



Article

Association Study between Antioxidant Nutrient Intake and Low Bone Mineral Density with Oxidative Stress-Single Nucleotide Variants: *GPX1* (rs1050450 and rs17650792), *SOD2* (rs4880) and *CAT* (rs769217) in Mexican Women

Rogelio F. Jiménez-Ortega ^{1,†} , Diana I. Aparicio-Bautista ^{1,†} , Adriana Becerra-Cervera ^{1,2}, Priscilla López-Montoya ¹ , Guadalupe León-Reyes ¹, Jeny Flores-Morales ¹, Manuel Castillejos-López ³, Alberto Hidalgo-Bravo ⁴, Jorge Salmerón ⁵, Berenice Rivera-Paredes ⁵ and Rafael Velázquez-Cruz ^{1,*}

- ¹ Laboratorio de Genómica del Metabolismo Óseo, Instituto Nacional de Medicina Genómica (INMEGEN), Mexico City 14610, Mexico; rogeliofrank.jimenez@uneve.edu.mx (R.F.J.-O.); daparicio@inmegen.gob.mx (D.I.A.-B.); abecerra@inmegen.edu.mx (A.B.-C.); priscilla_lopez92@comunidad.unam.mx (P.L.-M.); greyes@inmegen.gob.mx (G.L.-R.); jfloresm@inmegen.gob.mx (J.F.-M.)
 - ² Consejo Nacional de Humanidades, Ciencias y Tecnologías (CONAHCYT), Mexico City 03940, Mexico
 - ³ Unidad de Epidemiología Hospitalaria e Infectología, Instituto Nacional de Enfermedades Respiratorias Ismael Cosío Villegas (INER), Mexico City 14080, Mexico; manuel.castillejos@iner.gob.mx
 - ⁴ Departamento de Medicina Genómica, Instituto Nacional de Rehabilitación (INR), Mexico City 14389, Mexico; ahidalgo@inr.gob.mx
 - ⁵ Centro de Investigación en Políticas, Población y Salud, Facultad de Medicina, Universidad Nacional Autónoma de México, Mexico City 04510, Mexico; drjorgesalmeron@unam.mx (J.S.); bereriverap@comunidad.unam.mx (B.R.-P.)
- * Correspondence: rvelazquez@inmegen.gob.mx; Tel.: +52-55-5350-1900 (ext. 1233)
† These authors contributed equally to this work.



Citation: Jiménez-Ortega, R.F.; Aparicio-Bautista, D.I.; Becerra-Cervera, A.; López-Montoya, P.; León-Reyes, G.; Flores-Morales, J.; Castillejos-López, M.; Hidalgo-Bravo, A.; Salmerón, J.; Rivera-Paredes, B.; et al. Association Study between Antioxidant Nutrient Intake and Low Bone Mineral Density with Oxidative Stress-Single Nucleotide Variants: *GPX1* (rs1050450 and rs17650792), *SOD2* (rs4880) and *CAT* (rs769217) in Mexican Women. *Antioxidants* **2023**, *12*, 2089. <https://doi.org/10.3390/antiox12122089>

Academic Editor: Soliman Khatib

Received: 1 November 2023

Revised: 29 November 2023

Accepted: 6 December 2023

Published: 8 December 2023



Copyright: © 2023 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

Abstract: Oxidative stress is essential in developing multiple bone metabolism diseases, including osteoporosis. Single-nucleotide variants (SNVs) have been associated with oxidative stress, promoting an imbalance between the production of reactive oxygen species and the ability to neutralize them, and it has been reported that antioxidant nutrient intake can influence bone mineral density (BMD). This work reports the association between oxidative stress-related SNVs (*GPX1*-rs1050450, rs17650792, *SOD2*-rs4880, and *CAT*-rs769217), BMD, and antioxidant nutrient intake. The study included 1269 Mexican women from the Health Workers Cohort Study. Genotyping was performed using predesigned TaqMan assays. Dietary data were collected using a 116-item semi-quantitative food frequency questionnaire. A dietary antioxidant quality score (DAQS) was used to estimate antioxidant–nutrient intake. Association analysis was estimated via linear, logistic, or quantile regression models. The results showed an association of the rs1050450-A and rs17650792-A alleles with femoral neck BMD ($p = 0.038$ and $p = 0.017$, respectively) and the SNV rs4880-A allele with total hip BMD ($p = 0.026$) in respondents aged 45 years or older. In addition, antioxidant–nutrient intake was associated with the rs4880-GG genotype, being significant for fiber ($p = 0.007$), riboflavin ($p = 0.005$), vitamin B6 ($p = 0.034$), and vitamin D ($p = 0.002$). The study showed an association between oxidative stress-related SNVs, BMD, and antioxidant–nutrient intake in Mexican women. Therefore, treatments for low BMD could be developed based on antioxidant supplementation.

Keywords: bone mineral density; postmenopausal women; oxidative stress; SNVs; antioxidants intake

1. Introduction

Most organisms, including humans, live in an aerobic environment and are exposed to various oxidizing agents that are intentionally produced as by-products of metabolism. It

has been reported that inflammation and oxidative stress affect vital biochemical reactions, generating reactive oxygen species (ROS) and impairing the cell's antioxidant defense mechanisms. These events contribute to the development of different metabolic disorders such as type 2 diabetes (T2D), obesity, cardiovascular diseases, dyslipidemias, hypertension, and bone metabolism diseases such as osteoporosis (OP) [1,2]. The relationship between T2D and BMD variation is complex. In recent years, it has been reported that T2D affects the metabolism of carbohydrates, fatty acids, and proteins, causing deregulation of calcium, phosphorus, and magnesium, contributing to development of bone metabolism disorders, including osteoporosis [3].

OP is described as a microstructural degeneration of bone tissue and decreased bone mass, resulting in increased bone fragility and fracture susceptibility [4]. There is an increased incidence of osteoporotic fractures at all ages; however, when women reach menopause, they have twice the risk of fractures compared to men due to estrogen deficiency, which causes an increase in bone turnover [5]. OP is a multifactorial and complex disease determined by genetic and environmental factors. In recent years, it has been proposed that oxidative stress (OS) may contribute to the development of OP. In vitro and animal model studies have shown that OS may induce bone loss by regulating the activation of cells responsible for bone remodeling [6–9]. Antioxidant defense mechanisms protect cells from free radical damage. These systems include enzymes, such as superoxide dismutase (SOD), glutathione reductase (GR), glutathione peroxidase (GPX), and catalase (CAT); and minerals, such as selenium (Se) and zinc (Zn); in addition to non-enzymatic antioxidants or nutrient-derived antioxidants, such as vitamins A, C, and E [10].

Epidemiological studies have reported an inverse association between intake of antioxidant vitamins and carotenoids with low BMD, fracture risk, and OP [11–13]. Numerous factors can alter the efficacy of antioxidant enzymes, such as single-nucleotide variants (SNVs) in genes encoding redox enzymes. Variants in *CAT* (rs769217), *SOD2* (rs4880), and *GPX1* (rs1050450 and rs17650792) genes have been associated with defense against oxidative stress [14].

Recent studies have demonstrated the association between genetic variants in antioxidant genes with oxidative stress in different types of cancer. Nikic et al. (2023) demonstrated that there is an association between SNVs in *GPX1* (rs1050450) and *SOD2* (rs4880), with the risk of developing urogenital bladder cancer, independently and in combination with smoking. Additionally, rs1050450 is associated with the aggressiveness of the disease [15]. In another study, Djokic et al. (2022) analyzed the association of SNVs in the antioxidant genes *GPX1* (rs1050450) and *SOD2* (rs4880) and the transcription factor *Nrf2* (rs6721961) with the risk of prostate cancer in the Serbian population. Furthermore, they propose that these SNVs could be used as risk biomarkers for the evolution of prostate cancer [16]. Despite the importance of these antioxidant mechanisms, there is a lack of studies investigating the relationship between antioxidant nutrient intake and bone mineral density (BMD) status. This study aims to analyze the relationship between SNVs in oxidative stress-related genes with the variation of BMD and antioxidant nutrient intake in a population of Mexican women. Additionally, we evaluated the role of SNVs in oxidative stress-related genes associated with metabolic traits, such as glucose levels and diabetes status.

2. Materials and Methods

2.1. Study Population

The population sample consisted of a total of 1269 unrelated women over 18 years of age who were recruited from the second wave (2010–2012) of the “Health Worker Cohort Study (HWCS)” by the Mexican Social Security Institute (IMSS) in the city of Cuernavaca, Morelos (central Mexico); this is a long-term study focused on lifestyle and factors leading to the development of chronic diseases. Women born in Mexico whose parents and grandparents identified themselves as mestizo-Mexican were included in this study [17].

2.2. Bone Mineral Density Measurement (Assessment)

BMD was assessed at the total hip (TH), femoral neck (FN), and lumbar spine (LS) L2-L4 body sites via dual-energy X-ray absorptiometry (DXA) on a Lunar DPX NT (Lunar Radiation Corp., Madison, WI, USA). Measurements are expressed in grams per square centimeter (cm²). BMD data were analyzed according to T-score, using the criteria defined by the World Health Organization (WHO) [18]. Low BMD at any skeletal site (osteopenia/osteoporosis) was defined as T-score ≤ -1.0 . The normal group (N) included women with T-scores above -1.0 .

2.3. Anthropometric and Clinical Evaluation

A venous blood sample was taken from each patient after eight hours of fasting, and each sample was separated via centrifugation to recover blood serum, which was used for biochemical assay. T2D was determined if the participants presented at least one of the following three criteria: (1) self-report T2D diagnosed by a physician, (2) use of hypoglycemic medication, and (3) fasting glucose ≥ 126 mg/dL [19]. Blood glucose was measured via an enzymatic method on a Selecta XL (Randco Laboratories Ltd., Antrim, UK) according to the manufacturer's instructions and processed at the IMSS laboratory in Cuernavaca, Morelos, following standardized procedures according to the guidelines of the International Federation of Clinical Chemistry and Laboratory Medicine [20]. An age of 45 years or more was used as a proxy indicator of menopausal status, as seen in previous studies [21–23].

2.4. DNA Extraction and Genotyping Analysis

Peripheral blood was collected from each participant in EDTA tubes stored at -20 °C until genomic DNA extraction. Total DNA was extracted using a commercial isolation kit (QIAGEN system Inc., Valencia, CA, USA) according to the manufacturer's instructions. Genotyping was performed according to TaqMan[®] SNP Genotyping Assays user guide shown in: https://assets.thermofisher.com/TFS-Assets/LSG/manuals/cms_040597.pdf (accessed on 15 August 2023), using the following predesigned TaqMan probes (Applied Biosystems, Massachusetts, MA, USA, EE.UU.): rs769217 (C__3102907_10) in the CAT gene, rs4880 (C__8709053_10) in SOD2, and rs1050450 and rs17650792 (C_175686987_10 and C__7911963_10, respectively) in GPX1 [14]. Real-time PCR was performed on a Quant Studio 7 Flex (Applied Biosystems, Massachusetts, MA, USA, EE.UU.). Data were analyzed using Sequence Detection System (SDS) software, version 2.2.1.

2.5. Dietary Assessment

Dietary intake information was evaluated using a 116-item semi-quantitative food frequency questionnaire (FFQ); its validity and reliability have been previously reported [23,24]. The data were collected from a self-administered questionnaire, and the reported frequency for each food item was converted to a daily intake. Food composition tables, compiled by the National Institute of Public Health, were used to determine the nutrient compositions of all foods and the diet parameters were adjusted for energy using the residual method [25,26].

A dietary antioxidant quality score (DAQS) was used to calculate antioxidant–nutrient intake. These scores refer to the intake of certain vitamins and minerals that have been proven to act as dietary antioxidants, including selenium, zinc, magnesium, vitamin A, vitamin C, and vitamin E. Both indices were created following the methodology published previously [27]. We compared the daily nutrient intake of participants with the recommended daily intake guidelines specifically for the DAQS [28].

2.6. Statistical Analysis

Data are presented as median and percentile 25–75 for continuous variables and percentages for categorical variables. All variables were examined for normality. The chi-square test was used to evaluate Hardy–Weinberg equilibrium (HWE) for each SNV. To

explore the associations of interest, we estimated linear regression or quantile regression models as appropriate. For biochemical variables such as glucose and lipids, we performed a logarithmic transformation. For binary variables, we estimated logistic regression models. The models were adjusted for age, body mass index (BMI), smoking status, and physical activity. The dietary parameters were adjusted for total energy intake using the residual method. All statistical assessments were two-sided and considered significant when the p -value was ≤ 0.05 .

3. Results

3.1. Population Characteristics

The characteristics of the participants are shown in Supplementary Table S1. Our study population comprised 1269 women with a median age of 53 years (P25–P75: 42–62); most of them were women aged ≥ 45 years old (70.3%) ($p < 0.001$). The median BMI in the total women was 26.7 (23.9–30.0) kg/m²; more than half of them (75.3%) had overweight/obesity. We observed statistically significant differences by age group. Women ≥ 45 years old had a higher median BMI ($p < 0.001$), a higher prevalence of overweight/obesity ($p = 0.0001$)/($p = 0.001$), a higher prevalence of diabetes ($p < 0.001$), elevated levels of triglycerides ($p < 0.001$), LDL ($p < 0.001$), and cholesterol ($p < 0.001$), lower BMD at different body sites ($p < 0.001$), and lower consumption of vitamin C ($p < 0.001$), omega-6 ($p = 0.0007$), and saturated fat ($p < 0.001$) compared to women < 45 years old.

3.2. Allele Frequencies of SNVs

The allele frequencies of the four SNVs are reported in Supplementary Table S2. We compared the allele frequency of the SNVs with those of the populations included in the 1000 Genomes Project. The SNVs showed differences in allele frequencies in our cohort compared to the CEU population but were similar to data from the MXL population.

3.3. Association Analyses between Oxidative Stress-Related SNVs and Bone Mineral Density

We explored the association between the SNVs in oxidative stress-related genes and BMD at different sites. We observed that individuals carrying at least one copy of the A allele of the rs17650792 variant had a lower median of femoral neck BMD ($p = 0.0472$) (Supplementary Table S3). In the adjusted models, a statistically significant association was found in the recessive model for total hip BMD ($p = 0.031$) and femoral neck BMD ($p = 0.012$) (Table 1). When stratified by age groups, we found that rs1050450 (codominant model AA = 0.025 and recessive $p = 0.021$) and rs17650792 (recessive $p = 0.028$) were associated with lower BMD at the total hip in women < 45 years old. Conversely, in women aged 45 and older, rs769217 ($p_{\text{codominant}} = 0.007$ and $p_{\text{dominant}} = 0.031$) and rs4880 ($p_{\text{additive}} = 0.040$, $p_{\text{dominant}} = 0.026$ and $p_{\text{recessive}} = 0.039$) were associated with higher total hip BMD (Supplementary Table S4). On the other hand, rs1050450 ($p_{\text{additive}} = 0.038$) and rs17650792 ($p_{\text{additive}} = 0.017$, $p_{\text{codominant}} = 0.002$ and $p_{\text{recessive}} = 0.002$) were linked to increased odds of having low femoral neck BMD (Table 2). Upon age stratification, the rs17650792 variant remained statistically significant for lower femoral neck BMD in both age groups (Supplementary Table S5). Furthermore, in women aged ≥ 45 years, rs4880 and rs769217 exhibited a protective effect against reduced total hip ($p_{\text{codominant}} = 0.026$ and $p_{\text{recessive}} = 0.009$) and lumbar spine BMD ($p_{\text{codominant}} = 0.035$ and $p_{\text{dominant}} = 0.031$, respectively) (Supplementary Table S5).

Table 1. Association of *GPX1*, *SOD2*, and *CAT* variants with BMD (g/cm²) in Mexican women.

BMD Site	Model	Genotype	rs1050450 (<i>GPX1</i>)		rs17650792 (<i>GPX1</i>)		rs4880 (<i>SOD2</i>)		rs769217 (<i>CAT</i>)	
			b (95%CI)	p Value	b (95%CI)	p Value	b (95%CI)	p Value	b (95%CI)	p Value
Total hip	Additive		−0.003 (−0.017, 0.010)	0.617	−0.001 (−0.012, 0.010)	0.806	0.007 (−0.003, 0.016)	0.181	0.0001 (−0.010, 0.011)	0.980
	Codominant	GG	0.0		0.0		0.0		0.0	
		GA	−0.0003 (−0.016, 0.016)	0.975	0.010 (−0.004, 0.024)	0.155	0.002 (−0.012, 0.016)	0.796	0.011 (−0.003, 0.025)	0.131
		AA	−0.022 (−0.069, 0.025)	0.359	−0.027 (−0.056, 0.001)	0.063	0.018 (−0.004, 0.039)	0.110	−0.017 (−0.043, 0.009)	0.196
	Dominant	GG	0.0		0.0		0.0		0.0	
		GA + AA	−0.002 (−0.017, 0.013)	0.791	0.005 (−0.009, 0.018)	0.475	0.005 (−0.008, 0.019)	0.449	0.006 (−0.007, 0.020)	0.341
	Recessive	GG + GA	0.0		0.0		0.0		0.0	
		AA	−0.022 (−0.069, 0.025)	0.359	−0.031 (−0.060, −0.003)	0.031	0.017 (−0.004, 0.037)	0.108	−0.022 (−0.047, 0.003)	0.085
Femoral neck	Additive		−0.006 (−0.019, 0.007)	0.355	−0.004 (−0.015, 0.007)	0.452	0.005 (−0.005, 0.014)	0.336	0.002 (−0.008, 0.013)	0.634
	Codominant	GG	0.0		0.0		0.0		0.0	
		GA	−0.004 (−0.019, 0.012)	0.642	0.007 (−0.006, 0.021)	0.294	0.004 (−0.010, 0.018)	0.579	0.012 (−0.001, 0.026)	0.080
		AA	−0.025 (−0.071, 0.021)	0.293	−0.033 (−0.061, −0.005)		0.010 (−0.010, 0.031)	0.346	−0.011 (−0.036, 0.014)	0.408
	Dominant	GG	0.0		0.0		0.0		0.0	
		GA + AA	−0.005 (−0.020, 0.009)	0.477	0.002 (−0.011, 0.015)	0.797	0.005 (−0.008, 0.018)	0.434	0.009 (−0.004, 0.022)	0.193
	Recessive	GG + GA	0.0		0.0		0.0		0.0	
		AA	−0.024 (−0.079, 0.022)	0.307	−0.035 (−0.063, −0.008)	0.012	0.008 (−0.012, 0.028)	0.423	−0.016 (−0.040, 0.008)	0.191

CI = Confidence Interval; BMD: Bone Mineral Density; *GPX1*: Glutathione peroxidase 1; *SOD2*: Superoxide dismutase 2; *CAT*: Catalase. Model adjusted for age, BMI, total energy, smoking status, physical activity, alcohol intake, calcium intake, calcium supplements, THR, and vitamin D intake.

Table 2. Association of *GPX1*, *SOD2*, and *CAT* variants with low BMD in Mexican women.

BMD Site	Model	Genotype	rs1050450		rs17650792		rs4880		rs769217	
			OR (95%CI)	p Value	OR (95%CI)	p Value	OR (95%CI)	p Value	OR (95%CI)	p Value
Total hip	Additive		1.02 (0.74–1.41)	0.909	1.16 (0.89–1.50)	0.267	0.88 (0.70–1.11)	0.277	1.06 (0.83–1.36)	0.639
	Codominant	GG	1.0		1.0		1.0		1.0	
		GA	1.00 (0.69–1.44)	0.991	1.02 (0.73–1.41)	0.924	1.11 (0.80–1.53)	0.541	0.93 (0.67–1.29)	0.655
		AA	1.19 (0.34–4.16)	0.783	1.77 (0.91–3.45)	0.092	0.61 (0.36–1.05)	0.072	1.37 (0.77–2.43)	0.286
	Dominant	GG	1.0		1.0		1.0		1.0	
		GA + AA	1.01 (0.71–1.44)	0.962	1.09 (0.80–1.50)	0.569	0.99 (0.72–1.35)	0.928	0.99 (0.72–1.35)	0.939
	Recessive	GG + GA	1.0		1.0		1.0		1.0	
		AA	1.19 (0.34–4.15)	0.782	1.76 (0.92–3.39)	0.090	0.58 (0.35–0.96)	0.036	1.42 (0.81–2.47)	0.217
Femoral neck	Additive		1.36 (1.02–1.82)	0.038	1.34 (1.05–1.70)	0.017	0.89 (0.72–1.10)	0.288	0.93 (0.74–1.17)	0.552
	Codominant	GG	1.0		1.0		1.0		1.0	
		GA	1.34 (0.96–1.88)	0.090	1.10 (0.82–1.49)	0.523	0.83 (0.61–1.13)	0.232	0.88 (0.65–1.19)	0.411
		AA	2.01 (0.72–5.58)	0.182	2.79 (1.46–5.33)	0.002	0.85 (0.53–1.34)	0.477	0.95 (0.55–1.65)	0.863
	Dominant	GG	1.0		1.0		1.0		1.0	
		GA + AA	1.38 (0.99–1.92)	0.053	1.24 (0.93–1.66)	0.137	0.83 (0.63–1.11)	0.216	0.89 (0.67–1.19)	0.438
	Recessive	GG + GA	1.0		1.0		1.0		1.0	
		AA	1.88 (0.68–5.20)	0.226	2.69 (1.42–5.10)	0.002	0.93 (0.60–1.43)	0.741	1.01 (0.60–1.72)	0.968

OR = Odds Ratio; CI = Confidence Interval; *GPX1*: Glutathione peroxidase 1; *SOD2*: Superoxide dismutase 2; *CAT*: Catalase. Model adjusted for age, BMI, total energy, smoking status, physical activity, alcohol intake, calcium intake, calcium supplements, THR, and vitamin D intake.

3.4. Dietary Antioxidant Intake and Oxidative Stress-Related SNV Association

We observed that the A allele of rs1050450 was associated with a higher median intake of vitamin B12 and omega-6. These associations remained statistically significant in the adjusted models (Table 3 and Supplementary Table S3). Additionally, we observed that carrying at least one copy of the A allele of rs1050450 and rs17650792 variants was associated with higher odds of having a high DAQS index consumption compared to women carrying the ancestral allele ($p_{\text{codominant}} = 0.003$ and $p = 0.04$, respectively) (Table 3). Under a recessive model, we found that the rs769217-C variant was associated with higher selenium intake ($p = 0.017$) (Table 4). Finally, the rs4880-A variant was associated with a lower intake of retinol ($p = 0.023$) (Supplementary Table S6), vitamin E ($p_{\text{recessive}} = 0.043$), and fiber ($p_{\text{recessive}} = 0.003$ and $p_{\text{codominant}} = 0.007$) and a higher intake of riboflavin ($p_{\text{codominant}} = 0.005$) and vitamin D ($p_{\text{codominant}} = 0.002$ and $p_{\text{recessive}} = 0.002$) (Table 5).

Table 3. Association between variants rs1050450 and rs17650792 in *GPX1* with different dietary parameters.

Model	Genotype	rs1050450				rs17650792			
		Vitamin B12 (mg/day)		Omega 6 (g/day)		DAQS		DAQS	
		Coefficient & (95%CI)	p Value	Coefficient & (95%CI)	p Value	OR (95%CI)	p Value	OR (95%CI)	p Value
Additive	GG	0.16 (0.01, 0.31)	0.035	0.30 (−0.09, 0.69)	0.125	1.54 (1.11–2.13)	0.009	1.30 (1.00, 1.71)	0.054
	GA	0.0		0.0		1.0		1.0	
	AA	0.23 (0.06, 0.41)	0.01	0.50 (0.05, 0.96)	0.030	1.76 (1.21–2.56)	0.003	1.19 (0.85–1.66)	0.324
Dominant	GA	−0.32 (0.84, 0.20)	0.225	0.20 (−1.12, 1.52)	0.768	1.22 (0.38–3.87)	0.736	2.12 (1.03–4.38)	0.042
	GG	0.0		0.0		1.0		1.0	
Recessive	GA + AA	0.19 (0.02, 0.36)	0.029	0.49 (0.06, 0.93)	0.026	1.71 (1.19–2.46)	0.004	1.28 (0.92–1.77)	0.141
	GG + GA	0.0		0.0		1.0		1.0	
	AA	−0.36 (−0.89, 0.17)	0.181	0.11 (−1.18, 1.41)	0.864	1.07 (0.34–3.35)	0.913	1.98 (0.98–4.05)	0.058

OR = Odds Ratio; CI = Confidence Interval. Model adjusted by age, BMI, smoking status, and physical activity.
 & Results of the quantile regression at the 50th percentile.

Table 4. Association between the rs769217 variant in *CAT* and selenium intake, glucose levels, and type 2 diabetes.

Model	Genotype	Selenium (µg/day)		Glucose levels (mg/dL)		Type 2 Diabetes	
		Coefficient (95%CI) &	p Value	β (95%CI)	p Value	OR (95%CI)	p Value
Additive	TT	0.63 (−0.86, 2.11)	0.410	0.02 (−0.0006, 0.03)	0.058	1.29 (1.01–1.66)	0.043
	TC	0.0		0.0		1.0	
	CC	−1.24 (−3.1, 0.60)	0.186	0.003 (−0.02, 0.03)	0.813	1.24 (0.89–1.74)	0.208
Dominant	TC	3.43 (−0.06, 6.92)	0.054	0.06 (0.02, 0.10)	0.008	1.77 (0.99–3.14)	0.052
	TT	0.0		0.0		1.0	
Recessive	TC + CC	−0.74 (−2.54, 1.06)	0.416	0.01 (−0.01, 0.03)	0.33	1.31 (0.95–1.81)	0.098
	TT + TC	0.0		0.0		1.0	
	CC	4.21 (0.76, 7.66)	0.017	0.06 (0.02, 0.10)	0.007	1.59 (0.92–2.76)	0.098

OR = Odds Ratio; CI = Confidence Interval. Model adjusted by age, BMI, smoking status, and physical activity.
 & Results of the quantile regression at the 50th percentile.

Table 5. Association between the rs4880 variant in *SOD2* and different dietary parameters.

Model	Genotype	Saturated fat (g/day)		Fiber (g/day)		Riboflavin (mg/day)		Vitamin B6 (mg/day)		Vitamin D (UI/day)		Vitamin E (mg/day)	
		Coefficient (95%CI)	p Value	Coefficient (95%CI)	p Value	Coefficient (95%CI)	p Value	Coefficient (95%CI)	p Value	Coefficient (95%CI)	p Value	Coefficient (95%CI)	p Value
Additive		−0.25 (−0.69, 0.19)	0.27	−0.70 (−1.47, 0.07)	0.073	0.04 (0.007, 0.08)	0.021	−0.03 (−0.06, 0.01)	0.167	0.28 (0.04, 0.53)	0.025	−0.09 (−0.26, 0.08)	0.282
Codominant	GG	0.0		0.0		0.0		0.0		0.0		0.0	
	GA	−0.92 (−1.56–0.30)	0.004	−0.14 (−1.18, 0.90)	0.796	0.03 (−0.03, 0.08)	0.310	0.002 (−0.05, 0.06)	0.949	0.05 (−0.30, 0.40)	0.767	0.009 (−0.24, 0.26)	0.942
	AA	0.17 (−0.81–1.14)	0.740	−2.23 (−3.83–0.62)	0.007	0.12 (0.04, 0.20)	0.005	−0.10 (−0.18–0.007)	0.034	0.85 (0.31, 1.39)	0.002	−0.37 (−0.75, 0.02)	0.060
Dominant	GG	0.0		0.0		0.0		0.0		0.0		0.0	
	GA + AA	−0.69 (−1.29–0.09)	0.024	−0.44 (−1.47, 0.58)	0.394	0.04 (0.02, 0.09)	0.171	−0.02 (−0.07, 0.04)	0.508	0.11 (−0.21, 0.44)	0.491	−0.04 (−0.27, 0.19)	0.723
Recessive	GG + GA	0.0		0.0		0.0		0.0		0.0		0.0	
	AA	0.60 (−0.33, 1.53)	0.207	−2.27 (−3.75–0.79)	0.003	0.10 (0.02, 0.18)	0.012	−0.10 (−0.18–0.01)	0.024	0.79 (0.28, 1.30)	0.002	−0.37 (−0.74–0.01)	0.043

CI = Confidence Interval. Model adjusted by age, BMI, smoking status, and physical activity. Results of the quantile regression at the 50th percentile.

3.5. Association Analyses between Oxidative Stress-Related SNVs and Metabolic Traits

Individuals carrying at least one copy of the T allele of the rs769217 variant were associated with a higher median of glucose ($p = 0.029$) and total cholesterol ($p = 0.045$) and a higher prevalence of diabetes ($p = 0.032$) (Supplementary Table S6). The adjusted models remained statistically significant for glucose levels ($p_{\text{codominant}} = 0.008$ and $p_{\text{recessive}} = 0.007$) and T2D ($p_{\text{additive}} = 0.043$) (Table 4). When stratified by age groups, the associations remained

significant in women ≥ 45 years for glucose levels (additive model $\beta = 0.02$, 95% CI 0.002, 0.047, $p = 0.037$) and T2D (additive model OR = 1.42, 95% CI 1.09–1.85, $p = 0.009$).

4. Discussion

Several studies suggest a tight association between oxidative stress and the pathogenesis of OP, which is considered a major public health problem worldwide. In this study, we explored the association between genetic variants in oxidative stress-related enzymes; rs1050450, rs17650792, rs769217, and rs4880; and their association with BMD and their effect on dietary antioxidant intake in Mexican women.

In our study, the SNV rs1050450-A was significantly associated with low BMD levels in the femoral neck and total hip. According to a study of Slovenian subjects, the C/C-rs1050450 genotype was significantly associated with high values of femoral neck and total hip BMD ($p < 0.026$ and $p = 0.023$, respectively). In contrast, the homozygous T/T genotype was associated with low BMD values in the lumbar spine and total hip ($p = 0.032$ and $p = 0.018$, respectively) [29]. These results were consistent with those obtained in this work, since an association was observed between the rs1050450 with femoral neck BMD ($p = 0.050$) and the low BMD in total hip in < 45 years of age. This variant has been linked to multiple oxidative stress-related diseases, such as polycystic ovary syndrome [30], endometriosis-related infertility [31], metabolic syndrome [32], and breast cancer, where the T allele of the rs1050450 variant is associated with reduced enzyme activity [33]. In this context, a lower GPX antioxidant activity has been related to OP in Mexican subjects ≥ 60 years of age, which could suggest that oxidative stress is a risk factor for OP [34].

The findings of this study revealed an association between the SNV rs17650792 and a low femoral neck BMD ($p = 0.047$). Although this SNV has not previously been associated with BMD values, some studies have reported its association with the development of prostate cancer. The products of *GPX1* can modify selenium transport and concentration, counteracting oxidative stress [14,35,36]. In bone metabolism, osteoblasts produce *GPX* to protect against ROS; however, changes in ROS and/or antioxidant systems seem to be involved in the pathogenesis of bone loss, contributing to the development of OP [37].

On the other hand, it has been reported that the DAQs index can favorably influence bone health in women [1,38]. In our study, we observed that variants rs1050450 and rs17650792 of the *GPX1* are positively associated with the DAQs index. However, carriage of risk alleles was associated with a risk of low BMD; the intake of individual antioxidants was analyzed. The rs1050450 variant presented an association under additive model with the intake of vitamin B12 ($p = 0.035$) and omega 6 under dominant model ($p = 0.026$). A high intake of antioxidants has a beneficial effect on bone health; however, it has been reported that high intake omega 6 fatty acids is negatively associated with BMD in postmenopausal women, which could be deleterious for bone health [39]. It is possible that individuals carrying the rs1050450 and rs17650792 variants, to compensate for the oxidative stress caused by the risk variant, tend to consume more antioxidant-rich foods. However, given that these variants are associated with lower oxidative capacity and a higher risk of low BMD, this complex interplay of genetic and dietary factors could explain our observed results. Additional studies are necessary to clarify the effect of those nutrient patterns on BMD.

Another key enzyme representing a barrier against oxidative damage is the antioxidant enzyme CAT, which converts ROS and hydrogen peroxide into water and oxygen to mitigate the toxic effects of hydrogen peroxide [40]. Our study observed a protective effect of the rs769217 variant in *CAT* gene on bone density. However, in a Hungarian population, only male carriers of the rs769217-T had lower femur density, suggesting that this variant might be sex-specific [41]. In addition, we found an association of this variant with elevated glucose levels ($p = 0.02$) and an increased risk of T2D ($p = 0.03$), while it was also related to higher selenium intake ($p = 0.017$). Recent studies have observed that the rs769217 variant might be associated with a higher concentration of hydrogen peroxide, which could be considered a risk factor for developing T2D, mainly in postmenopausal women [42]. A

possible explanation is that catalase deficiency can chronically increase hydrogen peroxide levels in pancreatic B cells, which are sensitive to the oxidation and production of insulin, which could contribute to developing T2D [43,44]. Additionally, it was observed that high consumption of antioxidant nutrients reduces the risk of skeletal fluorosis. It has been reported that selenium could have an antioxidant function by scavenging free radicals, repairing membrane damage, and reducing fluoride-induced apoptosis [45,46]. In addition, selenium could enhance the activity of antioxidant enzymes SOD and GPX, reduce the toxic effect of fluoride, improve liver function, and inhibit apoptosis to a certain extent, improving BMD levels [47]. The rs769217 variant is associated with elevated glucose levels and an increased risk of type 2 diabetes and is linked to higher selenium consumption. An explanation for these results is that individuals carrying the rs769217 variant may be proactively adjusting their diet and lifestyle choices, including higher selenium consumption, as a conscious measure to reduce their risk of diabetes. These findings suggest a complex interaction between genetics, diet, and antioxidant pathways in influencing oxidative stress and its impact on glucose metabolism.

On the other hand, manganese superoxide dismutase 2 is encoded by the *SOD2* gene, whose function is to convert superoxide into hydrogen peroxide, which is subsequently eliminated via its conversion into water and molecular oxygen by other oxidizing enzymes: catalase and glutathione peroxidase [48]. Interestingly, our results revealed that the SNV rs4880 ancestral allele is linked to low total hip BMD ($p = 0.036$), indicating a protective effect conferred by the A allele (OR = 0.58; 95% CI, 0.35–0.96). In the same way, in a population of postmenopausal women from Asian India, the ancestral allele was also significantly associated with the risk of osteoporosis combined with high levels of oxidative stress; consequently, the presence of a higher frequency of allele C indicates the risk of disease [49]. These data were consistent with the results reported in this work, where we observed an association between rs4880 and low total hip BMD ($p = 0.036$), with an OR indicating a protective effect conferred by the A allele (OR = 0.58; 95% CI, 0.35–0.96) equivalent to the T allele reported in the previous study. For dietary parameters, we found an association between the rs4880-AA genotype with intake of fiber, riboflavin, vitamin B6, and vitamin D. It is worth noting that we did not directly assess the relationship between diet and BMD in our study.

Our study's observed association between the rs4880 variant and some antioxidant nutrient intake suggests that genetic factors may influence dietary choices. This association highlights the relevance of exploring potential mechanisms by which oxidative stress-related genetic variants may indirectly impact bone health via dietary patterns. However, it is essential to recognize that further research is needed to fully elucidate the underlying mechanisms and the extent of their contribution to the observed outcomes in terms of bone health.

The strengths of the current study are described below. First, this analysis included a large sample of women ($n = 1269$) compared to other observational studies. Second, this is the first effort to understand the effect of oxidative stress variants, dietary antioxidant intake, and BMD in Mexican women. This study has some limitations. First, total oxidant status was not evaluated, so we cannot determine the direct effect of these variants on the antioxidant activity of the enzymes. Furthermore, it was a cross-sectional study that only partially analyzed dietary antioxidant intake. The cross-sectional design limits our ability to establish causal relationships or capture minor changes over time. Therefore, comprehensive longitudinal analyses are warranted to provide a more in-depth understanding of the dynamic interplay between genetic variants, dietary factors, and bone mineral density. Second, the FFQ data were self-reported; this can be subject to random measurement errors, leading to underestimating the association. However, the FFQ was designed and validated by the National Institute of Nutrition in Mexico to assess long-term exposure to different nutrients to study their potential role as risk factors for chronic disease. Third, we did not adjust for multiple comparisons because of the size found and the limited statistical power. However, recent studies have observed that adjustment via multiple tests

controls global type-I error but considerably inflates type-II error [50]. Fourth, while our analysis did not identify a direct mediation relationship, it is important to acknowledge the complexity of the interplay between genetic factors, dietary components, and bone health. Additional factors, such as gene–environment interactions and other lifestyle variables, could contribute to the observed associations.

Our analysis has limited statistical power; nonetheless, it sheds light on the interplay between genetic variants, dietary factors, and bone mineral density BMD in Mexican women. These data hold relevance as we represent a population with distinct genetic and lifestyle characteristics. While our findings provide valuable insights, we recognize the importance of further research with larger sample sizes to corroborate and expand upon these observations. Nevertheless, our study contributes to the growing body of knowledge regarding the influence of genetic variations and dietary choices on bone health in the Mexican population, which may inform future strategies for bone disease prevention and management.

5. Conclusions

The study showed a positive association between oxidative stress-related rs17650792 and rs1050450-A variants and low BMD despite high DAQs intake, whereas rs769217 and rs4880 variants showed a protective effect with BMD probably associated with increased antioxidant intake in Mexican women. Antioxidant supplementation may be beneficial in preventing bone loss; however, studies regarding oxidant status are needed to determine the impact of antioxidant supplements on BMD. Our findings highlight the importance of understanding the interaction between genetic variants, dietary intake, and bone health in the Mexican population, which could have significant implications for preventing and treating bone diseases. A longitudinal study to evaluate the interaction between dietary antioxidant intake and oxidative stress SNVs on bone health would be helpful to the population. Therefore, based on the result obtained in this study, a dietary antioxidant intake could be suggested as an alternative treatment for low BMD (osteopenia/osteoporosis). In the future, these personalized nutritional recommendations could reduce the burden of oxidative stress-related diseases in the demographic group.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/antiox12122089/s1>, Table S1: Demographic characteristics of the study population; Table S2: Allele frequencies of the SNVs derived from 1000 Genomes Project populations and the cohort from the current study; Table S3: Demographic characteristics of the study population by rs1050450 and rs17650792 (*GPX1*); Table S4: Association of *GPX1*, *SOD2* and *CAT* variants with BMD (g/cm²) in Mexican women stratified by age; Table S5: Association of *GPX1*, *SOD2* and *CAT* variants with low BMD in Mexican women stratified by age; Table S6: Demographic characteristics of the study population by rs769217 (*CAT*) and rs4880 (*SOD*).

Author Contributions: Conceptualization, G.L.-R. and R.V.-C.; methodology, A.B.-C., P.L.-M. and J.F.-M.; formal analysis, B.R.-P.; investigation, M.C.-L.; data curation, B.R.-P.; writing—original draft preparation, R.F.J.-O. and D.I.A.-B.; writing—review and editing, R.F.J.-O., D.I.A.-B., A.B.-C.; P.L.-M., A.H.-B., B.R.-P. and R.V.-C.; supervision, J.S. and R.V.-C.; funding acquisition, M.C.-L.; A.H.-B., J.S. and R.V.-C. All authors have read and agreed to the published version of the manuscript.

Funding: This research was partially funded by the Instituto Nacional de Medicina Genómica, grant number 266–17/2016/I. R.F.J.-O. is supported by a Postdoctoral Fellowship from the Consejo Nacional de Ciencia y Tecnología (Grant Ciencia de Frontera CF 2019-102962). A.B.-C. is the recipient of a Postdoctoral Fellowship from the Consejo Nacional de Humanidades, Ciencia y Tecnología (CONAHCYT-Estancia Posdoctoral de Incidencia Inicial 2022 with CVU 508876).

Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee from Mexican Social Security Institute (No. 12CEI 09 006 14), and the National Institute of Genomic Medicine (266–17/2016/I).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data presented in this study are available on request from the corresponding author, R.V.-C. The data are not publicly available due to their containing information that could compromise the privacy of research participants.

Acknowledgments: The authors would like to thank the Health Workers Cohort Study participants and the staff of the Epidemiological Research Unit and Services of Health-IMSS, Cuernavaca, Morelos.

Conflicts of Interest: The authors declare no conflict of interest. The funder had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results.

References

- Correa-Rodríguez, M.; Schmidt-RioValle, J.; Rueda-Medina, B. Dietary antioxidant quality score (DAQs) is associated with bone mass assessed by calcaneal quantitative ultrasound in young women. *Nutr. Hosp.* **2017**, *34*, 613–618. [\[CrossRef\]](#) [\[PubMed\]](#)
- Raut, S.K.; Khullar, M. Oxidative stress in metabolic diseases: Current scenario and therapeutic relevance. *Mol. Cell Biochem.* **2023**, *478*, 185–196. [\[CrossRef\]](#) [\[PubMed\]](#)
- Lin, H.H.; Hsu, H.Y.; Tsai, M.C.; Hsu, L.Y.; Chien, K.L.; Yeh, T.L. Association between type 2 diabetes and osteoporosis risk: A representative cohort study in Taiwan. *PLoS ONE* **2021**, *16*, e0254451. [\[CrossRef\]](#) [\[PubMed\]](#)
- Arceo-Mendoza, R.M.; Camacho, P.M. Postmenopausal Osteoporosis: Latest Guidelines. *Endocrinol. Metab. Clin. N. Am.* **2021**, *50*, 167–178. [\[CrossRef\]](#) [\[PubMed\]](#)
- Zhou, S.; Tao, Z.; Zhu, Y.; Tao, L. Mapping theme trends and recognizing hot spots in postmenopausal osteoporosis research: A bibliometric analysis. *PeerJ* **2019**, *7*, e8145. [\[CrossRef\]](#)
- Garrett, I.R.; Boyce, B.F.; Oreffo, R.O.; Bonewald, L.; Poser, J.; Mundy, G.R. Oxygen-derived free radicals stimulate osteoclastic bone resorption in rodent bone in vitro and in vivo. *J. Clin. Investig.* **1990**, *85*, 632–639. [\[CrossRef\]](#)
- Lean, J.M.; Davies, J.T.; Fuller, K.; Jagger, C.J.; Kirstein, B.; Partington, G.A.; Urry, Z.L.; Chambers, T.J. A crucial role for thiol antioxidants in estrogen-deficiency bone loss. *J. Clin. Investig.* **2003**, *112*, 915–923. [\[CrossRef\]](#)
- Bai, X.C.; Lu, D.; Bai, J.; Zheng, H.; Ke, Z.Y.; Li, X.M.; Luo, S.Q. Oxidative stress inhibits osteoblastic differentiation of bone cells by ERK and NF-kappaB. *Biochem. Biophys. Res. Commun.* **2004**, *314*, 197–207. [\[CrossRef\]](#)
- Wauquier, F.; Leotoing, L.; Coxam, V.; Guicheux, J.; Wittrant, Y. Oxidative stress in bone remodelling and disease. *Trends Mol. Med.* **2009**, *15*, 468–477. [\[CrossRef\]](#)
- Incalza, M.A.; D’Oria, R.; Natalicchio, A.; Perrini, S.; Laviola, L.; Giorgino, F. Oxidative stress and reactive oxygen species in endothelial dysfunction associated with cardiovascular and metabolic diseases. *Vascul. Pharmacol.* **2018**, *100*, 1–19. [\[CrossRef\]](#)
- Yang, Z.; Zhang, Z.; Penniston, K.L.; Binkley, N.; Tanumihardjo, S.A. Serum carotenoid concentrations in postmenopausal women from the United States with and without osteoporosis. *Int. J. Vitam. Nutr. Res.* **2008**, *78*, 105–111. [\[CrossRef\]](#) [\[PubMed\]](#)
- Sahni, S.; Hannan, M.T.; Blumberg, J.; Cupples, L.A.; Kiel, D.P.; Tucker, K.L. Inverse association of carotenoid intakes with 4-y change in bone mineral density in elderly men and women: The Framingham Osteoporosis Study. *Am. J. Clin. Nutr.* **2009**, *89*, 416–424. [\[CrossRef\]](#)
- Sugiura, M.; Nakamura, M.; Ogawa, K.; Ikoma, Y.; Ando, F.; Shimokata, H.; Yano, M. Dietary patterns of antioxidant vitamin and carotenoid intake associated with bone mineral density: Findings from post-menopausal Japanese female subjects. *Osteoporos. Int.* **2011**, *22*, 143–152. [\[CrossRef\]](#) [\[PubMed\]](#)
- Pascual-Geler, M.; Robles-Fernandez, I.; Monteagudo, C.; Lopez-Guarnido, O.; Rodrigo, L.; Gálvez-Ontiveros, Y.; Cozar, J.M.; Rivas, A.; Alvarez-Cubero, M.J. Impact of oxidative stress SNPs and dietary antioxidant quality score on prostate cancer. *Int. J. Food Sci. Nutr.* **2020**, *71*, 500–508. [\[CrossRef\]](#) [\[PubMed\]](#)
- Nikic, P.; Dragicevic, D.; Jerotic, D.; Savic, S.; Djukic, T.; Stankovic, B.; Kovacevic, L.; Simic, T.; Matic, M. Polymorphisms of Antioxidant Enzymes SOD2 (rs4880) and GPX1 (rs1050450) Are Associated with Bladder Cancer Risk or Its Aggressiveness. *Medicina* **2023**, *59*, 131. [\[CrossRef\]](#)
- Djokic, M.; Radic, T.; Santric, V.; Dragicevic, D.; Suvakov, S.; Mihailovic, S.; Stankovic, V.; Cekerevac, M.; Simic, T.; Nikitovic, M.; et al. The Association of Polymorphisms in Genes Encoding Antioxidant Enzymes GPX1 (rs1050450), SOD2 (rs4880) and Transcriptional Factor Nrf2 (rs6721961) with the Risk and Development of Prostate Cancer. *Medicina* **2022**, *58*, 1414. [\[CrossRef\]](#)
- Denova-Gutierrez, E.; Flores, Y.N.; Gallegos-Carrillo, K.; Ramirez-Palacios, P.; Rivera-Paredes, B.; Munoz-Aguirre, P.; Velazquez-Cruz, R.; Torres-Ibarra, L.; Meneses-Leon, J.; Mendez-Hernandez, P.; et al. Health workers cohort study: Methods and study design. *Salud Publica Mex.* **2016**, *58*, 708–716. [\[CrossRef\]](#)
- Kanis, J.A.; Melton LJ 3rd; Christiansen, C.; Johnston, C.C.; Khaltaev, N. The diagnosis of osteoporosis. *J. Bone Miner Res.* **1994**, *9*, 1137–1141. [\[CrossRef\]](#)
- American Diabetes Association. 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes—2021. *Diabetes Care* **2021**, *44* (Suppl. S1), S15–S33.
- Tate, J.R.; Berg, K.; Couderc, R.; Dati, F.; Kostner, G.M.; Marcovina, S.M.; Rifai, N.; Sakurabayashi, I.; Steinmetz, A. International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) Standardization Project for the Measurement of Lipoprotein(a). Phase 2: Selection and properties of a proposed secondary reference material for lipoprotein(a). *Clin. Chem. Lab. Med.* **1999**, *37*, 949–958. [\[CrossRef\]](#)

21. Berger, C.; Langsetmo, L.; Joseph, L.; Hanley, D.A.; Davison, K.S.; Josse, R.; Kreiger, N.; Tenenhouse, A.; Goltzman, D.; Canadian Multicentre Osteoporosis Study Research Group. Change in bone mineral density as a function of age in women and men and association with the use of antiresorptive agents. *CMAJ* **2008**, *178*, 1660–1668. [\[CrossRef\]](#)
22. Davis, S.R.; Lambrinoudaki, I.; Lumsden, M.; Mishra, G.D.; Pal, L.; Rees, M.; Santoro, N.; Simoncini, T. Menopause. *Nat. Rev. Dis. Primers* **2015**, *1*, 15004. [\[CrossRef\]](#) [\[PubMed\]](#)
23. Rivera-Paredes, B.; Quezada-Sánchez, A.D.; Robles-Rivera, K.; Hidalgo-Bravo, A.; Denova-Gutiérrez, E.; León-Reyes, G.; Flores, Y.N.; Salmerón, J.; Velázquez-Cruz, R. Dietary inflammatory index and bone mineral density in Mexican population. *Osteoporos. Int.* **2022**, *33*, 1969–1979. [\[CrossRef\]](#) [\[PubMed\]](#)
24. Hernández-Avila, M.; Romieu, I.; Parra, S.; Hernández-Avila, J.; Madrigal, H.; Willett, W. Validity and reproducibility of a food frequency questionnaire to assess dietary intake of women living in Mexico City. *Salud Publica Mex.* **1998**, *40*, 133–140. [\[CrossRef\]](#) [\[PubMed\]](#)
25. Aranceta, J.; Serra-Majem, L.; Pérez-Rodrigo, C.; Llopi, J.; Mataix, J.; Ribas, L.; Tojo, R.; Tur, J.A. Vitamins in Spanish food patterns: The eVe Study. *Public Health Nutr.* **2001**, *4*, 1317–1323. [\[CrossRef\]](#) [\[PubMed\]](#)
26. Wright, M.E.; Mayne, S.T.; Stolzenberg-Solomon, R.Z.; Li, Z.; Pietinen, P.; Taylor, P.R.; Virtamo, J.; Albanes, D. Development of a comprehensive dietary antioxidant index and application to lung cancer risk in a cohort of male smokers. *Am. J. Epidemiol.* **2004**, *160*, 68–76. [\[CrossRef\]](#)
27. U.S. Department of Health and Human Services; U.S. Department of Agriculture. *2015–2020 Dietary Guidelines for Americans*, 8th ed.; December 2015. Available online: <https://health.gov/our-work/food-nutrition/previous-dietary-guidelines/2015> (accessed on 15 August 2023).
28. Wang, W.; Wang, X.; Cao, S.; Duan, Y.; Xu, C.; Gan, D.; He, W. Dietary Antioxidant Indices in Relation to All-Cause and Cause-Specific Mortality Among Adults With Diabetes: A Prospective Cohort Study. *Front. Nutr.* **2022**, *9*, 849727. [\[CrossRef\]](#)
29. Mlakar, S.J.; Osredkar, J.; Prezelj, J.; Marc, J. The antioxidant enzyme GPX1 gene polymorphisms are associated with low BMD and increased bone turnover markers. *Dis. Markers* **2010**, *29*, 71–80. [\[CrossRef\]](#)
30. Sun, Y.; Li, S.; Liu, H.; Gong, Y.; Bai, H.; Huang, W.; Liu, Q.; Guan, L.; Fan, P. Association of GPx1 P198L and CAT C-262T Genetic Variations With Polycystic Ovary Syndrome in Chinese Women. *Front. Endocrinol.* **2019**, *10*, 771. [\[CrossRef\]](#)
31. Irimia, T.; Pușcașiu, L.; Mitranovici, M.I.; Crișan, A.; Budianu, M.A.; Bănescu, C.; Chiorean, D.M.; Niculescu, R.; Sabău, A.H.; Cocuz, I.G.; et al. Oxidative-Stress Related Gene Polymorphism in Endometriosis-Associated Infertility. *Medicina* **2022**, *58*, 1105. [\[CrossRef\]](#)
32. Ravn-Haren, G.; Olsen, A.; Tjønneland, A.; Dragsted, L.O.; Nexø, B.A.; Wallin, H.; Overvad, K.; Raaschou-Nielsen, O.; Vogel, U. Associations between GPX1 Pro198Leu polymorphism, erythrocyte GPX activity, alcohol consumption and breast cancer risk in a prospective cohort study. *Carcinogenesis* **2006**, *27*, 820–825. [\[CrossRef\]](#)
33. Kuzuya, M.; Ando, F.; Iguchi, A.; Shimokata, H. Glutathione peroxidase 1 Pro198Leu variant contributes to the metabolic syndrome in men in a large Japanese cohort. *Am. J. Clin. Nutr.* **2008**, *87*, 1939–1944. [\[CrossRef\]](#) [\[PubMed\]](#)
34. Sánchez-Rodríguez, M.A.; Ruiz-Ramos, M.; Correa-Muñoz, E.; Mendoza-Núñez, V.M. Oxidative stress as a risk factor for osteoporosis in elderly Mexicans as characterized by antioxidant enzymes. *BMC Musculoskelet. Disord.* **2007**, *8*, 124. [\[CrossRef\]](#) [\[PubMed\]](#)
35. Geybels, M.S.; van den Brandt, P.A.; Schouten, L.J.; van Schooten, F.J.; van Breda, S.G.; Rayman, M.P.; Green, F.R.; Verhage, B.A. Selenoprotein gene variants, toenail selenium levels, and risk for advanced prostate cancer. *J. Natl. Cancer Inst.* **2014**, *106*, dju003. [\[CrossRef\]](#) [\[PubMed\]](#)
36. Martin-Way, D.; Puche-Sanz, I.; Cozar, J.M.; Zafra-Gomez, A.; Gomez-Regalado, M.D.C.; Morales-Alvarez, C.M.; Hernandez, A.F.; Martinez-Gonzalez, L.J.; Alvarez-Cubero, M.J. Genetic variants of antioxidant enzymes and environmental exposures as molecular biomarkers associated with the risk and aggressiveness of bladder cancer. *Sci. Total Environ.* **2022**, *843*, 156965. [\[CrossRef\]](#) [\[PubMed\]](#)
37. Abdollahi, M.; Larijani, B.; Rahimi, R.; Salari, P. Role of oxidative stress in osteoporosis. *Clin. Pract.* **2005**, *2*, 787. [\[CrossRef\]](#)
38. Rivas, A.; Romero, A.; Mariscal-Arcas, M.; Monteagudo, C.; López, G.; Lorenzo, M.L.; Ocaña-Peinado, F.M.; Olea-Serrano, F. Association between dietary antioxidant quality score (DAQs) and bone mineral density in Spanish women. *Nutr. Hosp.* **2012**, *27*, 1886–1893. [\[PubMed\]](#)
39. Ilesanmi-Oyelere, B.L.; Brough, L.; Coad, J.; Roy, N.; Kruger, M.C. The Relationship between Nutrient Patterns and Bone Mineral Density in Postmenopausal Women. *Nutrients* **2019**, *11*, 1262. [\[CrossRef\]](#)
40. Serra, V.; Castrica, M.; Agradi, S.; Curone, G.; Vigo, D.; Di Giancamillo, A.; Modina, S.C.; Riva, F.; Balzaretto, C.M.; De Bellis, R.; et al. Antioxidant Activity of Different Tissues from Rabbits Fed Dietary Bovine Colostrum Supplementation. *Animals* **2023**, *13*, 850. [\[CrossRef\]](#)
41. Vitai, M.; Kocsordi, K.; Buday, B.; Literati Nagy, B.; Kulcsar, E.; Bezzegh, K.; Peterfai, E.; Koltay, L.; Koranyi, L. Effects of catalase gene (RS769217) polymorphism on energy homeostasis and bone status are gender specific. *Orv. Hetil.* **2010**, *151*, 923–931. [\[CrossRef\]](#)
42. Goth, L.; Nagy, T. Acatlasemia and diabetes mellitus. *Arch. Biochem. Biophys.* **2012**, *525*, 195–200. [\[CrossRef\]](#)
43. Goth, L.; Vitai, M.; Rass, P.; Sukei, E.; Pay, A. Detection of a novel familial catalase mutation (Hungarian type D) and the possible risk of inherited catalase deficiency for diabetes mellitus. *Electrophoresis* **2005**, *26*, 1646–1649. [\[CrossRef\]](#) [\[PubMed\]](#)

44. Nandi, A.; Yan, L.J.; Jana, C.K.; Das, N. Role of Catalase in Oxidative Stress- and Age-Associated Degenerative Diseases. *Oxid. Med. Cell. Longev.* **2019**, 2019, 9613090. [[CrossRef](#)] [[PubMed](#)]
45. Feng, P.; Wei, J.; Zhang, Z. Intervention of selenium on chronic fluorosis-induced injury of blood antioxidant capacity in rats. *Biol. Trace Elem. Res.* **2011**, 144, 1024–1031. [[CrossRef](#)] [[PubMed](#)]
46. Gao, J.; Tian, X.; Yan, X.; Wang, Y.; Wei, J.; Wang, X.; Yan, X.; Song, G. Selenium Exerts Protective Effects Against Fluoride-Induced Apoptosis and Oxidative Stress and Altered the Expression of Bcl-2/Caspase Family. *Biol. Trace Elem. Res.* **2021**, 199, 682–692. [[CrossRef](#)] [[PubMed](#)]
47. Miao, K.; Zhang, L.; Yang, S.; Qian, W.; Zhang, Z. Intervention of selenium on apoptosis and Fas/FasL expressions in the liver of fluoride-exposed rats. *Environ. Toxicol. Pharmacol.* **2013**, 36, 913–920. [[CrossRef](#)]
48. Sakamoto, T.; Imai, H. Hydrogen peroxide produced by superoxide dismutase SOD-2 activates sperm in *Caenorhabditis elegans*. *J. Biol. Chem.* **2017**, 292, 14804–14813. [[CrossRef](#)]
49. Botre, C.; Shahu, A.; Adkar, N.; Shouche, Y.; Ghaskadbi, S.; Ashma, R. Superoxide Dismutase 2 Polymorphisms and Osteoporosis in Asian Indians: A Genetic Association Analysis. *Cell. Mol. Biol. Lett.* **2015**, 20, 685–697. [[CrossRef](#)]
50. Sutton, A.; Khoury, H.; Prip-Buus, C.; Cepanec, C.; Pessayre, D.; Degoul, F. The Ala16Val genetic dimorphism modulates the import of human manganese superoxide dismutase into rat liver mitochondria. *Pharmacogenetics* **2003**, 13, 145–157. [[CrossRef](#)]

Disclaimer/Publisher’s Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.