ORIGINAL ARTICLE

Association between osteoporosis and refined grain consumption in postmenopausal women: A case-control study

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Background: Osteoporosis is the leading pathological cause of skeletal fragility. The aim of this study was to investigate the relationship between the consumption of refined grain and osteoporosis in postmenopausal women with and without osteoporosis. **Materials and Methods:** This case–control study involved 356 menopausal women aged 45–85 in Tehran, Iran. The age-matching methodology has been used to mitigate the confounding influence of age. The dual-energy X-ray absorptiometry was utilized to evaluate the bone mineral density. The bone mass status was assessed using the World Health Organization (World Health Organization) criteria. All the participants were divided into two groups based on their T-score: the osteoporosis group and the nonosteoporosis group. A convenience sampling method was applied to select the participants, comprising two groups: case (n = 178) and control (n = 178). Data were gathered utilizing demographic and anthropometric information questionnaires, a validated 147-item food frequency questionnaire, and a physical activity questionnaire. SPSS-27 was used for statistical analyses and $P < 0.05$ was considered statistically significant. **Results:** The findings revealed substantial disparities in body mass index ($P < 0.001$) and physical activity ($P < 0.001$). The mean ± standard error of the mean consumption of refined grains was greater in participants with osteoporosis (case) (316.76 ± 12.49) compared to the control group (271.50 ± 13.29) ($P < 0.001$). Upon adjusting for confounding variables, the consumption of refined grains was positively associated with a risk of osteoporosis (odds ratio = 3.26; 95% confidence interval: 1.16–9.17, $P = 0.025$; Nagelkerke $R^2 = 0.610$). **Conclusions:** We found an association between refined grain consumption and osteoporosis. Additional research is necessary to comprehend this relationship.

Key words: Bone resorption, diet, edible grain, osteoporosis, postmenopausal bone losses

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INTRODUCTION

Osteoporosis is characterized by reduced bone mineral density (BMD) and compromised bone microarchitecture, leading to an increased susceptibility to low-impact fragility fractures.[1] This results in a reduction in bone strength and resistance.[2] Osteoporosis is associated with an increased risk of fractures in the femur, pelvis, and spine, leading to higher mortality rates, disability, and increased healthcare costs.[3]

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The global prevalence of osteoporosis is 18.3%, with higher rates in women (23.1%) compared to men (11.7%). The highest prevalence was observed in Africa (39.5%).[4] In Iran, osteoporosis affects 62% of women over 60 years old and 24% of men over 60 years old. The prevalence increases with age, exceeding 80% in women over 75 years old. In addition, the economic burden of osteoporosis in the country was estimated to be close to $400 million in 2021, based on conducted studies. Women are more at risk of developing osteoporosis than men, and the prevalence of osteoporosis is higher in women, which can

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be attributed to lower bone mass or menopause in women. The decrease in estrogen levels during menopause is one of the most important factors leading to osteoporosis.[5]

Food groups play a crucial role in bone health.[6-8] Specifically, dairy products enhance bone mineralization by providing calcium, which is efficiently absorbed due to lactose and casein phosphorylated peptides.[9] They also boost insulin-like growth factor I secretion, stimulating bone formation and skeletal development.[9] In other words, nutrition plays a vital role in osteoporosis, contributing to both the attainment of peak bone mass – the highest level of bone strength and density reached by the age of 30 years – and the prevention of bone mass reduction in the later stages of life.[10,11] Whole grain foods are a source of carbohydrates, nutrients, and dietary fiber. These grains contrast with refined grains such as pastries, white bread, rice, and white flour.[12] During the milling process, whole grains are converted to refined grains.[13] Refined grains are favored for their softer texture and longer shelf life.[14] However, this refining process removes valuable nutrients such as fiber, iron, and B vitamins from the grains.[15]

Refined grains are the main source of dietary calories for Iranians, constituting 55%–60% of total calorie intake and generally having a high glycemic index.[16] Studies indicate that consuming refined grains may lead to increased serum triglycerides, abdominal obesity, and reduced serum high-density lipoprotein (HDL). Kan *et al*. reported that higher cholesterol levels and triglycerides are associated with a greater risk of osteoporosis.[17] Other studies have also reported that high levels of low-density lipoprotein cholesterol (LDL-C) and low HDL cholesterol (HDL-C) are linked to reduced bone mass.[18] Besides, high glycemic index increases inflammatory markers and inflammation significantly impacts bone metabolism, resulting in soaring bone resorption and a higher risk of fractures.

Considering the rising prevalence of osteoporosis, its substantial economic burden, and the associated severe complications, particularly among the aging population, and considering the high consumption of refined grains in Iran, this study investigates the relationship between refined grain consumption and osteoporosis in postmenopausal women, both those diagnosed with osteoporosis and those without, taking into account Iranian dietary culture.

MATERIALS AND METHODS

Study population

This case-control study was conducted in Tehran, Iran, from March 2018 to February 2019. Using G-Power 3.1.9.2 software and an *F*-test for linear multiple regression (with an R^2 deviation from zero; $\alpha = 0.05$, power = 0.90, effect size = 0.1), the required sample size was determined to be 146 participants. Considering a dropout rate of 20% of the participants, the information of at least 178 people in each group was collected. A convenience sampling method was utilized to select the participants. In this study, we deployed the age-matching method to lessen the confounding influence of age, and the participants in both groups were women who were postmenopausal, defined as having not had a menstrual period for at least 12 months. The dual-energy X-ray absorptiometry was applied to evaluate the BMD of the lumbar vertebrae and femoral neck. The bone mass status was assessed using World Health Organization (WHO) criteria: a T-score >−1 indicates normal BMD, a T-score between −1 and −2.5 signifies osteopenia, and a T-score of −2.5 or lower denotes osteoporosis. The diagnosis of the osteoporosis case group was validated by a rheumatology specialist. Participants were categorized into the osteoporosis group and the non-osteoporosis group based on their T-score. A total of 356 postmenopausal women (178 cases and 178 controls), aged 45–85, who fulfilled the eligibility criteria, were selected from individuals referred to Shariati Hospital, private clinics, and health centers. The control group was selected from the visitors and participants' companions who traveled to these institutions from various locations in Tehran and did not have any familial ties to the patients. All participants received a comprehensive explanation of the research objectives and subsequently signed written consent. Subsequently, the participants' information was collected by a qualified expert.

Inclusion and exclusion criteria

The inclusion criteria were as follows

Not following a specific diet during the past year; not smoking or consuming alcohol; not taking supplements or drugs that influence the bone metabolisms such as anticoagulants, glucocorticoids, thyroxin, calcitonin, antacids, Vitamin D (more than 15 μg/day) and calcium (more than 500 mg/day), consumption of therapeutic doses of vitamins or minerals, glucosamine, omega-3, and bisphosphonate; not have been diagnosed with endocrine, rheumatoid, hormone therapy, gastrointestinal, or renal diseases which effect density of bone mineral status.

The exclusion criteria were as follows

Individuals who did not answer more than 20% of the questions of the Food Frequency Questionnaire (FFQ) and women with a total daily energy intake of <800 kcal and more than 4200 kcal.[19]

Data collection

All the participants completed the valid questionnaires throughout the interviews, and an expert nutritionist assessed all measurement. The general questionnaire collected information regarding age, education, alcohol consumption, breastfeeding, and contraceptive use. A valid

physical activity questionnaire, developed in Europe, was administered to assess physical activity status, and its validity was confirmed by the Daily Activity Questionnaire. The results were expressed in metabolic equivalent hours per day (Met-h/day). The questionnaire's validity and reliability have been confirmed in Iran.[20]

Body weight was measured using digital scales (Tefal) after participants donned lightweight attire. Body weight was recorded within 100 g (0.1 kg) of precision. The height was assessed by a tape meter and was reported within 0.1 cm of accuracy while the contributors were standing and removing their shoes. Body mass index (BMI) was calculated as weight divided by height squared (kg/m^2). BMI categories were defined according to the (WHO) criteria: underweight (<18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2), overweight (25.0–29.9 kg/m^2), and obese (≥30 kg/m^2).[21]

Assessment of dietary intake

The participants' dietary intake was assessed using a 147-item FFQ,[22] which has demonstrated validity and reliability in Iran.[22] It evaluates the frequency of consumption of each food item over the past year. The Nutritionist IV program, specifically designed for Iranian cuisine, was utilized to transform the frequency of each food item in the FFQ into its equivalent weight in grams per day.

Assessment of the consumption of refined grains

Jacobs *et al.*'s method was used to classify the grains into two groups: Whole grains and refined grains.[23] Based on this, refined grains include noodles (made from refined flour), pasta, white rice, crackers, vermicelli, biscuits, cakes, wet and dry sweets, baguettes, and lavash.

Statistical analysis

Statistical analysis was performed using the SPSS software version 27 (IBM Corporation, Armonk, NY, USA). The Kolmogorov–Smirnov test was used to check for normality. An independent sample *t*-test was used to compare the normal quantitative variables between two groups, and a one-way analysis of variance test (ANOVA) was used between the several groups. A Chi-square test was used for qualitative comparisons between the groups. Multiple logistic regression examined the relationship between refined grain intake and osteoporosis status, considering confounding effects. Finally, the odds ratio (OR) was calculated with a 95% confidence interval (CI). Less than 0.05 is considered statistically significant.

RESULTS

Demographic, anthropometric characteristics, and physical activity

Table 1 shows the demographic characteristics and physical activity levels of the case and control groups.

Table 1: Demographic and anthropometric characteristics of the two study groups of participants

Variables	Case	Control	*P*
Age (years)	55.62±0.48	55.31±0.43	0.634[a]
BMI (kg/m²)	29.11±0.32	27.49±0.26	<0.001[a]
PA (MET-hour-week)	1521.22±63.83	2116.63±83.42	<0.001[a]
Age of first pregnancy	21.11±0.34	20.50±0.29	0.175[a]
Number of pregnancies	3.02±0.10	3.16±0.08	0.274[a]
Lactation period	29.79±1.84	34.53±2.28	0.107[a]
Last time to take OCP	4.19±0.56	4.12±0.58	0.928[a]
Duration of taking OCP	14.51±2.07	14.89±2.13	0.898[a]
Education			
Undergraduate	150 (84.3)	133 (74.7)	0.074[b]
Graduate	26 (14.6)	43 (24.2)	
Postgraduate	2 (1.1)	2 (1.1)	
Marital status			
Single	13 (7.3)	10 (5.6)	0.518[b]
Married	165 (92.7)	168 (94.4)	
History of twining			
Yes	7 (3.9)	3 (1.7)	0.199[b]
No	171 (96.1)	175 (98.3)	
Breast-feeding			
Yes	162 (91.0)	153 (86.0)	0.135[b]
No	16 (9.0)	25 (14.0)	
OCP			
Yes	61 (34.3)	57 (32)	0.652[b]
No	117 (65.7)	121 (68)	

[a]Resulted from independent *t*-test for quantitative variables; [b]Resulted from Chi-square test for qualitative variables. *P*<0.05 was considered significant. Quantitative variables=Mean±SEM; Qualitative variables=Frequency (%). OCP=Oral contraceptive pills; BMI=Body mass index; PA=Physical activity; METs=Metabolic equivalents; SEM=Standard deviation

According to this table, among the quantitative variables of the study, there was a significant difference in BMI ($P < 0.001$) and physical activity ($P < 0.001$) between the two groups. Specifically, the case group had a higher mean BMI (29.11 ± 0.32 kg/m^2) compared to the control group (27.49 ± 0.26 kg/m^2). Conversely, the control group exhibited higher physical activity levels (2116.63 ± 83.42 metabolic equivalent of task [MET]-hour-week) compared to the case group (1521.22 ± 63.83 MET-hour-week). No significant differences were observed in age, number of pregnancies, age of first pregnancy, lactation period, duration of taking oral contraceptive pills (OCP), or the last time OCP was taken ($P > 0.05$). Among the qualitative variables, no significant differences were found in marital status, history of twins, breastfeeding, OCP use, or education level between the two groups ($P > 0.05$).

Daily intake of nutrients and food groups between the two groups

Table 2 shows the daily intake of nutrients and food groups in both the case and control groups. Based on this table, the control group had significantly higher intakes of protein ($P = 0.009$), fiber, Vitamin B1, Vitamin B5, Vitamin B6, Vitamin B9, Vitamin C, Vitamin K,

Table 2: Daily nutrient and food group intake comparison between two groups

Variables	Case[b]	Control[b]	*P*[a]
Energy intake (kcal/day)	2738.10±66.5	2604.23±65.53	0.151
Protein (g/day)	84.29±1.94	92.37±2.38	0.009
Carbohydrates (g/day)	354.12±8.14	368.87±9.39	0.236
Fat (g/day)	106.73±3.35	81.66±2.43	<0.001
Cholesterol (mg/day)	265.62±11.99	272.11±12.62	0.709
fiber (g/day)	36.91±1.05	44.55±1.53	<0.001
Saturate fatty acid (g/day)	32.60±1.12	27.27±1.02	<0.001
MUFA (g/day)	37.34±1.22	28.09±0.98	<0.001
PUFA (g/day)	23.40±0.85	18.01±0.70	<0.001
Thiamin (mg/day)	2.15±0.05	2.42±0.07	0.003
Riboflavin (mg/day)	2.16±0.06	2.451±0.08	0.067
Niacin (mg/day)	24.80±0.59	26.34±0.80	0.126
Pantothenic acid (mg/day)	5.47±0.12	6.94±0.20	<0.001
Pyridoxine (mg/day)	1.63±0.03	2.20±0.06	<0.001
Total folate (μg/day)	538.04±11.16	621.06±18.35	<0.001
Cobalamin (μg/day)	5.92±0.31	4.66±0.28	0.003
Vitamin C (mg/day)	101.01±6.15	181.19±10.97	<0.001
Vitamin D (μg/day)	2.58±0.15	2.58±0.17	0.984
Vitamin K (μg/day)	156.41±12.49	233.57±16.35	<0.001
Vitamin E (mg/day)	15.77±0.44	13.05±0.46	<0.001
Vitamin A (RAE/day)	698.24±30.90	797.72±47.93	0.082
Potassium (mg/day)	3317.24±85.57	4382.70±146.46	<0.001
Phosphorus (mg/day)	1547.69±37.11	1887.33±59.49	<0.001
Magnesium (mg/day)	409.77±10.43	542.68±18.98	<0.001
Calcium (mg/day)	1048.24±30.58	1282.59±45.15	<0.001
Zinc (mg/day)	12.21±0.28	14.84±0.49	<0.001
Manganese (mg/day)	6.71±0.20	8.71±0.36	<0.001
Iron (mg/day)	18.71±0.44	21.16±0.70	0.090
Copper (mg/day)	1.97±0.05	2.24±0.08	0.127
Whole grain (g/day)	146.92±8.34	249.91±20.05	<0.001
Refined grain (g/day)	316.76±12.49	271.50±13.29	0.015
Fruit (g/day)	208.57±17.65	487.29±33.16	<0.001
Vegetables (g/day)	206.44±15.08	365.17±17.55	<0.001
Dairy products (g/day)	348.64±17.88	474.59±27.69	<0.001
Meat and processed products (g/day)	76.82±3.62	80.76±5.45	0.547
Fish (g/day)	5.25±0.62	10.22±1.01	<0.001
Nuts and seeds (g/day)	50.11±2.97	91.17±5.33	<0.001
Coffee and tea (g/day)	498.96±23.47	379.56±25.16	<0.001
Sweetened beverages (g/day)	118.91±9.73	26.30±3.85	<0.001
Salt (g/day)	2.70±0.15	2.09±0.12	0.002

[a]Resulted from independent *t*-test; [b]Quantitative variables=Mean±SEM. *P*<0.05 was considered significant. MUFA=Monounsaturated fatty acid; PUFA=Polyunsaturated fatty acid; RAE=Retinol activity; SEM=Standard error of mean

potassium, phosphorus, magnesium, calcium, zinc, manganese, whole grains, fruits, vegetables, dairy products, fish, and nuts and seeds (all $P < 0.001$, except protein). Conversely, the case group had significantly higher intakes of total fat, saturated fatty acid (SFA), MUFA, PUFA, Vitamin B12 ($P = 0.003$), Vitamin E, refined grains ($P = 0.015$), coffee and tea, sweetened beverages, and salt ($P = 0.002$) (all $P < 0.001$, unless otherwise noted). No significant differences were observed for energy intake ($P = 0.151$), carbohydrates ($P = 0.236$), cholesterol ($P = 0.709$), Vitamin B2 ($P = 0.067$), Vitamin B3 ($P = 0.126$), Vitamin D ($P = 0.984$), Vitamin A ($P = 0.082$), copper ($P = 0.127$), iron ($P = 0.090$), and meat and processed products ($P = 0.547$) ($P > 0.05$).

Demographic characteristics, nutrient intake, and food group consumption across refined grain consumption tertiles in two groups

Table 3 shows demographic characteristics, nutrient intake, and food group consumption across refined grain consumption tertiles in two groups. Based on this table, there were no significant differences ($P > 0.05$) in age, physical activity, age at first pregnancy, duration of breastfeeding, time of last meal, duration of oral

Table 3: Demographic characteristics, nutrient intake, an.d food group consumption across refined grain consumption tertiles in two groups

Variables	Case - Teritile of refined grain consumption			P[a]	Control - Teritile of refined grain consumption			P[a]
	T1 (*n*=42) (<199.40 g/day)	T2 (*n*=65) (41.199–336.12 g/day)	T3 (*n*=71) (>336.13 g/day)		T1 (*n*=77) (<199.40 g/day)	T2 (*n*=54) (41.199–336.12 g/day)	T3 (*n*=47) (>336.13 g/day)	
Age (years)	56.76±0.86	55.15±0.76	55.37±0.83	0.411	55.29±0.66	55.41±0.81	55.23±0.82	0.988
BMI (kg/m^2)	27.24±0.60	28.49±0.43	30.78±0.54	<0.001	27.09±0.36	27.56±0.50	28.07±0.53	0.321
PA (MET-hour-week)	1485.79±128.25	1479.71±94.89	1580.20±111.84	0.755	2127.45±122.12	2104.56±165.10	2112.77±157.99	0.993
Energy intake (kcal/day)	2279.28±122.12	2556.24±104.53	3176.00±91.61	<0.001	2377.58±97.12	2580.94±116.88	3002.33±116.97	<0.001
Age of first pregnancy	21.36±0.77	20.78±0.49	21.27±0.57	0.764	20.91±0.50	19.87±0.50	20.55±0.48	0.332
Number of pregnancies	2.81±0.21	3.02±0.16	3.14±0.16	0.443	2.99±0.12	3.26±0.14	3.34±0.20	0.209
Lactation period	28.26±4.28	28.03±2.58	32.31±3.07	0.540	36.05±3.52	33.56±4.09	33.17±4.49	0.845
Last time to take OCP	4.67±1.28	4.89±1.00	3.27±0.76	0.407	3.19±0.75	6.44±1.32	2.96±0.95	0.030
Duration of taking OCP	13.67±4.44	15.82±3.61	13.82±3.08	0.894	12.48±3.16	21.89±4.44	10.81±3.36	0.090
Education								
Undergraduate	32 (76.2)	58 (89.2)	60 (84.5)	0.323	58 (75.3)	37 (68.5)	38 (80.9)	0.444
Graduate	9 (21.4)	6 (9.2)	11 (15.5)		19 (24.7)	16 (29.6)	8 (17)	
Postgraduate	1 (2.4)	1 (1.5)	0		0	1 (1.9)	1 (2.1)	
Marital status								
Single	2 (4.8)	5 (7.7)	6 (8.5)	0.758	5 (6.5)	2 (3.7)	3 (6.4)	0.765
Married	40 (95.2)	60 (92.3)	65 (9.5)		72 (93.5)	52 (96.3)	44 (93.6)	
History of twining								
Yes	2 (4.8)	2 (3.1)	3 (4.2)	0.896	0	2 (3.7)	1 (2.1)	0.259
No	40 (95.2)	63 (96.9)	68 (95.8)		77 (100)	52 (96.3)	46 (97.9)	
Breast-feeding								
Yes	39 (92.9)	61 (93.8)	62 (87.3)	0.369	67 (87)	45 (83.3)	41 (87.2)	0.802
No	3 (7.1)	4 (6.2)	9 (12.7)		10 (13)	9 (16.7)	6 (12.8)	
OCP								
Yes	12 (28.6)	25 (38.5)	24 (33.8)	0.571	19 (24.7)	23 (42.6)	15 (31.9)	0.096
No	30 (71.4)	40 (61.5)	47 (66.2)		58 (75.3)	31 (57.4)	32 (68.1)	
Total protein (g/day)	74.22±3.72	81.36±2.93	92.94±3.14	<0.001	90.79±3.89	90.53±4.26	97.08±4.12	0.498
Total carbohydrates (g/day)	298.68±18.06	335.31±12.87	404.13±10.13	<0.001	337.55±14.47	371.41±16.92	417.26±15.92	0.002
Total fat (g/day)	89.67±5.94	104.86±5.77	118.52±5.17	0.003	77.93±3.46	77.80±4.02	92.19±5.39	0.034
Total cholesterol (mg/day)	247.63±26.68	242.80±19.08	297.15±18.35	0.099	293.91±23.78	240.46±16.30	272.78±19.89	0.203
Total fiber (g/day)	39.22±2.38	36.89±1.83	34.71±1.49	0.256	44.63±2.66	39.83±2.09	49.85±2.88	0.343
Saturate fatty acid (g/day)	28.73±2.32	29.54±1.70	37.70±1.74	<0.001	26.34±1.63	25.73±1.67	30.55±2.01	0.154
MUFA (g/day)	31.48±2.27	35.75±2.11	42.27±1.82	0.002	26.85±1.50	26.61±1.47	31.83±2.18	0.075
PUFA (g/day)	19.04±1.54	23.12±1.50	26.23±1.27	0.005	16.74±1.01	16.73±1.01	21.56±1.68	0.010
Thiamin (mg/day)	1.67±0.10	2.01±0.07	2.55±0.06	<0.001	2.11±0.12	2.46±0.12	2.87±0.10	<0.001
Riboflavin (mg/day)	1.94±0.12	2.00±0.09	2.44±0.08	<0.001	2.45±0.13	2.28±0.13	2.64±0.15	0.026
Niacin (mg/day)	19.50±1.07	23.29±0.82	29.32±0.85	<0.001	23.52±1.31	26.75±1.37	30.47±1.24	0.002
Pantothenic acid (mg/day)	4.95±0.28	5.15±0.19	6.07±0.17	<0.001	6.73±0.33	6.75±0.33	7.49±0.36	0.261
pyridoxine (mg/day)	1.60±0.09	1.53±0.05	1.73±0.06	0.69	2.06±0.10	2.22±0.10	2.41±0.11	0.094
Total folate (μg/day)	441.29±21.59	498.17±16.00	631.76±13.73	<0.001	533.51±30.77	621.68±25.55	763.75±27.67	<0.001
Cobalamin (μg/day)	4.17±0.40	5.50±0.51	7.32±0.52	<0.001	4.88±0.56	4.02±0.27	5.02±0.43	0.324
Vitamin C (mg/day)	125.19±15.64	90.46±8.78	96.38±9.15	0.84	182.22±17.92	177.17±18.44	184.11±20.82	0.969
Vitamin D (μg/day)	2.06±0.34	2.42±0.25	3.03±0.21	0.038	2.88±0.30	2.12±0.26	2.64±0.35	0.202
Vitamin K (μg/day)	255.48±39.63	128.18±15.56	123.65±11.57	<0.001	248.82±28.68	205.73±25.45	240.55±28.01	0.524
Vitamin E (mg/day)	13.85±0.88	16.04±0.75	16.65±0.69	0.48	12.11±0.67	12.47±0.68	15.26±1.03	0.015
Vitamin A (RAE/day)	707.31±65.98	622.01±49.99	762.67±48.13	0.137	883.29±92.01	687.89±60.34	783.73±72.02	0.225
Potassium (mg/day)	3357.20±195.97	3092.25±121.78	3499.58±139.83	0.111	4392.25±249.62	4245.82±228.41	4524.33±271.96	0.775
Phosphorus (mg/day)	1432.00±81.48	1462.79±57.32	1693.85±56.26	0.005	1857.83±99.69	1862.63±103.90	1964.03±101.06	0.744
Magnesium (mg/day)	417.90±27.97	390.72±123.12	422.40±124.92	0.380	547.07±33.23	541.62±32.11	536.72±29.98	0.976
Calcium (mg/day)	970.56±69.42	955.79±45.25	1178.83±46.27	0.002	1253.9±67.97	1198.19±75.86	1426.57±94.49	0.141
Zinc (mg/day)	11.17±0.66	11.66±0.43	13.32±0.42	0.005	14.53±0.86	14.58±0.80	15.64±0.79	0.624
Manganese (mg/day)	6.61±0.51	6.76±0.34	6.72±0.28	0.958	8.41±0.62	9.30±0.67	8.52±0.53	0.573

Contd...

Table 3: Contd...

Variables	Case - Teritile of refined grain consumption			P[a]	Control - Teritile of refined grain consumption			P[a]
	T1 (*n*=42) (<199.40 g/day)	T2 (*n*=65) (41.199–336.12 g/day)	T3 (*n*=71) (>336.13 g/day)		T1 (*n*=77) (<199.40 g/day)	T2 (*n*=54) (41.199–336.12 g/day)	T3 (*n*=47) (>336.13 g/day)	
Iron (mg/day)	16.00±0.99	17.38±0.66	21.53±0.56	<0.001	19.51±1.20	21.22±1.15	23.79±1.14	0.048
Copper (mg/day)	1.72±0.10	1.82±0.83	2.26±0.06	<0.001	2.15±0.15	2.16±0.12	2.46±0.13	0.275
Whole grain (g/day)	165.51±20.00	158.25±13.61	125.56±11.67	0.107	289.64±37.49	274.85±33.06	156.17±18.64	0.018
Fruit (g/day)	278.71±46.29	191.75±22.70	182.48±27.25	0.085	510.21±56.88	480.51±58.46	457.55±51.79	0.808
Vegetables (g/day)	310.48±33.99	194.40±24.83	155.91±19.92	<0.001	363.76±29.41	343.84±24.58	391.96±36.34	0.589
Dairy products (g/day)	328.48±42.62	322.87±27.01	384.17±27.51	0.270	490.42±40.14	418.65±47.51	512.92±60.91	0.392
Meat and processed products (g/day)	62.58±5.99	71.38±5.30	90.22±6.51	0.006	82.84±11.28	74.18±5.24	84.93±7.20	0.722
Fish (g/day)	7.02±1.36	3.88±0.87	5.47±1.08	0.161	11.48±1.71	10.01±2.02	8.41±1.21	0.470
Nuts and seeds (g/day)	61.40±7.60	46.49±4.42	46.74±4.26	0.107	97.78±9.24	79.25±6.67	94.04±10.89	0.326
Coffee and tea (g/day)	526.88±53.59	508.19±39.63	473.99±34.14	0.659	352.74±37.41	360.66±45.01	445.20±51.28	0.294
Sweetened beverages (g/day)	63.49±14.76	121.18±17.10	149.62±15.50	0.003	18.78±4.48	21.37±5.10	44.29±10.86	0.018
Salt (g/day)	2.71±0.35	2.61±0.24	2.79±0.23	0.880	2.07±0.19	1.87±0.20	2.35±0.27	0.367

[a]All quantitative variables resulted from ANOVA, and all qualitative variables resulted from the chi-square test. Quantitative variables: mean ± SEM; qualitative variables: frequency (percentage). P-value < 0.05 was considered significant. OCP=Oral Contraceptive Pills, BMI=Body mass index, PA=physical activity, METs=Metabolic Equivalents, Kcal=Kilo calorie, gr=Gram, mg=Milligram, µg=Microgram, MUFA=Monounsaturated fatty acid, PUFA=Polyunsaturated fatty acid, RAE: Retinol activity

contraceptive use, education level, marital status, history of twins, breastfeeding, use of oral contraceptives, cholesterol, fiber, Vitamin B6, Vitamin C, Vitamin E, Vitamin A, potassium, magnesium, whole grains, fruits, dairy, fish, nuts and seeds, coffee and tea, and salt intake across refined grain consumption tertiles in the case group. However, there were significant differences ($P < 0.05$) between the consumption tertiles of refined grains regarding the variables such as BMI, energy intake, protein, carbohydrates, total fat, SFA, MUFA, PUFA, B1, B2, B3, B5, B9, B12, Vitamin D, Vitamin K, phosphorus, calcium, zinc, iron, copper, vegetable intake, meat and processed products, and sweetened beverages. In the control group, there were no significant differences ($P > 0.05$) in variables such as age, BMI, physical activity, age at first pregnancy, number of pregnancies, duration of breastfeeding, duration of oral contraceptive use, education level, marital status, history of twins, breastfeeding, oral contraceptive use, protein, cholesterol, fiber, MUFA, Vitamin B2, B5, B6, B12, C, D, K, A, potassium, phosphorus, magnesium, calcium, zinc, manganese, copper, fruit, vegetable, dairy, meat and processed products, fish, nuts and seeds, coffee, tea, and salt teritile of refined grain consumption. However, there were significant differences ($P < 0.05$) between the groups in terms of energy intake, time since last oral contraceptive use, carbohydrates, total fat, PUFA, Vitamins B1, B3, B9, E, iron, whole grains, and sugar-sweetened beverages.

Odds ratio of osteoporosis

Table 4 shows the ORs and 95% CI for the association between refined grain consumption and osteoporosis after adjusting for multiple variables. In the crude model, we found that the risk of osteoporosis increased with higher refined grain consumption (OR = 2.77; 95% CI: 1.63–4.68, $P = 0.001$). After adjusting for the effect of confounding variables (BMI, physical activity, and energy intake) in Model 1, we found that higher refined grain consumption (OR = 2.16; 95% CI: 1.18–3.93, $P = 0.012$) was found to increase the risk of having osteoporosis. However, in Model 2, after further adjusting the effect of confounding variables (fruits, vegetables, dairy products, meat and processed products, fish, nuts and seeds, coffee and tea, sweetened beverages, and salt), no significant relationship was observed (OR = 1.07; 95% CI: 0.50–2.28, $P = 0.857$). After adjusting for the potential confounding variables (Vitamins [K, E, C, and folic acid], and calcium) in Model 3, we found that the risk of developing osteoporosis increased with higher consumption of refined grains (OR = 3.26; 95% CI: 1.16–9.17, $P = 0.025$; Nagelkerke $R^2 = 0.610$).

DISCUSSION

This case–control study investigated the relationship between the consumption of refined grains and osteoporosis in Iranian postmenopausal women. Previous studies showed that refined grain consumption is associated with an increased risk of stomach cancer,[24] dyslipidemia, insulin resistance, arterial hypertension, and increased abdominal fat level. Considering the role of diet in preventing osteoporosis[25] and also regarding the relationship seen between the consumption of refined grains and chronic diseases, it seems that the consumption of refined grains can be related to the risk of osteoporosis.

After adjusting for the effect of confounding variables (food groups) in Model 2, a relationship was observed, but

Table 4: Crude and multivariable-adjusted odds ratio and 95% confidence interval for the association of refined grain consumption and osteoporosis

	Tertile of refined grain consumption					
	T1 (low) (*n*=119) (<199.40 g/day)		T2 (*n*=119) (199.41–336.12 g/day)		T3 (high) (*n*=118) (>336.13 g/day)	
	OR (CI)[a]	*P*	OR (CI)[a]	*P*	OR (CI)[a]	*P*
Crude model	1.00	<0.001	2.20 (1.31–3.71)	0.003	2.77 (1.63–4.68)	<0.001
Model 1	1.00	0.010	1.96 (1.12–3.42)	0.017	2.16 (1.18–3.93)	0.012
Model 2	1.00	0.871	1.19 (0.60–2.35)	0.604	1.07 (0.50–2.28)	0.857
Model 3	1.00	0.072	2.06 (0.92–4.64)	0.078	3.26 (1.16–9.17)	0.025

[a]Based on logistic regression, values were shown presented as OR with 95% CI. Model 1: Adjusted for BMI, PA, and energy intake, Model 2: Adjusted for BMI, PA, energy intake, and the intake of food groups (fruits, vegetables, dairy products, meat and processed products, fish, nuts and seeds, coffee and tea, sweetened beverages, and salt), Model 3: Adjusted for BMI, PA, energy intake, the intake of food groups (fruits, vegetables, dairy products, meat and processed products, fish, nuts and seeds, coffee and tea, sweetened beverages, and salt), Vitamins (K, E, C, and folic acid), and calcium. *P*<0.05 was considered significant. OR=Odds ratio; CI=Confidence interval; BMI=Body mass index; PA=Physical activity

it was not statistically significant. And as far as we know, there are no similar studies to examine the results. However, Melaku showed that the western pattern (high levels of white bread) had a positive association with low BMD.[26] Besides, Shin and Joung reported a negative association between white rice consumption and bone health in Korean postmenopausal women. Their study included 3735 Korean postmenopausal women with a mean age of 64.1 years and a mean BMI of 24.1,[27] and Park *et al*. showed traditional dietary patterns (high in rice) associated with a greater risk for osteoporosis in postmenopausal women, and their study included 1725 postmenopausal Korean women aged 40–69, and the BMI average was 25 kg/m^2.[28] Our study is in the same direction as the mentioned studies; however, the lack of statistical significance in our analysis may be because of the differences in race, culture, intake of refined grains, food group consumption, whole flour refinement level, and the variety of refined grains.

After adjusting for confounding variables in the final model, a significant association between refined grain consumption and osteoporosis was observed. Refined grains are the main source of calories in the Iranian diet, which generally have a high glycemic index.[16] García-Gavilán *et al*. reported that a high glycemic index was associated with a higher risk of osteoporosis-related fractures in an elderly Mediterranean population.[29] Buyken *et al*. reported that there is a relationship between the glycemic index of the diet and inflammation.[30] Further studies showed that the high consumption of foods with a high glycemic index increases inflammatory markers, increases the activation of Nuclear Factor-kB (NF-κB) in mononuclear cells,[31] increasing the levels of high-sensitivity C-reactive protein, increasing levels of interleukin-6 (IL-6), IL-7, IL-18 and also causing an increase in free radicals.[32] Abu-Amer reported that NF-κB activity is central to inflammatory responses and is considered a potent mediator of inflammatory osteolysis.[33] Ni *et al*. showed that formononetin (a phytoestrogen belonging to the isoflavone family) caused fewer osteoclast cells to form by inhibiting NF-κB activity, as well as by inhibiting the phosphorylation of ERK and JNK proteins, which are part of the signaling MAPK pathway, and reduce the inflammatory response. These effects protect the knee bone against injury.[34] Therefore, inflammation can be an important risk factor in the development of the disease, and targeted anti-inflammatory therapy may have a potential role in preventing bone loss.

Studies show that the consumption of refined grains causes an increase in serum triglycerides, abdominal obesity, and a decrease in serum HDL.[35,36] Kan *et al*. reported that higher cholesterol and triglyceride levels were associated with a higher risk of osteoporosis.[17] Furthermore, Toru Yamaguchi *et al*. stated that high levels of LDL-C and low HDL-C are associated with decreased bone mass.[37] It is worthmentioning that Zhang *et al*. also reported that low HDL levels may be associated with osteoporosis in postmenopausal women.[18] Chen *et al*., in their meta-analysis study, stated that serum cholesterol levels are higher in postmenopausal patients with osteoporosis.[38] Cholesterol can bind to a protein called smoothened and activate the Hedgehog signaling pathway. This signaling pathway inhibits the differentiation of osteoblasts and thus leads to reduced bone formation.

On the other hand, oxidized lipids can also directly bind to other receptors on osteoclasts. Connect to EP2/DP. This connection activates the cAMP/PKA signaling pathway and leads to increased differentiation and activity of osteoclasts. As a result, bone destruction increases.[39]

As mentioned, refined grains, unlike whole grains, their bran and germ are removed during processing. This not only deprives them of nutrients such as B vitamins, iron, and dietary fiber, but also of phytochemicals that have antioxidant properties.[15] These antioxidants are very important in neutralizing free radicals and preventing oxidative stress, which can lead to chronic diseases.[40] Zhou *et al*. also stated that oxidative stress plays an essential role in the initiation and progression of postmenopausal osteoporosis.[41] In order to explain the possible mechanism of the effect of oxidative stress on

osteoporosis, Iantomasi *et al*. stated that oxidative stress stimulates bone resorption by increasing the activity of osteoclasts and decreasing the activity of osteoblasts. This imbalance is caused by reactive oxygen species and inflammatory pathways that are triggered by molecular signals such as MAPK. Thus, the microRNAs regulated lead to osteoporosis.[42]

Strengths and limitations

To our knowledge, this is the first case–control study in our country examining the link between refined grain consumption and osteoporosis. To reduce the information bias, we used validated FFQ to accurately capture long-term dietary habits and MET questionnaires for data collection. In addition, we employed an age-matching method to mitigate the confounding effects of age.

This study has some limitations. The FFQ method relies on memory, which may introduce the reporting errors. The convenience sampling method could limit external validity. In addition, differences in food culture, food availability, and cooking methods across countries may introduce the potential errors. These limitations should be considered when interpreting the findings**.**

CONCLUSIONS

The findings of this study showed that there is a significant relationship between the consumption of refined grains and osteoporosis in postmenopausal Iranian women. Consequently, given the observed possible association, it is advisable to decrease refined grain consumption in the diets of postmenopausal women. Extensive prospective studies are required to confirm this relationship, particularly to assess the causal link in this area; thus, randomized clinical trials are essential.

List of abbreviations

PBM: Peak bone mass; FFQ: Food Frequency Questionnaire; BMI: Body Mass Index; DXA: Dual-energy X-ray absorptiometry; Met: Metabolic Equivalent; BMD: Bone mineral density; SFA: Saturated Fatty Acid; IGF-I: Insulin-like growth factor I; MUFA: Monounsaturated fatty acids; PUFA: Polyunsaturated fatty acids; MAPK: Mitogen-Activated Protein Kinase; cAMP: Cyclic adenosine monophosphate; PKA: Protein kinase A; ERK: Extracellular signal-Regulated Kinase; JNK: C-Jun N-terminal Kinase.

Ethics approval and consent to participate

The Biomedical Research Ethics Committee of Islamic Azad University-Science and Research Branch in Tehran, Iran, approved the research.(IR.IAU.SRB.REC.1402.259). All participants signed a written informed consent form approved by the Ethics Committee.

Consent for publication

Not applicable.

Availability of data and materials

Data are available from the authors upon reasonable request and with the permission of correspondence.

Author's contributions

MMH contributed to writing and original draft preparation and agreed to be accountable for all aspects of the work. MY participated in data analysis and agreed to be accountable for all aspects of the work. BA contributed to conceptualization, review, and editing, and agreed to be accountable for all aspects of the work and the approval of the final version of the manuscript.

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Conflicts of interest

There are no conflicts of interest.

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