at the enrollment. The 2-h urine was selected mainly because it implies a more standardized procedure to collect urine that is less affected by immediate dietary factors. Thus, the first early morning urine could correspond to different horary intervals and can be affected by nocturnal meals. Samples were stored at 4 °C, transported to the laboratory in chilled containers, and phytate concentrations were immediately measured, according to the following procedure [25].

Five milliliters of fresh urine (acidified with HCl 1:1 to pH 3–4) was transferred to a column containing 0.2 g of anion-exchange resin (the inner diameter was 4 mm). The first eluate was discarded, and then, the column was washed with 50 ml of 50 mM HCl. The second eluate was discarded. Then, the column was washed with 3 ml of 2 M HNO3. The determination of phytate was carried out by direct phosphorus analysis of this last eluate using the ICP-AES and appropriate calibration graph. The method shows a good level of precision (RSD = 2.4 %) and accuracy (97–105 %), and the results were statistically comparable to another one based on GC/mass detection, indicating a good specificity and confirming a high accuracy [26].

All individuals consumed an unrestricted diet during the sample collection period. The 157 postmenopausal women were classified into three groups according to urinary phytate concentrations: low ($\leq$0.76 μM), high ($\geq$1.42 μM) and intermediate (0.76–1.42 μM). After 12 months, the phytate analysis was repeated and those women whose phytate urinary concentration was not $\leq$0.76 μM for the low group, between 0.76 and 1.42 μM for the intermediate group or $\geq$1.42 μM for the high group, were excluded from the statistical analysis, since this implies a probable change in dietary habits related to phytate consumption during the period of 12 months and consequently did not assure a low or high intake of phytate during such period. The demographic characteristics of women with low and high urinary phytate concentrations are shown in Table 2.

Table 1 Eligibility criteria

Inclusion criteria	Exclusion criteria
Female gender	Menopause >5 years in duration
Presence of menopause	Family history of osteoporosis
Willingness to participate in the study and provision of informed consent	Treatment with bisphosphonates or other drugs prescribed to treat osteoporosis
	Weight <57 kg
	Surgical menopause
	Presence of any osteoporosis-related disease

Table 2 Demographic characteristics of postmenopausal women with low and high urinary phytate concentrations

Characteristic	Urinary phytate concentrations		
	Low	Intermediate	High
Number of postmenopausal women	45	20	29
Age (years)	53.0	52.8	51.4
Weight (kg)	66.7	61.4	64.7
Height (cm)	160	159	160
Body mass index (kg/m^2)	26.2	24.2	25.1
Duration of menopause (years)	2.7	2.8	2.9
Smokers (%)	26.7	21.1	27.6
Fracture history (%)	8.9	10.5	6.9
Glucocorticoids (%)	8.9	5.3	6.9
Alcohol (%)	11.1	15.8	13.8
BMD femoral neck (g/cm^2)	0.813	0.843	0.879[a]

[a] $p < 0.05$ versus low urinary phytate group

Determination of bone mineral density

T scores and bone mineral densities of the lumbar spine (L2–L4) and femoral neck were determined by dual X-ray absorptiometry (DXA; Norland Excell bone densitometer; MEC Osteoporosis Bone Densitometry, Minster, OH, USA), by a single technician, to avoid interobserver bias. Densitometric measurements were performed at the time of enrollment and 12 months later. Lost bone mass was classified as none (when the value at 12 months was higher than that at enrollment), 0–2 or >2 %.

Fracture risk assessment through FRAX®

The following clinical data were collected: family history of osteoporotic hip fracture in parents, history of fragility fracture (a fracture that occurred in adult life spontaneously or a fracture caused by trauma, which would not have happened in a healthy individual), current tobacco consumption, consumption of 3 or more doses per day of alcohol (one unit is 8–10 g of alcohol), rheumatoid arthritis and use of oral corticosteroids for more than 3 months (daily dose of 5 mg or more of prednisolone or equivalent doses of other glucocorticoids).

Other causes of secondary osteoporosis were also collected, such as type 1 diabetes, imperfect osteogenesis in adults, untreated chronic hyperthyroidism, hypogonadism, early menopause (before age 45), chronic malnutrition, malabsorption and chronic liver disease. The age was included, and the height and weight were determined by certified and calibrated scale and measuring board, to calculate the body mass index. Finally, the values of bone mineral density of femoral neck were also included. FRAX® models have been developed from the study of population groups in Europe, North America, Asia and Australia. In our study, the FRAX® index was calculated using the computer tool developed by WHO and available on line for the Spanish population (http://www.shef.ac.uk/FRAX/tool.jsp?country=4, consulted September 2011), assessing the 10-year probability of hip fracture and major osteoporotic fractures (clinical spine, forearm, hip or shoulder fracture).

Statistics

Values are expressed as mean ± SE (standard error). One-way ANOVA was used to calculate significance of differences. All statistical analyses were performed using G-stat 2.0 software, and a p value <0.05 was taken to indicate statistical significance.

Results

Of the 157 women included in the study, 70 had low, 42 intermediate and 45 high urinary phytate concentrations. After the period of 12 months, 45 women remained in the low group, 20 in the intermediate group and 29 in the high phytate urinary concentrations. Statistical calculations were based on these 94 evaluable women. No statistically significant difference in any demographic characteristic between women with low and high urinary phytate concentrations was evident (Table 2).

The mean urinary phytate levels in the groups with low, intermediate and high concentrations were 0.47 ± 0.03 μM, 1.09 ± 0.05 μM and 2.29 ± 0.14 μM at the enrollment and 0.47 ± 0.03 μM, 0.97 ± 0.05 μM and 2.05 ± 0.12 μM at 12 months, respectively (Fig. 1). Measurements of T and Z scores in the lumbar spine (L2–L4, Table 3) at $t = 0$ and $t = 12$ months showed a positive correlation with phytate urinary levels, being the variation over the period of 12 months statistically lower in women with high urinary phytate concentrations compared to those with low phytate values. Measurements of T and Z scores

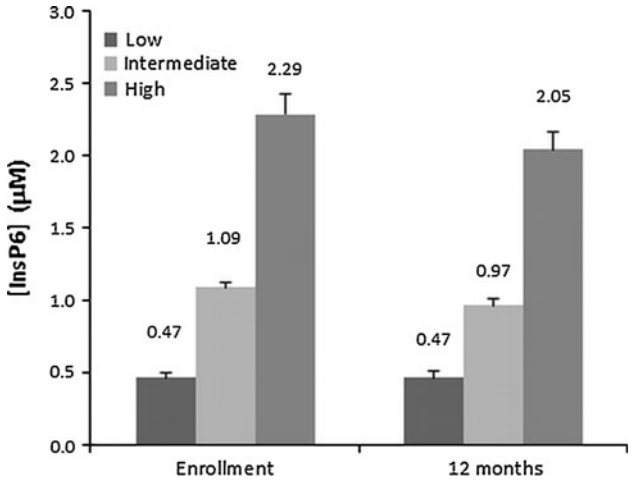

Fig. 1 Ins*P*6 urinary levels of low, intermediate and high groups at enrollment and 12 months

in the femoral neck (Table 4) revealed a significantly higher baseline in women with high urinary phytate concentrations compared to women with low phytate levels. T scores represent a comparison between the mean bone mineral density of a patient and that for a 30-year-old person of the same ethnic group and sex. Z scores represent the same comparison but with a person of the same age.

Baseline and 12-month BMDs in lumbar spine were statistically higher in the high-phytate group compared to the other groups. The overall bone mass loss over 23 months was found to be statistically lower in the high urinary phytate group when comparing with the low-phytate group (Table 5).

Baseline and 12-month BMDs in femoral neck were also significantly higher in the high-phytate group compared to the low-phytate group (Table 5).

When we classified women into two groups based on the percentage of bone mass loss (thus <2 and >2 %), we found that a higher proportion of women with low than with high urinary phytate had bone mass losses >2 % in the lumbar spine (Fig. 2) and femoral neck (Fig. 3), whereas the proportions of women with <2 % loss at either location were greater in women with high than with low urinary phytate concentrations.

Figure 4 shows a box diagram of bone mass loss at the lumbar spine in the three groups of women.

The FRAX® results revealed that the risk of major fracture (clinical spine, forearm, hip and shoulder fractures) was significantly higher in the group of postmenopausal women with low urinary phytate when compared with the high urinary phytate group. The average risk in the low urinary phytate group was 2.45 ± 0.24 %, while in the intermediate and high urinary phytate group, was 2.29 ± 0.33 % and 1.83 ± 0.11 % respectively, being the differences statistically significant between the

Table 3 Variation of T and Z scores in lumbar spine over 12 months

	Low urinary phytate ($n = 45$)			Intermediate urinary phytate ($n = 20$)			High urinary phytate ($n = 29$)		
	0 months	12 months	Absolute variation	0 months	12 months	Absolute variation	0 months	12 months	Absolute variation
T score	−1.26 ± 0.19	−1.49 ± 0.18	−0.23 ± 0.05	−1.08 ± 0.33	−1.24 ± 0.32	−0.16 ± 0.06	0.65 ± 0.25[a,b]	0.62 ± 0.25[a,b]	−0.02 ± 0.04[a]
Z score	−0.10 ± 0.15	−0.20 ± 0.14	−0.11 ± 0.05	0.02 ± 0.28	0.00 ± 0.27	−0.02 ± 0.06	1.30 ± 0.21[a,b]	1.36 ± 0.21[a,b]	0.05 ± 0.04[a]

[a] $p < 0.05$ versus low urinary phytate group

[b] $p < 0.05$ versus intermediate urinary phytate group

Table 4 Variation of T and Z scores in femoral neck over 12 months

	Low urinary phytate ($n = 45$)			Intermediate urinary phytate ($n = 20$)			High urinary phytate ($n = 29$)		
	0 months	12 months	Absolute variation	0 months	12 months	Absolute variation	0 months	12 months	Absolute variation
T score	−0.25 ± 0.12	−0.30 ± 0.12	−0.06 ± 0.10	0.03 ± 0.27	−0.12 ± 0.25	−0.15 ± 0.12	0.35 ± 0.20[a]	0.14 ± 0.20[a]	−0.20 ± 0.12
Z score	0.70 ± 0.15	0.68 ± 0.13	−0.02 ± 0.11	0.96 ± 0.29	0.84 ± 0.26	−0.13 ± 0.11	1.21 ± 0.24[a]	1.10 ± 0.23	−0.11 ± 0.13

[a] $p < 0.05$ versus low urinary phytate group

Table 5 Percentage of bone mass losses over 12 months

	Low urinary phytate ($n = 45$)			Intermediate urinary phytate ($n = 20$)			High urinary phytate ($n = 29$)		
	BMD (g/cm^2) 0 months	BMD (g/cm^2) 12 months	% bone mass loss	BMD (g/cm^2) 0 months	BMD (g/cm^2) 12 months	% bone mass loss	BMD (g/cm^2) 0 months	BMD (g/cm^2) 12 months	% bone mass loss
Lumbar spine	0.914 ± 0.019	0.887 ± 0.017	2.82 ± 0.60	0.937 ± 0.035	0.919 ± 0.034	1.87 ± 0.68	1.118 ± 0.026[a,b]	1.113 ± 0.025[a,b]	0.34 ± 0.55[a]
Femoral neck	0.813 ± 0.013	0.801 ± 0.012	0.97 ± 1.50	0.843 ± 0.029	0.819 ± 0.27	2.46 ± 1.32	0.879 ± 0.022[a]	0.857 ± 0.021[a]	2.25 ± 1.72

[a] $p < 0.05$ versus low urinary phytate group

[b] $p < 0.05$ versus intermediate urinary phytate group

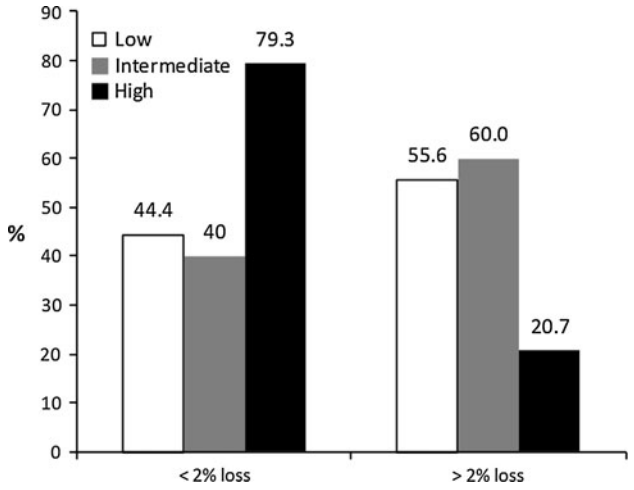

Fig. 2 Percentages of postmenopausal women with low (≤0.76 μM), intermediate (0.76–1.42 μM) and high (≥1.42 μM) urinary phytate concentrations showing <2 and >2 % loss of lumbar spine bone mass over 12 months

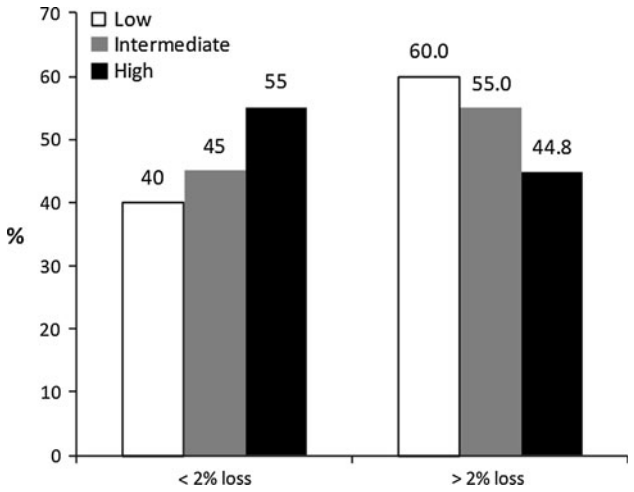

Fig. 3 Percentage of postmenopausal women with low, intermediate and high urinary phytate concentrations showing <2 and >2 % loss of femoral neck bone mass over 12 months

low- and high-phytate groups. The risk of hip fracture was also significantly higher in the low urinary phytate group compared to the high urinary phytate group (0.37 ± 0.06 % vs 0.18 ± 0.04 %). These results are shown in Figs. 5 and 6.

Discussion

We have shown here that bone mass loss in lumbar spine was greater in postmenopausal women with lower urinary phytate concentration (indicating lower phytate consumption) than in women with higher phytate urinary concentration. Notably, a significantly greater proportion of

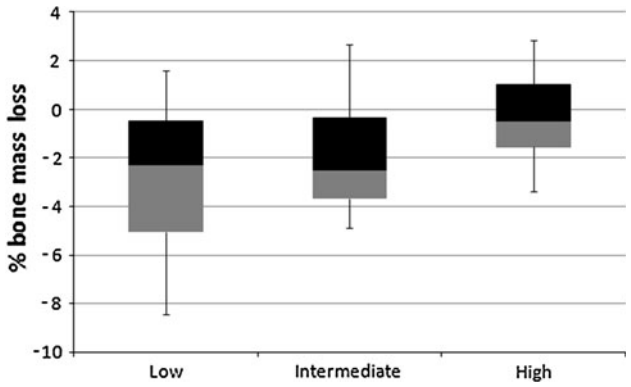

Fig. 4 Percentage bone mass loss over 12 months at the lumbar spine in women with low and high urinary phytate concentrations. The boxes represent the 25, 50 and 75th percentiles, and the bars, the 10 and 90th percentiles

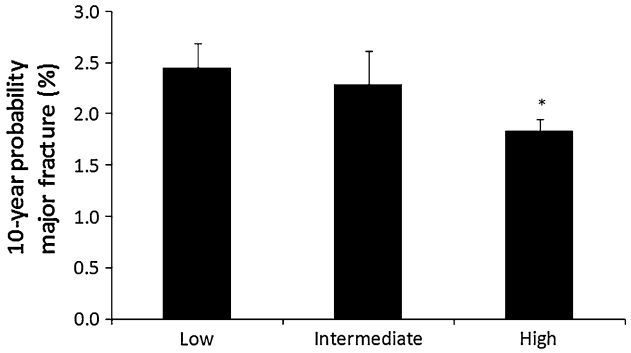

Fig. 5 10-year probability (%) of major osteoporotic fracture (clinical spine, forearm, hip or shoulder fracture) assessed through FRAX®. *$p < 0.05$ versus low urinary phytate concentrations group

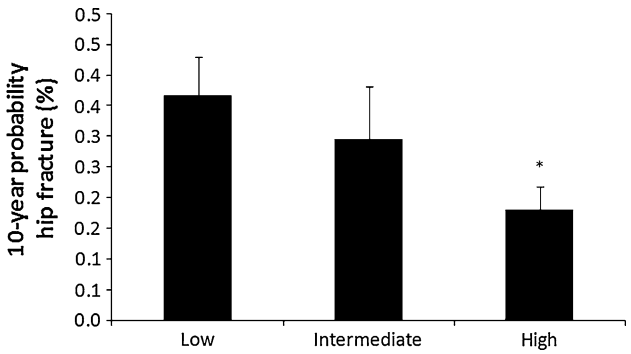

Fig. 6 10-year probability (%) of hip fracture assessed through FRAX®. *$p < 0.05$ versus low urinary phytate concentrations group

women with low than with high urinary phytate concentration had bone mass losses >2 %, whereas a greater percentage of women with high than with low urinary phytate concentration showed no or <2 % loss of bone mass. These findings indicate that phytate protects against loss of bone mass; moreover, these findings confirm other in vivo results, both in animal models [21] and in retrospective clinical trials in the general population [22] and

postmenopausal women [23]. Probably, high phytate physiological levels are meant which negatively correlate with 10-year probability of hip and major osteoporotic fracture.

Phytate has been shown to stop or slow pathological processes involving calcification. The substance prevents development of renal stones [19, 27–31], cardiovascular calcifications [32–35], sialolithiasis [36] and dental calculi [37]. As all these processes are associated with disorders of calcium metabolism, phytate likely has a single mechanism of action, based on adsorption to the nuclei or faces of calcium crystals, disturbing crystal development [38, 39] and thereby protecting against pathological calcification.

The activity of phytate to bind to forming or growing crystals, thus inhibiting crystallization, also allows the material to inhibit redissolution of already formed calcium crystals, as observed when osteoclast-mediated dissolution of HAP crystals was measured during the osteoporotic process [40]. Thus, phytate is an anti-resorptive agent, similar to the bisphosphonates, although the mechanisms of action differ, in that phytate exerts a purely physicochemical effect based on superficial adsorption. In contrast, bisphosphonates, which are internalized by bone-resorbing osteoclasts, interfere with various intracellular biochemical processes. First-generation, non-nitrogen-containing bisphosphonates can be metabolically incorporated into non-hydrolyzable analogs of adenosine triphosphate (ATP), inhibiting ATP-dependent intracellular enzymes and inducing osteoclast apoptosis [41]. In contrast, second-generation, nitrogen-containing bisphosphonates inhibit farnesyl pyrophosphate synthase, a key enzyme in the mevalonate pathway, preventing the biosynthesis of isoprenoid compounds that are essential for posttranslational modification of small guanosine triphosphate (GTP)-binding proteins (GTPases). This results in a loss of osteoclast activity [42, 43].

Assays of the effects of phytate on osteoblast and osteoclast activity [43] have shown that phytate has an anti-resorptive activity, attributable to both to a simple physicochemical process and to a deeper biochemical effect at the cellular level. However, these findings are preliminary in nature, derived from in vitro studies, and further research is required.

The compound strikes a balance between efficacy and safety; thus in the context of this study and provided well-balanced diets are consumed, negative side effects might not be relevant. As there is little information on the phytic acid metabolism in the organism, it can be assumed that the urinary phytate level primarily depends on exogenous phytate sources and the mean daily dietary intake of phytate [44].

Phytate occurs in significant quantities in diets rich in whole grains, oil seeds, legumes and nuts. In plant seeds, phytate is associated with divalent cations, including calcium and magnesium (the so-called phytin salt), where it acts as a phosphate and ion store. However, because of cereal refinement processes, the removal of seed bran and hulls, and consumption of low-fiber foods, human diets in developed countries are gradually becoming poorer in phytate.

Phytate is found in mammalian tissues and organs at levels dependent on dietary intake, but above a maximum intake level (20.9 mg/kg/day for Wistar rats) [45], no further increase in absorption occurs. When extrapolated to humans weighing 70 kg, the minimum phytate intake necessary to obtain maximum absorption is 1.463 g of phytate/day, which corresponds to the phytate consumption typical in the so-called Mediterranean diet (1 g of phytate/day).

The results of this study were based on Ins*P*6 physiological levels (epidemiologic data), and although an important role of phytate in bone metabolic diseases was foreseen, these findings are limited to the design of this clinical trial and further validation is needed to confirm these results with larger and intervention clinical trials. The method applied is a highly sensitive one but also an unspecific method that might also include other inositol phosphates such as inositol pentaphosphate (Ins*P*5). Thus, the correlation data might be non-specific for phytate and also might contain a certain content of lower inositol phosphates. However, these lower inositol phosphates can be also assumed to play its role in the anti-calcification processes due to its high calcium binding affinity. At the moment, however, there is no analytical method available which satisfactorily discriminates Ins*P*6 from Ins*P*5 and other inositol phosphates in the difficult matrix of urine at those low concentration levels.

In conclusion, we have shown here that higher levels of urinary phytate are associated with a drop in intermediate-to-long-term loss of bone mass at the lumbar spine of postmenopausal women and reduce the risk of hip and major osteoporotic fracture. These findings confirm the results of previous studies [21–23] and suggest that the compound may become important in the treatment of bone-related diseases, especially in patients who cannot tolerate standard treatments, since phytate predicts a positive benefit/risk balance.

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Conflict of interest F.G. and J.P. declare that they are inventors of a pending patent application based on some aspects of this work. F.T. is employee at Laboratoris Sanifit. J.P. is employee and stockholder at Laboratoris Sanifit.

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