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The influence of serum calcium and magnesium levels in the radiological evolution of knee osteoarthritis

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ABSTRACT

Calcium and magnesium are minerals with important functions throughout the body. The deficiency has been associated with an increased risk of cardiovascular disease, diabetes, and prostate cancer, and affects the skin and teeth. Some studies have associated it with osteoarthritis. Knee osteoarthritis is a degenerative pathology with a high prevalence that affects the knee joint, and prevention is necessary in the context of the lack of understanding of pathophysiology. The role of serum calcium and magnesium levels was considered in this regard. The study included a group of 371 hospitalized patients for unilateral or bilateral knee pain, of whom 326 patients had knee osteoarthritis and were the subject of the research. The risk factors such as age, gender, body mass index, weight status, and certain anatomical changes were analyzed, including the varus and valgus alignment. The results show the inverse relationship of Ca values with the radiological classification of knee osteoarthritis and the importance of risk factors such as age, gender, and obesity for the onset and progression of the pathology. Serum Mg values were not statistically significant in this study group.

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Introduction

Calcium (Ca) and magnesium (Mg) are minerals with important functions throughout the body [1], especially in the skeletal and muscular system where, along with other components, they ensure the biological, metabolic and mechanical functions [2]. They also maintain healthy skin and teeth and its deficiency causes dehydration of the skin and yellowing of tooth enamel [3].

Calcium has implications in cell divisions, protein secretion, glycogen metabolism, and muscle contractions [2], including heart muscle. Calcium has a role in digestion and regulating blood pressure [3] and makes an important contribution to maintaining bone homeostasis, as well as in bone remodeling. The bone consists of an organic component containing mainly type I collagen with a role in flexibility and an inorganic component with a role in ensuring resistance to compressive forces, consisting mainly of Ca and other minerals [4]. Calcium homeostasis in the body is dependent on parathyroid hormone, vitamin D [5, 6, 7], calcitonin [3], and kidney function. Calcium and Mg absorption is achieved in the intestine [8], and is stimulated by the active form of vitamin D with the recommendation of a daily intake of 400 IU in adults. Magnesium helps to convert vitamin D into its active form so that they are combined in the treatment of various resistant forms of rickets [9-11].

Magnesium has a role in energy metabolism [12], protein synthesis, nucleic acids, and maintaining the electrical potential of tissues [13]. It is involved in the differentiation and proliferation of chondrocytes as well as reducing serum levels of inflammatory cells such as interleukin-1 or tumor necrosis factor- α and free radicals [14]. By preventing Ca and phosphorus precipitation, Mg

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with an inhibitor of interleukin-6 has a role in reducing the formation of large hydroxyapatite crystals [15].

Ca and Mg deficiency has been associated with an increased risk of cardiovascular diseases, diabetes [16], prostate cancer, and even osteoarthritis [17]. Some of the drugs widely used to treat the patients' comorbidities may be involved in Ca and Mg metabolism [18-20]. For example, certain calcium channel blockers have a role in reducing the process of cartilage destruction by inhibiting genes involved in maintaining inflammation and stimulating the production of proteoglycans [21]. Drugs such as diuretics can increase renal excretion of Ca and Mg. This can generate disturbances in serum levels, with implications in bone homeostasis [22].

Knee osteoarthritis (KOA) is a degenerative pathology that progressively affects the anatomical structures of the knee joint and represents one of the main causes of functional impairment worldwide. Risk factors such as age, weight, gender, systemic inflammatory mediators, cellular and biochemical processes that may influence bone homeostasis or anatomical changes and local trauma are usually associated [23]. Thus, the onset of the disease and its slow progression make it possible to have radiological changes even at the first consultation [24].

The prevalence of KOA is alarmingly increasing and it is estimated that in 2032, compared to 2012, the consultations may increase by 15.7% [25], the costs of multiple hospitalizations is high, and improvement in quality of life is unfortunately not significant [26]. The pathophysiology of KOA has not been fully understood and in this context, it is essential to detect and reduce potentially modifiable risk factors, especially with individualized prevention strategies and the detection of factors that may have a protective role [27]. Early administration of mineral supplements should be considered, which may slow the progression of the disease and improve the symptoms [28]. The recommended daily intake is for Mg 4-6 mg/kg/day [29] and for Ca the ideal recommended dose is 1000 mg / day, but in European countries the daily mean is 687-1171 mg / day for men and 508/1047 mg / day for women [30]. Calcium and Mg overdose may cause gastrointestinal or cardiovascular symptoms including arrhythmias [31] or myocardial infarction [32].

Summarizing these data, the researchers argue that serum Ca and Mg levels could influence the imaging changes in ostheoarthritis [28].

The aim of the study is to evaluate the influence of serum Ca and Mg values in the radiological evolution of KOA, in relation to specific risk factors.

Materials and Methods

A retrospective study included 371 patients admitted to the Military Emergency Clinical Hospital "Dr. Iacob Czihac" Iasi between July 2017 - July 2018. Criteria for inclusion were: uni- or bilateral knee pain, knee radiography performed for diagnostic purpose, and Ca and Mg serum levels present in medical records. Criteria for exclusion included previous knee surgery, or renal, intestinal, or parathyroid diseases.

The collected blood samples were stored at room temperature and processed within 2-3 hours of collection. Values were obtained using two automated biochemistry analyzers with spectrophotometric and turbidimetric reading methods (BA 400 and ILAB 650). Laboratory reference levels were: total serum Ca - 8.5-10 mg / dl and Mg - 1.6-2.4 mg/ dl.

Radiographs were taken with the Philips Optimies Telediagnostic conventional radiology device. The measurements of the narrowing of the tibio-femoral joint space were performed on radiographs, digitized in the FCR Prima Console Viewer program. We performed the measurements using as a reference the middle portion of the lateral and medial joint spaces of each knee and we determined the maximum height of the radiotransparent area between the edges of the tibio-femoral articular surfaces. Radiographs that showed a joint space of less than 5 mm were graded according to the Kellgren-Lawrence (KL) classification:

•Grade 0: Absence of radiological changes;

•Grade 1: possible narrowing of the joint space with a tendency for osteophyte formation;

•Grade 2: detecting osteophytes and possible narrowing of the joint space;

•Grade 3: definite narrowing of the joint space, significant osteophytosis and possible bone deformities;

•Grade 4: marked narrowing of the joint space accompanied by deformations, bone sclerosis and major osteophytes [33].

According to the KL classification, two groups were established. The control group comprised 45 patients without KOA (grade 0) and the cases group 326 patients with KOA in grades I-IV.

Body mass index (BMI) was calculated using the formula: BMI = weight (kg) / height (m) 2 and we classified patients in the following degrees of obesity: underweight - BMI <18.5; normal weight - BMI between 18.51 - 24.99; overweight - BMI between 25.00 - 29.99; obesity degree I - BMI between 30.00 - 34.99; grade II obesity - BMI between 35.00 - 39.99; morbid obesity - BMI of 40.00 or more.

We correlated the serum values of Ca and Mg with the radiological classification KL in association with specific risk factors that have significant influence for KOA severity.

Statistical analyses

Statistical analysis was performed in SPSS 24.0. Continuous data were characterized by mean values and

standard deviations, and categorical data were expressed as percentages. We performed univariate data analysis using the Chi-square, t-Student, Mann-Whitney U and Kruskal Wallis tests. Next, we used a multinomial logistic regression model of Forward Entry type that included the variables that showed statistically significant differences in the univariate analysis; the dependent variable in the model was knee osteoarthritis, characterized by the 4 degrees analyzed compared to grade 0, used as a reference category and the characterization of the predictors was performed by calculating odds ratios (ORs) with the 95% confidence interval. All tests were 2-tailed; a P value ≤0.05 was considered statistically significant. Ethical clearance for the study was obtained from the institutional ethical committee.

Results

In the study group there were no statistically significant differences between the KOA diagnosis at the left and the right knee, 51.2% of cases having grade I KOA on the left, while 49.7% having grade I KOA on the right. The KOA in grade II was found in a proportion of 15.6% on the left and 18.7% on the right; grade III at 7.7% on the left and 7.4% on the right, and grade IV 7.4% on the left and 10.4% on the right (Table 1). Statistically significant differences were not found between types of knee alignment, valgus alignment being more common in the left knee (15.0%) than the right knee (12.9%) and varus alignment being more common in the right knee (67.8%) than the left (62.3%), and the symmetrical narrowing were (5.5% compared to 4.6). The distribution by gender was approximately balanced (48.5% men and 51.5% women). The mean age of patients was significantly higher ($p < 0.001$) for patients with KOA (59.22 ± 13,486) than patients in the control group (43.04 ± 13.984). The BMI was significantly higher ($p < 0.001$) in patients with KOA (28.94 ± 4.068) compared to those in the control group (26.23 ± 3.773).

Obesity show statistically significant differences between the two groups: grade I obesity was more frequently found in KOA patient group (32.8% compared to 6.7% in the control group) and normal weight was less found in KOA patients group (12.3% compared to 26.7% in the control group).

Table 1. Characteristics of patients in the study group and the control group

	Knee osteoarthritis (n=326) †		**Control group (n=45)** †	Test statistic	p-value‡
Age (years)	59.22 ± 13.486		43.04 ± 13.984	2903.0	<.001*
Sex (M/F)	158 / 168 (48.5% / 51.5%)		33 / 12 (73.3% / 26.7%)	9.789	0.002*
BMI	28.94 ± 4.068		26.23 ± 3.773	4260.0	<.001*
Normal weight	**40 (12.3%)**		12 (26.7%)	23.412	<.001*
Over weight	-		1 (2.2%)		
Over weight	164 (50.3%)		27 (60.0%)		
obesity grade I	**107 (32.8%)**		3 (6.7%)		
obesity grade II	12 (3.7%)		2 (4.4%)		
Obesity grade IV	3 (0.9%)		-		
Kellgren-Lawrence classification	Left	Right			
Grade 0	59 (18.1%)	45 (13.8%)		4.598	0.331
Grade I	167 (51.2%)	162 (49.7%)			
Grade II	51 (15.6%)	61 (18.7%)			
Grade III	25 (7.7%)	24 (7.4%)			
Grade IV	24 (7.4%)	34 (10.4%)			
Alignment type	Left	Right			
Normal	59 (18.1%)	45 (13.8%)		3.460	0.326
Valgus alignment	49 (15.0%)	42 (12.9%)			
Varus alignment	203 (62.3%)	221 (67.8%)			
Symmetrical narrowing	15 (4.6%)	18 (5.5%)			
Insall-Salvatti index left	1.08 ± 0.142		1.07 ± 0.123	1364.5	0.652
Insall-Salvatti index right	1.09 ± 0.132		1.10 ± 0.097	0.433	0.665
Total serum Ca	9.23 ± 0.395		9.33 ± 0.367	5951.0	.039*
Mg	2.11 ± 0.229		2.14 ± 0.190	6500.5	0.211

† Values were expressed as numbers (mean ± SD) or percentages %;
‡ Student t or Mann-Whitney U Test; Chi-square test or Fisher's exact test
(*) Marked effects are significant at p < .05

The Insall-Salvatti index could influence normal biomechanics, but it was not significantly different between patients with KOA and those in the control group in either knee (1.08 ± 0.142 compared to 1.07 ± 0.123 in the control group) for the left knee and (1.09 ± 0.132 compared to 1.10 ± 0.097 in the control group) for the right. However, it was noted that total serum Ca levels were significant lower (p = 0.039*) in patients with KOA (9.23

± 0.395) compared to the control group (9.33 ± 0.367) and Mg levels were lower in patients with KOA (2.11 ± 0.229) compared to those in the control group (2.14 ± 0.190), though the difference was not statistically significant.

We performed univariate analysis of serum and Mg values compared on samples of interest, defined by the degree of obesity of patients, the degree of KOA, and the type of varus and valgus alignment for both knees (Tables 2, 3). Table 2 shows serum Ca levels in the following: a significant decrease in patients with grade I obesity compared to overweight patients (which, however, is not reflected in other obesity groups, so it may not have clinical relevance).

Calcium levels decrease significantly as the degree of KOA worsens, which is also correlated with the varus and valgus alignment bilateral. In the case of left knee alignment, the serum Ca level is significantly lower only in patients with varus alignment, compared to normal knees - the other discrepancies, although present, have no statistical significance.

Table 2. Comparative study of serum Ca values in groups (only the statistically significant comparisons between samples are enlisted)

	Mean ± SD		Test statistic	p-value‡
Obesity			4.809	0.186
Normal weight	9.29 ± 0.397	Over weight vs. Obesit.I	9069.0	0.047*
Over weight	9.30			
Over weight	9.26 ± 0.385			
Obesity grade I	9.19 ± 0.395			
Obesity grade II	9.19 ± 0.453			
Morbid obesity	8.86 ± 0.251			
Kellgren-Lawrence classification - left.			43.219	<.001*
Grade 0	9.32 ± 0.344	Grade 0 vs. Grade II	1617.0	<.001*
Grade I	9.29 ± 0.366	Grade 0 vs. Grade III	886.0	0.013*
Grade II	9.11 ± 0.360	Grade 0 vs. Grade IV	438.5	<.001*
Grade III	9.17 ± 0.520	Grade I vs. Grade II	2953.5	0.001*
Grade IV	8.87 ± 0.428	Grade I vs. Grade III	1528.5	0.030*
		Grade I vs. Grade IV	724.0	<.001*
		Grade II vs. Grade IV	300.0	<.001*
		Grade III vs. Grade IV	169.5	0.009*
Kellgren-Lawrence classification - right.			44.396	<.001*
Grade 0	9.36 ± 0.380	Grade 0 vs. Grade I	5851.5	0.009*
Grade I	9.26 ± 0.364	Grade 0 vs. Grade II	1896.0	0.001*
Grade II	9.21 ± 0.333	Grade 0 vs. Grade III	641.5	0.002*
Grade III	9.11 ± 0.485	Grade 0 vs. Grade IV	569.0	<.001*
Grade IV	8.95 ± 0.430	Grade I vs. Grade III	1349.0	0.015*
		Grade I vs. Grade IV	1227.0	<.001*
		Grade II vs. Grade III	543.5	0.064
		Grade II vs. Grade IV	495.0	<.001*
Alignment type - left.			10.256	0.017*
Normal	9.32 ± 0.344	Norm. vs. Varus	8258.0	0.002*
Valgus alignment	9.22 ± 0.326			
Varus alignment	9.20 ± 0.419			
Symmetrical narrowing	9.32 ±0.476			
Alignment type - right.			21.414	<.001*
Normal	9.36 ± 0.380	Norm. vs. Varus	7006.5	<.001*
Valgus alignment	9.27 ± 0.364	Norm. vs. Sym. Narrow	380.0	<.001*
Varus alignment	9.20 ± 0.399	Valgus vs. Sym. Narrow	253.5	0.043*
Symmetrical narrowing	9.07 ±0.276			

‡ Kruskal Wallis or Mann-Whitney U Test
(*) Marked effects are significant at p < .05

The comparative study of Mg levels is detailed in Table 3. There is a significant decrease in Mg levels as the degree of obesity worsens, respectively the degrees of KOA and the type of knees alignment. Regarding knee alignment, there is a tendency for lowered serum Mg levels, but with a statistically significant difference only for the right knee with varus alignment, compared to the control group.

Table 3. Comparative study of Mg values in groups (only the statistically significant comparisons between samples are enlisted)

	Mean ± SD		Test statistic	p-value‡
Obesity			16.006	0.001*
Normal weight	2.17 ± 0.213	Normal vs. Obezit.I	1998.0	0.002*
Over weight	2.00	Normal vs. Obezit.II	171.5	0.002*
Over weight	2.13 ± 0.235	Suprapond vs. Obezit.I	8921.0	0.028*
Obesity grade I	2.07 ± 0.202	Suprapond vs. Obezit.II	807.5	0.013*
Obesity grade II	1.98 ± 0.207			
Morbid obesity	2.06 ± 0.305			
Kellgren-Lawrence classification - left.			38.188	<.001*
Grade 0	2.20 ± 0.209	Grade 0 vs. Grade I	6895.5	0.004*
Grade I	2.12 ± 0.225	Grade 0 vs. Grade II	1480.0	<.001*
Grade II	2.03 ± 0199	Grade 0 vs. Grade III	810.5	0.003*
Grade III	2.04 ± 0.231	Grade 0 vs. Grade IV	464.0	<.001*
Grade IV	1.95 ± 0.171	Grade I vs. Grade II	3269.5	0.011*
		Grade I vs. Grade IV	1109.5	<.001*
Kellgren-Lawrence classification - right.			19.645	<.001*
Grade 0	2.15 ± 0.192	Grade 0 vs. Grade III	717.5	0.011*
Grade I	2.13 ± 0.230	Grade 0 vs. Grade IV	837.0	<.001*
Grade II	2.10 ± 0.248	Grade I vs. Grade III	1408.5	0.028*
Grade III	2.01 ± 0.238	Grade I vs. Grade IV	1723.0	0.001*
Grade IV	2.00 ± 0.180	Grade II vs. Grade IV	762.0	0.031*
Alignment type - left.			22.798	<.001*
Normal	2.20 ± 0.209	Norm. vs. Valgus	1858.0	0.006*
Valgus alignment	2.10 ± 0.244	Norm. vs. Varus	7371.0	<.001*
Varus alignment	2.08 ± 0.214	Norm. vs. Sym. Narrow.	421.0	0.004*
Symmetrical narrowing	2.01 ± 0.255			
Alignment type - right.			5.664	0.129
Normal	2.15 ± 0.192	Norm. vs. Varus	8498.5	0.042*
Valgus alignment	2.12 ± 0.250			
Varus alignment	2.10 ± 0.231			
Symmetrical narrowing	2.05 ± 0.228			

‡ Kruskal Wallis or Mann-Whitney U Test
(*) Marked effects are significant at p < .05

Table 4. Model coefficients and Wald test in multimodal logistic regression on predictive factors of osteoarthritis

Multinomial logistic regression		**B**	**SE**	**Wald**	**Sig. P**	**Odd ratio Exp(β)**	**95% CI for Exp(B)**	
							Lower	**Upper**
Dependent variable: left knee osteoarthritis								
KL I	Age	0.063	.011	31.883	.000*	**1.065**	1.042	1.089
KL II	Sex = F	0.853	.403	4.471	.034*	**2.347**	1.064	5.175
	Age	0.108	.017	39.231	.000*	**1.114**	1.077	1.153
	Seric Ca (mg/dl)	-1.080	.543	3.965	.046*	**.339**	.117	.983
KL III	Age	0.119	.022	28.572	.000*	**1.127**	1.079	1.177
KL IV	Sex = F	1.546	.608	6.472	.011*	**4.690**	1.426	15.429
	Age	0.129	.024	28.003	.000*	**1.138**	1.085	1.193
	Seric Ca (mg/dl)	-3.339	.826	16.339	.000*	**.035**	.007	.179
Dependent variable: right knee osteoarthritis								
KL I	Sex = F	0.687	.317	4.711	.030*	**1.988**	1.069	3.697
	Age	0.064	.012	29.274	.000*	**1.066**	1.042	1.091
KL II	Sex = F	0.818	.396	4.262	.039*	**2.266**	1.042	4.926
	Age	0.105	.016	41.420	.000*	**1.111**	1.076	1.147
KL III	Sex = F	2.115	.629	11.325	.001*	**8.293**	2.419	28.429
	Age	0.109	.023	22.718	.000*	**1.115**	1.066	1.166
	Seric Ca (mg/dl)	-1.366	.697	3.842	.050*	**.255**	.065	1.000
KL IV	Sex = F	1.409	.518	7.397	.007*	**4.092**	1.482	11.296
	Age	0.141	.022	40.489	.000*	**1.151**	1.102	1.202
	Seric Ca (mg/dl)	-2.657	.699	14.443	.000*	**.070**	.018	.276

We used a multinomial logistic regression model, forward entry, to identify the predictive power of several independent variables on KL classification; the independent variables tested were those for which we identified statistically significant differences between the control group and the group of patients with KOA in the univariate analysis (Table 1): gender, age, obesity, and serum Ca levels. The type of knee alignment would also have been interesting to test, but the univariate analysis did not show a significant association between its presence and KL classification. The analysis was performed separately for KL classification for each knee and the reference category used for comparisons was KL 0, respectively healthy persons. The results are presented in table 4.

The regression model constructed for the left knee KOA assessment is valid, and is characterized by a correct case classification percentage of 51.2%, superior to the null model (without any predictor), in which the same percentage is 45.0%. The model identifies 3 significant predictors out of the 4 tested, namely the age, gender, and serum Ca values of the patients. The results in Table 4 show that the age of patients has an important role in KOA prediction, in all its degrees; female sex is an important predictor for KOA grade II and IV KL, with associated highest OR values. The serum Ca values are also significantly involved only in the case of grade II or IV KOA, having a protective role: as the level of serum Ca increases, the risk of KOA progression decreases significantly - this phenomenon is observed especially in grade IV KOA KL, where a one-unit increase in serum Ca results in a 0.035-fold decrease in OR risk.

The regression model constructed for the KOA assessment at the right knee is also valid, and is characterized by a percentage of correct case classification of 51.5%, superior to the null model (without any predictor), in which the same percentage is 43.7%. The model identifies the same 3 significant predictors among the 4 tested, namely age, gender, and serum Ca values of the patients. The results in Table 4 show that the female patients and age play an important role in the prediction of KOA, in all its degrees; being female is in fact the most important predictor, having associated the highest OR values. Serum Ca values are significantly involved only in the case of KOA grade III or IV KL, having a protective role: as the level of serum Ca increases, the risk of KOA progression decreases significantly - this phenomenon is observed especially in KOA grade IV KL, where a one-unit increase in serum Ca results in a 0.070-fold decrease in OR risk.

Discussions

Knee osteoarthritis is a degenerative pathology that affects the knee joint, for which medical services are increasingly required [34]. Significant structural and functional changes occur in cartilage that has a limited regenerative capacity [35] and because the pathophysiology of KOA is not completely understood, the importance of detecting the modifiable risk factors and those with a protective role for the joint has been emphasized [27].

The changes in KOA are closely related to a proinflammatory status [36, 37] so it is important to evaluate the protective role that Ca could have for cartilage, as it is used in various forms in the treatment of periapical dental inflammation, acute edema or urticaria.

The researchers have demonstrated by experimental administration of calcium gluconate supplements its role in preventing the reduction of cartilage thickness by inhibiting chondrocytes and prostaglandin apoptosis [35]. Salem et al. have shown an inverse association between serum Ca values and prostate cancer risk [38] and other authors associate elevated serum Mg levels with oral cancer (39), providing new research opportunities.

The importance of calcium for the skin is also emphasized in the context of psoriasis, when lower levels of serum Ca were detected compared to the control group (40). It is interesting to study the influence of Ca and Mg serum levels in radiologic changes in psoriatic arthritis.

Consequently, the hypothesis was also taken into account for KOA. Yazmalar et al. did not obtain statistically significant differences between serum Ca levels in KOA patients compared to the control group [41], the same conclusions being reported in a study that looked at the role of serum Ca levels in hand osteoarthritis [42].

Our results contradict these studies, the total serum Ca levels for patients with KOA (9.23 ± 0.395) was significantly lower ($p = 0.039$*) compared to the control group (9.33 ± 0.367) and thus underline the conclusions of Hui Li et al., which support an inverse association between serum Ca values and radiological progression of KOA [17].

The role of serum Ca levels in the evolution of KOA has been demonstrated by studies that have highlighted the effects of Ca on chondrocytes in terms of matrix protein synthesis, cytoskeletal remodeling and apoptosis and regulation of proteoglycans involved in static cartilage compression [43].

Laboratory mice testing show that Mg deficiency generated a decrease in size and number of chondrocytes and proteoglycans that led to a reduction in size of articular cartilage [44]. Although some studies on human subjects have indicated an important role of Mg intake in preventing the onset and progression of KOA [45], they have been contradicted by studies that did not obtain a lower risk of KOA in increased Mg intake [28], or that noticed only modest inverse associations between them [46]. On the other hand, Wang and colleagues claim a lower risk of KOA in association with higher serum Mg values, but more evaluations are needed to confirm this hypothesis [47].

Consistently, the results developed from our research group show slightly lower Mg values in patients with KOA (2.11 ± 0.229) than in the control group (2.14 ± 0.190), but without a statistically significant difference. The protective role of Mg against the installation or progression of KOA could be explained by its participation in the preservation of muscular mass and strength that ensures a normal biomechanics [48].

Biomechanics can be altered especially by local risk factors such as anatomical changes in position involving the patella or abnormalities in the femoral or tibial extremities [49, 50].

A number of risk factors associated with the onset or progression of KOA are age, sex, body mass index, or anatomical changes (Table 1), as evidenced by the literature [51]. Changes in chondrocytes and articular cartilage are exacerbated by aging and unfortunately support local inflammation [52], so that most studies associate an increased frequency of osteoarthritis in older people [24, 53]. Our results support these conclusions, patients with KOA have a mean age of (59.22 ± 13,486) compared to the control group (43.04 ± 13,984).

Although it has reported that females have an increased frequency [54], we found a relatively balanced frequency though with a slight predominance of women (48.5% men and 51.5% women). In the research group, BMI was significantly higher (p <.001) in patients with KOA (28.94 ± 4.068) compared to the control group (26.23 ± 3.773). The degrees of obesity was statistically significant for grade I obesity in the case of patients with KOA (32.8% compared to 6.7% in the control group). Most researchers agree that obesity is the main risk factor for KOA [51, 55], with potential for change through lifestyle and diet modification [56, 57].

Another potential risk factor, though not statistically significant, was the Insall-Salvatti index, which did not show very different values between patients with KOA and the control group. The most common type of varus and valgus alignment in patients with KOA was varus alignment (62.3% left and 67.8% right). Valgus alignment was found in 15.0% in the left knee and 12.9% in the right knee and symmetrical narrowing in 5.5 % left and 4.6 % right. These differences are caused by the individualized biomechanics and load distribution.

We obtained an inverse association of the serum Ca levels with the varus alignment on the left side, and of Mg levels with the varus alignment on the right side. The Mg level, although not significant, showed an inverse relationship between KOA degrees and obesity. Factors with that significantly predicted bilateral KOA grades were gender (with the highest OR values for females), age, obesity, and serum Ca level of the patients [58-60]. Especially for patients with KL grade IV in both knees, we found that an increase of one unit of serum Ca level leads to a decrease in the risk of KOA (OR = 0.035) for the left knee and (OR = 0.07) for the right knee. Analysis of serum calcium and magnesium levels could be correlated with other pathologies in the future [61-63]. Also, it would be interesting to correlate the pathologies with other biomarkers that may have important predictive or diagnostic roles [64, 65].

Conclusions

In conclusion, the serum Ca levels have an inverse relationship with the severity of KOA and could have a protective role. As the Mg serum levels did not present statistically significant differences between the two groups, and there are no definite conclusions regarding its protective role for KOA in the specialized literature, new research opportunities are open.

Conflict of interest disclosure

There are no known conflicts of interest in the publication of this article. The manuscript was read and approved by all authors.

Compliance with ethical standards

Any aspect of the work covered in this manuscript has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

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