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Serum Calcium and Magnesium Levels in Patients with Type 2 Diabetes and COVID-19 Infection Requiring Hospitalization—Correlations with Various Parameters

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Abstract: The purpose of this research was to analyze the impact of SARS-CoV-2 infection on ionic calcium, total calcium and serum magnesium upon hospital admission, taking into account the association of type 2 diabetes as a metabolic comorbidity. Our study included 57 patients: a group of 28 patients without diabetes, but with SARS-CoV-2 virus infection, and a second group of 29 patients with type 2 diabetes and SARS-CoV-2 virus infection. The serum level of calcium and magnesium of the patients included in the study did not differ statistically significantly in those with type 2 diabetes compared to those without type 2 diabetes who were infected with the SARS-CoV-2 virus at the time of hospitalization. Ionic calcium, total calcium, and serum magnesium did not statistically significantly influence the survival of the patients with COVID-19 infection included in this research, but the type of infection severity (mild or moderate) did influence the survival rate. Concerning the diabetic patients, a statistically significant correlation was found between serum total calcium and total serum proteins, and another one between ionic calcium and uric acid, urea, and total cholesterol. Serum total calcium and D-dimers were statistically significantly correlated with being transferred to the intensive care unit. On the other hand, magnesium significantly correlated with lipids (triglycerides, total lipids) and inflammatory (fibrinogen, ESR) biomarkers.

Keywords: serum ionic calcium; total serum calcium; serum magnesium; SARS-CoV-2; COVID-19; type 2 diabetes

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1. Introduction

The pandemic generated by the SARS-CoV-2 virus had numerous implications on the general population, with complex changes both in the metabolism of people without associated comorbidities, but especially in patients with cardiovascular, diabetic, renal, or other chronic diseases [1–12]. Regarding the impairment of the main electrolytes in the body, serum calcium and serum magnesium, precise data concerning the effects of infection with the novel coronavirus are not known, and the physio-pathological mechanisms have not been fully described [13–19]. Both calcium and magnesium fulfill numerous functions within the human body, roles that can be disrupted by COVID-19 infection [20–22].

Calcium is an essential mineral with multiple functions such as muscle contraction, myocardial contractility, cardiac activity, neurotransmitter release, platelet adhesion, blood

clotting, and bone and tooth structure [23,24]. Serum calcium is found in the human body in both free form and bound to proteins, primarily albumin, and is only bound to globulins to a small extent [25], with calcium bound to plasma proteins being very sensitive to variations in blood pH [25]. The total level of calcium in the blood is quantified under the term "total serum calcium", while the free form of serum calcium, which is not bound to albumin, is known as "ionic calcium" [26]. Viral infections, including SARS-CoV-2, can influence calcium metabolism, altering calcium homeostasis and facilitating viral entry and replication, with negative effects on calcium channels and pumps at both the plasma membrane and intracellular organelles [27]. Studies in the literature have shown that there is a link between the spike protein of SARS-CoV-2 and calcium, for which this viral protein has a high affinity [28]. The SARS-CoV-2 spike protein receptor-binding domain has a significant impact on endothelial cells in COVID-19, altering intracellular calcium regulation and affecting the vascular endothelium of the respiratory system [29].

Another essential mineral in the human body is magnesium, which has numerous roles, including regulating calcium levels, metabolizing glucose and preventing the onset of diabetes, activating ATP (adenosine triphosphatase) and energy metabolism, anti-inflammatory and antioxidant functions, preventing cardiovascular diseases, activating vitamin D, antiplatelet and antithrombotic effects, muscle contraction and relaxation, effects on the nervous system, effects on protein biosynthesis, as well as an anti-infectious role against viral infections by activating cytotoxic T lymphocytes and Natural Killer cells [30–32]. In the specialized literature, a low level of serum magnesium has been correlated with an acute increase in inflammatory parameters, decreased immunity, and the presence of oxidative stress. On the other hand, some studies mention that individuals who have received magnesium supplements have shown a reduction in reactive oxygen species (ROS), improved mitochondrial activity and, consequently, a decrease in inflammation [33].

Therefore, the dynamics of calcium and magnesium play an important role in COVID-19 pathogenesis throughout various pathways leading to clinical and therapeutical implications [34–37] (Figures 1 and 2).

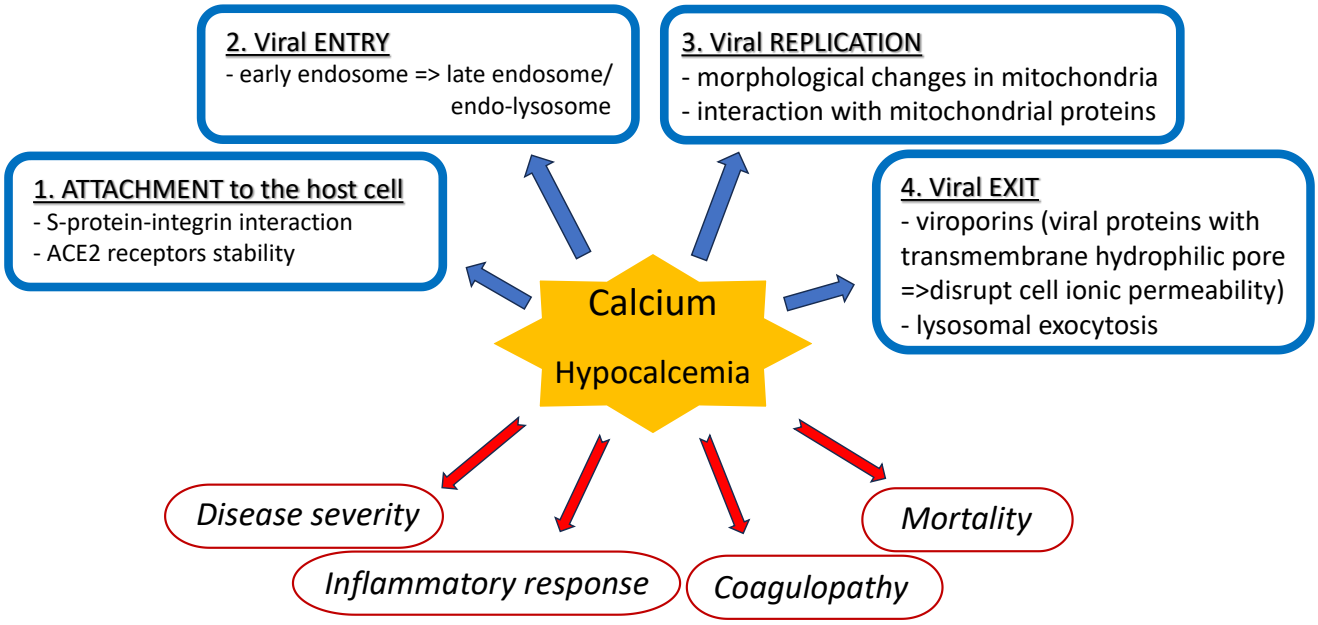

Figure 1. Calcium signaling involvement in COVID-19 pathogenesis.

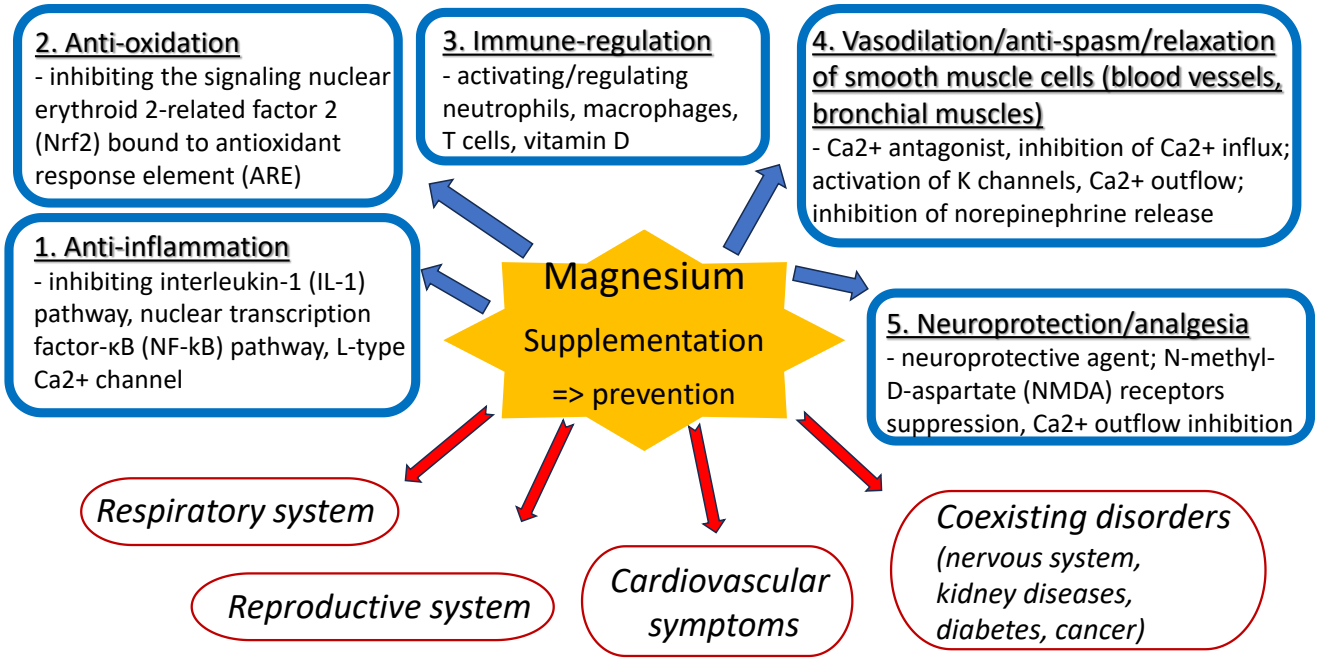

Figure 2. Role of magnesium in COVID-19 pathogenesis.

Multiple factors associated with greater severity and an unfavorable prognosis of COVID-19 infection have been identified, including elevated fibrinogen and D-dimer levels, increased CRP levels, advanced age, and the presence of comorbidities, including type 2 diabetes mellitus [38–43]. Certain research describes the degree of decrease in total cholesterol, LDL cholesterol, HDL cholesterol, and apolipoprotein A1 as predictors of mortality in SARS-CoV-2 infection [44]. Excepting the currently assessed biomarkers, such as the hematological, biochemical, coagulation, and inflammatory ones associated with COVID-19 severity progression, potential new biomarkers have been reported as significantly increased. These include homocysteine, angiotensin II, and parameters such as the neutrophil–lymphocyte ratio and monocyte–lymphocyte ratio [45–47].

The purpose of this study is to analyze the relationship between serum levels of calcium, magnesium upon hospital admission, and the severity of SARS-CoV-2 infection, other biochemical markers, as well as the influence of the presence of type 2 diabetes mellitus as a comorbidity on these electrolytes in COVID-19 infection. This study complements our previous research, in which other biomarkers such as ceruloplasmin, angiotensin-converting enzyme (ACE), transferrin, interleukin-6 (IL-6) were correlated with SARS-CoV-2 severity in patients with type 2 diabetes [48].

2. Materials and Methods

2.1. Study Design

This research aims to analyze serum calcium and magnesium levels upon admission with SARS-CoV-2 infection, taking into account the association with type 2 diabetes mellitus as a comorbidity, compared to the absence of this metabolic pathology. The present study includes 57 patients: a first group of 28 patients without diabetes but with SARS-CoV-2 infection and a second group of 29 patients with type 2 diabetes mellitus and SARS-CoV-2 infection admitted to the Municipal Clinical Hospital "Dr. Gavril Curteanu ORADEA" between October 2021 and December 2021. Our study was conducted in accordance with the Declaration of Helsinki. Before participating in this research, each participant provided informed written consent to their inclusion. The study protocol was approved by the Ethics Committee of the Municipal Clinical Hospital "Gavril Curteanu Oradea" (No. 32652/16.11.2020) and by the Ethics Committee of the University of Oradea (No. 5/A, 21.09.2020).

The inclusion criteria for the patients were as follows: the presence of infection with the SARS-CoV-2 virus, confirmed by RT-PCR test at admission to the hospital department, and the forms of severity assessed on chest CT at hospital admission (mild, moderate or severe); the presence of type 2 diabetes in the group that included patients with diabetes, without exhibiting changes in calcium or magnesium until that moment; and the patient's consent to participate in this study.

The exclusion criteria included patients known to have had hypo/hypercalcemia or hypo/hypermagnesemia in previous admissions, patients diagnosed with hypercalcemia or hypocalcemia, patients diagnosed with hypomagnesemia or hypermagnesemia, patients undergoing treatment with calcium and/or magnesium or vitamin D, patients with familial dyslipidemia, patients with renal diseases, patients with osteoporosis, patients with thyroid disorders, and patients with neoplasms.

2.2. Data Collection

The main variables referring to the following biomedical parameters of the patients were collected, including general data such as gender, age, place of origin, blood type, and Rh; family history such as a history of myocardial infarction, history of congestive heart failure, history of stroke, history of permanent atrial fibrillation, history of dilated cardiomyopathy, and blood glucose.

Serum laboratory parameters upon admission were also recorded, including the ionic calcium, total calcium, magnesium, creatinine, urea, uric acid, total proteins, total lipids, triglycerides, VLDL cholesterol, D-dimers, fibrinogen, and ESR, as well as the following parameters related to SARS-CoV-2 infection severity on admission: CT scan—clinical form of SARS-CoV-2 disease (absent = 0, mild = 1, moderate = 2, severe = 3).

2.3. Statistical Analysis

The statistical analysis was performed using SPSS software, version 20. For the results interpretation regarding the intensity of the relationship between two quantitative variables, the coefficient of determination, $d = R^2$, was also used. Adequate statistical tests were used for the performed analysis (Student's *t*-test, ANOVA test, Student's *t*-test for paired samples, chi-square test, normality tests (Kolmogorov–Smirnov), non-parametric tests (Kruskal–Wallis).

The significance threshold for the statistical tests used in the analyses was the one typically applied in medical research, $p = 0.05$ (=5%). Additionally, a significance threshold of $p = 0.01$ was used for cases where the analysis result was strongly significant ($p < 0.01$).

3. Results

In this study, we comparatively analyzed patients with SARS-CoV-2 infection without type 2 diabetes mellitus and patients with type 2 diabetes mellitus, evaluating the serum levels of calcium and magnesium, lipid profile, inflammatory parameters, as well as the level of total serum proteins. The normal laboratory values for total serum calcium are 8.8–10.6 mg/dL. For serum ionic calcium, the normal value is 4.2–5.2 mg/dL, and the normal value for serum magnesium is 1.9–2.5 mg/dL. The biomarkers levels of the patients were assessed upon hospital admission (Table 1).

Table 1. Descriptive evaluation of parameters assessed at admission.

	Number	Minimum	Maximum	Mean	Std. Deviation	Skewness		Kurtosis	
	Statistic	Statistic	Statistic	Statistic	Statistic	Statistic	Std. Error	Statistic	Std. Error
Age (years)	57	31	87	64.79	10.903	−0.760	0.316	1.022	0.623
Serum Ionic Ca (mg/dL)	46	3.1500	4.6100	4.057609	0.2948384	−0.289	0.350	0.744	0.688
Serum Total Ca (mg/dL)	53	6.3000	10.7500	8.474151	0.8741137	−0.028	0.327	0.686	0.644
Serum Mg (mg/dL)	43	1.7100	6.0300	2.266047	0.6574704	4.649	0.361	26.403	0.709
d-DIMERS (ng/mL)	40	99.0000	4067.4100	1122.946750	1010.4190813	1.456	0.374	1.771	0.733

Table 1. *Cont.*

	Number	Minimum	Maximum	Mean	Std. Deviation	Skewness		Kurtosis	
	Statistic	Statistic	Statistic	Statistic	Statistic	Statistic	Std. Error	Statistic	Std. Error
Fibrinogen (mg/dL)	56	51.2000	1121.4000	525.100000	196.2542692	0.183	0.319	0.955	0.628
ESR	49	3	128	56.51	32.631	0.465	0.340	−0.282	0.668
Serum Uric Acid (mg/dL)	44	1.9700	13.9900	5.940000	3.0565484	1.018	0.357	0.587	0.702
Serum Urea (mg/dL)	57	13.0000	184.0000	49.525439	33.5982742	2.042	0.316	5.346	0.623
Triglycerides (mg/dL)	35	40.00	509.00	174.5103	108.88252	1.416	0.398	1.814	0.778
Total Cholesterol (mg/dL)	35	73.00	245.00	151.7226	42.92284	0.487	0.398	−0.057	0.778
VLDL Cholesterol (mg/dL)	35	8	102	34.83	21.850	1.420	0.398	1.810	0.778
Total Lipids (mg/dL)	30	317.00	1016.00	598.1837	161.68525	0.630	0.427	0.322	0.833
Total Serum Proteins (g/dL)	49	2.0600	13.1000	5.812041	1.4208741	2.400	0.340	14.678	0.668

Within the group with diabetes mellitus, 16 patients presented decreased serum ionic calcium, 19 patients showed decreased total serum calcium, and the majority had normal serum magnesium levels. On the other hand, within the group without diabetes mellitus, 16 patients had decreased ionic calcium, 17 had decreased total calcium, and the vast majority had normal magnesium levels. Thus, the serum levels of ionic calcium, total calcium (*t*-test), and magnesium (Mann–Whitney nonparametric test) upon admission did not differ significantly between those with diabetes and those without diabetes ($p > 0.05$) (Table 2).

Table 2. Ionic calcium, total calcium, and magnesium within the groups.

	DZ	Number	Mean	Std. Deviation	*p*-Value
Serum Ionic Calcium	YES	26	4.063077	0.3123430	0.888
	NO	20	4.050500	0.2782554	
Serum Total Calcium	YES	28	8.600714	0.7911872	0.269
	NO	25	8.332400	0.9548049	
Serum Magnesium	YES	26	2.365769	0.8089854	0.263
	NO	17	2.113529	0.2669022	

DZ = diabetes mellitus.

Out of all the patients participating in the study, 49 patients presented severe forms on chest CT at admission, 5 patients had moderate forms, and 3 patients had mild forms of infection. Among the group of patients with type 2 diabetes mellitus, two patients showed mild forms on a CT scan, while in the group without diabetes, only one patient had a mild form. Out of the five patients with moderate forms, four patients had diabetes mellitus and one patient did not. When the Mann–Whitney nonparametric test was applied, the serum levels of ionic calcium, total calcium, and magnesium upon admission did not differ significantly between those with mild COVID-19 and those with moderate or severe forms ($p > 0.05$), as these levels were significantly influenced by the severity (Tables 3 and 4).

The concentration of ionic calcium from the reference interval was not statistically significantly associated with survival (Fisher's test, $p = 0.729 > 0.05$) (Table 5).

The concentration of total calcium from the reference interval was not statistically significantly associated with survival (chi-square test, $p = 0.155 > 0.05$), (Table 6).

Table 3. Ionic calcium, total calcium, magnesium, and mild forms of COVID-19 infection.

	Mild Form	Number	Mean	Std. Deviation	*p*
Serum Ionic Ca	0 (no)	44	4.055227	0.2938872	0.893
	1 (yes)	2	4.110000	0.4384062	
Serum Total Ca	0 (no)	50	8.473800	0.8469077	0.525
	1 (yes)	3	8.480000	1.5143315	
Serum Magnesium	0 (no)	42	2.269048	0.6651419	0.968
	1 (yes)	1	2.140000		

Table 4. Ionic calcium, total calcium, magnesium, and severe forms of COVID-19 infection.

	Severe Form	Number	Mean	Std. Deviation	*p*
Serum Ionic Calcium	0 (no)	4	3.777500	0.5191259	0.127
	1 (yes)	42	4.084286	0.2594379	
Serum Total Calcium	0 (no)	7	8.795714	1.5493747	0.202
	1 (yes)	46	8.425217	0.7377827	
Serum Magnesium	0 (no)	4	2.125000	0.3433657	0.672
	1 (yes)	39	2.280513	0.6827535	

Table 5. Ionic calcium and survival.

		Serum Lonic Calcium		Total
		0 = (<4.2)	1 = (4.2–5.2)	
Survival	0 (no)	23 $_{a}$	10 $_{a}$	33
	1 (yes)	10 $_{a}$	3 $_{a}$	13
Total		33	13	46

Each subscript letter denotes a subset of ionic Ca categories whose column proportions do not differ significantly from each other at the 0.05 level.

Table 6. Total calcium and survival.

Count					
		Serum Total Calcium			Total
		(0) Values Lower than the Lower Limit	(1) Values within the Reference Range	(2) Value Higher than the Upper Limit of the Reference Range	
Survival	0 (no)	25 $_{a}$	7 $_{a}$	1 $_{a}$	33
	1 (yes)	11 $_{a}$	9 $_{a}$	0 $_{a}$	20
Total		36	16	1	53

Each subscript letter denotes a subset of serum total calcium categories whose column proportions do not differ significantly from each other at the 0.05 level.

The concentration of magnesium from the reference interval was not statistically significantly associated with survival (chi-square test, $p = 0.848 > 0.05$), (Table 7).

Table 7. Serum magnesium and survival.

		Magnesium			Total
		(0) Values Lower than the Lower Limit	(1) Values within the Reference Range	(2) Value Higher than the Upper Limit of the Reference Range	
Survival	0 (no)	6 $_{a}$	18 $_{a}$	6 $_{a}$	30
	1 (yes)	2 $_{a}$	9 $_{a}$	2 $_{a}$	13
Total		8	27	8	43

Each subscript letter denotes a subset of Mg categories whose column proportions do not differ significantly from each other at the 0.05 level.

Out of all the patients participating in the study, 22 patients survived and 35 patients died (Table 8).

According to the result obtained from the chi-square test ($p > 0.05$), the distribution of subjects in intensive care did not differ statistically significantly between those with diabetes and those without diabetes (Table 9).

The distribution of all patients according to the infection severity assessed by CT was presented below (Table 10).

Table 8. Distribution of groups by survival.

		Type 2 Diabetes Mellitus		Total
		NO	YES	
Survival	NO	14 $_{a}$	21 $_{a}$	35
	YES	14 $_{a}$	8 $_{a}$	22
Total		28	29	57

Each subscript letter denotes a subset of DZ categories whose column proportions do not differ significantly from each other at the 0.05 level.

Table 9. Distribution by transfer to intensive care unit.

		Type 2 Diabetes Mellitus		Total
		NO	YES	
Intensive care	NO	8 $_{a}$	6 $_{a}$	14
	YES	20 $_{a}$	23 $_{a}$	43
Total		28	29	57

Each subscript letter denotes a subset of DZ categories whose column proportions do not differ significantly from each other at the 0.05 level.

Table 10. Distribution by severity of COVID-19 on CT.

		Type 2 Diabetes Mellitus		Total
		NO	YES	
COVID-19 severity on CT	1 (mild)	1 $_{a}$	2 $_{a}$	3
	2 (moderate)	1 $_{a}$	4 $_{a}$	5
	3 (severe)	26 $_{a}$	23 $_{a}$	49
Total		28	29	57

Each subscript letter denotes a subset of DZ categories whose column proportions do not differ significantly from each other at the 0.05 level.

Survival was statistically significantly associated (Fisher's test, $p = 0.004 < 0.05$) with mild and moderate forms of COVID-19 (Table 11).

Table 11. Survival by severity of COVID-19.

Severe Form * Survival Crosstabulation				
Count				
		Survival		Total
		NO	YES	
Severe form	No	1 $_{a}$	7 $_{b}$	8
	Yes	34 $_{a}$	15 $_{b}$	49
Total		35	22	57

* Each subscript letter denotes a subset of SUPRAVIETUIRE categories whose column proportions do not differ significantly from each other at the 0.05 level.

In the following tables (Tables 12–14), only the columns with variables that were statistically significantly correlated with serum ionic calcium, total serum calcium, and magnesium for at least one of the three groups (group without diabetes, group with type 2 diabetes mellitus, and the total participants in the study forming the combined group) were included.

From the previous table (Table 12), it can be observed that for subjects without diabetes mellitus, magnesium was statistically significantly correlated with the inflammatory parameters fibrinogen and ESR (erythrocyte sedimentation rate), while for those with diabetes mellitus, magnesium was not statistically significantly correlated with any parameter in

the study. In the combined group, statistically significant correlations of magnesium were found with fibrinogen, triglycerides, total lipids, and ESR (direct correlation). It should be noted that although fibrinogen and ESR were statistically significantly correlated with magnesium only for subjects without diabetes, this condition (diabetes) did not seem to significantly influence the level of correlations in the general population (subjects with and without diabetes).

From the previous table (Table 13), it can be observed that for the group without diabetes mellitus, serum total calcium was statistically significantly correlated with urea, total cholesterol, total serum proteins, and with serum ionic calcium; while in the group with diabetes mellitus, serum total calcium was statistically significantly correlated only with total serum proteins. In the combined group that included both groups (all patients), statistically significant correlations of serum total calcium were found, including total serum proteins (direct correlation) and serum ionic calcium. It should be noted that urea and total cholesterol were statistically significantly correlated with serum total calcium only for subjects without diabetes, and this condition significantly influences the level of correlations in the general population (subjects with and without diabetes).

Table 12. Correlations of magnesium in subjects with type 2 diabetes mellitus, without diabetes mellitus, and the combined group.

Magnesium	DZ		Fibrinogen	ESR	Triglycerides	VLDL Cholesterol	Total Lipids
	NO	Pearson R Correlation	0.529	0.680	0.473	0.462	0.267
	-	P	0.029	0.005	0.103	0.112	0.378
	-	N	17	15	13	13	13
	YES	Pearson R Correlation	0.183	0.070	0.250	0.252	−0.008
	-	P	0.380	0.768	0.263	0.257	0.974
	-	N	25	20	22	22	17
	Total subjects	Spearman Rho Correlation	0.470	0.551	0.579	0.574	0.397
	-	P	0.002	0.001	0.000	0.000	0.030
	-	N	42	35	35	35	30

Table 13. Correlations of total serum calcium in subjects with Type 2 diabetes mellitus, without diabetes mellitus, and the combined group.

Serum Total Calcium	DZ		Uric Acid	Urea	Total Cholesterol	Total Lipids	Total Serum Proteins
	NO	Pearson R Correlation	−0.463	−0.411	0.566	0.525	0.473
	-	P	0.053	0.041	0.044	0.065	0.026
	-	N	18	25	13	13	22
	YES	Pearson R Correlation	0.100	−0.229	0.126	−0.041	Rho = 0.726
	-	P	0.635	0.240	0.575	0.875	0.000
	-	N	25	28	22	17	25
	Total subjects	Pearson R Correlation	−0.047	−0.201	0.267	0.192	Rho = 0.611
	-	P	0.763	0.150	0.122	0.309	0.000
	-	N	43	53	35	30	47

Rho = Spearman's correlation coefficient.

From the previous table (Table 14), it can be observed that for the group without diabetes mellitus, ionic calcium was statistically significantly correlated only with serum total calcium, while in the group with diabetes, ionic calcium was not statistically significantly correlated with serum total calcium. Additionally, in the group with diabetes, ionic calcium was statistically significantly correlated with uric acid (inverse correlation), urea (inverse correlation), total cholesterol (direct correlation), and not statistically significantly correlated with total lipids. In the combined group, statistically significant correlations of ionic calcium were found with serum total calcium (direct correlation), uric acid (inverse

correlation), urea (inverse correlation), total cholesterol (direct correlation), and total lipids (direct correlation).

Serum total calcium and D-dimers have statistically significantly different means in subjects who were admitted to the intensive care unit compared to those who did not require transfer to the intensive care unit ($p < 0.05$). The other biomedical quantitative parameters did not differ statistically significantly based on transfer to the intensive care unit (Table 15).

Table 14. Correlations of ionic calcium in the group with Type 2 diabetes mellitus, without diabetes mellitus, and the combined group.

Ionic Calcium	DZ		Serum Total Calcium	Uric Acid	Urea	Total Cholesterol	Total Lipids
	NO	Pearson R Correlation	0.677	−0.191	−0.274	0.381	0.255
	-	P	0.001	0.463	0.243	0.198	0.401
	-	N	20	17	20	13	13
	YES	Pearson R Correlation	0.081	−0.584	−0.472	0.631	0.48
	-	P	0.696	0.002	0.015	0.002	0.051
	-	N	26	25	26	22	17
	Total subjects	Pearson R Correlation	0.341	−0.425	−0.379	0.535	0.405
	-	P	0.020	0.005	0.009	0.001	0.027
	-	N	46	42	46	35	30

Table 15. Comparison of means of quantitative parameters in relation to transfer to intensive care unit of subjects.

Intensive Care Transfer		Number	Mean	Std. Deviation	*p*
Serum Ionic Ca	0 (no)	7	4.165714	0.2542215	0.297
	1 (yes)	39	4.038205	0.3003320	
Serum Total Ca	0 (no)	14	8.898571	0.9024229	0.033
	1 (yes)	39	8.321795	0.8226717	
Serum Magnesium	0 (no)	7	2.734286	1.4660930	
	1 (yes)	36	2.175000	0.3128441	0.353
D-dimers	0 (no)	6	247.066667	147.1468201	
	1 (yes)	34	1277.513824	1019.4082105	0.000
Fibrinogen	0 (no)	13	495.723077	128.0370594	0.543
	1 (yes)	43	533.981395	213.0857688	
ESR	0 (no)	13	50.38	35.099	0.436
	1 (yes)	36	58.72	31.921	
Uric acid	0 (no)	4	4.265000	1.6925819	0.255
	1 (yes)	40	6.107500	3.1247061	
Urea	0 (no)	14	40.428571	21.5289225	0.247
	1 (yes)	43	52.487209	36.4018888	
Triglycerides	0 (no)	3	201.9533	64.82535	0.655
	1 (yes)	32	171.9375	112.48052	
Total cholesterol	0 (no)	3	116.4300	21.05480	0.139
	1 (yes)	32	155.0313	43.13032	

Table 15. *Cont.*

Intensive Care Transfer		Number	Mean	Std. Deviation	*p*
VLDL cholesterol	0 (no)	3	40.33	13.204	0.655
	1 (yes)	32	34.31	22.565	
Total lipids	0 (no)	3	554.1700	78.70932	0.628
	1 (yes)	27	603.0741	168.62268	
Serum Total Proteins	0 (no)	9	5.530000	1.5370507	0.516
	1 (yes)	40	5.875500	1.4062971	

4. Discussion

In this study, we evaluated the influence of type 2 diabetes mellitus as a metabolic comorbidity on serum calcium and magnesium levels upon admission in patients who contracted the SARS-CoV-2 virus and required hospitalization, in contrast to patients who developed COVID-19 without being diagnosed with type 2 diabetes mellitus.

An important aspect of our research is that the presence of type 2 diabetes mellitus did not statistically significantly influence serum levels of calcium and magnesium at the time of hospitalization ($p > 0.05$). Although our study was conducted on a small sample size due to the high number of exclusion criteria, regarding the influence of SARS-CoV-2 infection on serum calcium values upon admission, we observed that hypocalcemia predominated in both groups, in accordance with other studies from the specialized literature.

In a recent study, 2/3 of patients infected with SARS-CoV-2 presented hypocalcemia upon hospital admission, and the decrease in serum calcium was associated with an increased need for oxygen therapy and transfer to the intensive care unit, suggesting a possible involvement of calcium in the virulence and mechanism of the novel coronavirus [49]. In our study, serum total calcium and D-dimers had statistically significantly different means in subjects who required transfer to the intensive care unit compared to those who did not require transfer to the intensive care unit ($p < 0.05$).

There are recent data in the specialized literature describing the association between hypercalcemia in COVID-19 and acute kidney injury, sepsis, patient transfer to intensive care with patient intubation, as well as mortality. These observations come from premises such as the alteration of calcium homeostasis, inflammatory changes, and endothelial cell lesions in the body caused by the novel coronavirus [50].

The alteration of calcium represents one of the important parameters of viral infection, with hypocalcemia being associated with the presence of cardiac comorbidities, hospitalization in a clinical ward, mechanical ventilation, superinfection, thrombosis risk, and an unfavorable prognosis, independent of vitamin D or parathormone [51]. Studies have shown that decreased serum calcium levels were present in patients who developed less severe forms of viral infection with the novel coronavirus [52].

In another study, a connection was established between serum calcium levels and the occurrence of multiple organ injuries in patients with SARS-CoV-2, including the link between hypocalcemia, inflammation, cytokine storm, and the influence of IL-6 on serum calcium concentration [53]. Recent studies have even calculated various scores between calcium and other electrolytes, thus exposing a ratio between magnesium and calcium in individuals who have contracted SARS-CoV-2 [54].

Hypomagnesemia in COVID-19 patients has been associated with the need for hospitalization and the severity of the infection with the novel coronavirus, with certain studies showing a connection between the low level of magnesium at admission and mortality caused by SARS-CoV-2 [55].

In our study, the magnesium level was predominantly normal at admission in the majority of patients included in the research, without influencing the survival or the severity of the viral infection. The decrease in serum magnesium levels with negative

effects on the body's defense and inflammatory processes has been mentioned in the literature as a high-risk factor, not only for severe prognosis, but also for the development of complications associated with SARS-CoV-2 [56]. Another study described a direct link between hypomagnesemia and symptomatic forms of COVID-19, the persistence of long COVID in elderly patients, prolonged hospitalization, high mortality, as well as a correlation between obese patients with low serum magnesium levels and post-viral death [57].

Recent studies highlight that hypermagnesemia increases the risk of death for COVID-19 patients, along with hyperphosphatemia and hypovitaminosis D, especially since magnesium is involved in the metabolism and activation of vitamin D [58].

Hypomagnesemia may contribute to viral infection and increase the inflammatory response, but it has also been suggested as a negative prognostic factor for some patients who died from SARS-CoV-2 infection [59]. Certain studies suggested that magnesium might inhibit TMPRSS2 (transmembrane serine protease 2) and furin proprotein convertase, human body proteases that can cleave the viral spike protein of SARS-CoV-2. Decreased serum magnesium levels have been associated with the exacerbation of the cytokine storm, disruption of metabolic and biochemical pathways, and it has been mentioned that patients with type 2 diabetes may be more predisposed to low serum calcium levels [59].

In another study, it was highlighted that hyperphosphatemia may lead to acute kidney injury and multiple organ failure in patients with SARS-CoV-2. Mild hypocalcemia was associated with severe forms of the disease, along with increased ferritin, creatinine, bilirubin, INR, and aspartate aminotransferase (AST) levels [60]. In a recent study, the increase in serum lipids was inversely associated with the level of acute-phase reactants [61]. Studies have also reported that the decrease in HDL cholesterol in infected patients was associated with the severity of COVID-19 infection [62].

In the specialized literature, a connection between decreased HDL cholesterol and the severity of COVID-19 has been presented, indicating that high levels of HDL cholesterol were directly associated with a lower risk of infection with the novel coronavirus [63]. Other research has indicated that even VLDL and LDL cholesterol have been affected by COVID-19 infection [64].

Some studies have described aspects related to the increase in LDL cholesterol, total cholesterol, along with elevated triglycerides, and decreased HDL cholesterol that have been identified in patients who have survived COVID-19 infection [65].

In this study, we noticed that the serum level of magnesium correlated significantly with VLDL cholesterol ($p < 0.001$), with total lipids ($p = 0.03$), triglycerides ($p < 0.001$), possibly through changes in lipid composition, as well as with inflammatory parameters such as fibrinogen ($p = 0.002$) and ESR ($p = 0.001$), most likely through the anti-inflammatory and antioxidant role of magnesium.

In our research, the serum level of total calcium correlates significantly with ionic calcium ($p = 0.02$) and with total proteins ($p < 0.001$). Additionally, in the present study, we identified a statistically significant correlation between ionic calcium and total calcium ($p = 0.02$), uric acid ($p = 0.005$), urea ($p = 0.009$), total cholesterol ($p = 0.001$), and total lipids ($p = 0.027$).

Some studies described the subject of decreased albumin as an independent factor for mortality in COVID-19, as well as its association with severe forms of infection, cytokine storm, advanced age, and multiple-organ failure [66,67]. In other specialized studies, serum urea, d-dimer, and troponin levels have been mentioned as negative prognostic factors in COVID-19, along with male gender, advanced age, and the presence of type 2 diabetes [68,69].

Another study analyzed the increase in serum creatinine levels, urea, and reduced filtration rate in patients admitted to the intensive care unit, as well as the fact that acute and chronic kidney disease, monitored through increased serum creatinine, are associated with increased mortality in SARS-CoV-2 [70].

Another important finding of our research is that the serum levels of ionized calcium and total calcium, as well as magnesium, assessed at the time of hospitalization, did not

statistically significantly influence the survival in the patients included in the study, although the majority of participants in this study had severe forms of COVID-19 infection on CT scan at admission. Diagnosis of severe forms of viral infection at the time of hospitalization and the link with the serum level of biochemical parameters, including calcium and magnesium, in patients with type 2 diabetes who, until viral infection with SARS-CoV-2, had normal serum levels of calcium and magnesium, is relevant for establishing an individualized therapeutic plan at the hospital, but also at discharge.

Among the limitations of this study are the low number of patients, single-center study, biomarkers/parameters were assessed only at admission. Future multi-center studies with much larger groups are needed to explore the evolution of serum levels of calcium and magnesium after SARS-CoV-2 viral infection and the long-term evolution of type 2 diabetes.

5. Conclusions

Regarding the influence of SARS-CoV-2 infection on serum calcium and magnesium, the pathophysiological mechanisms are not fully elucidated. However, it is known that calcium homeostasis is altered in viral infections, including SARS-CoV-2, and the virus's spike protein has a high affinity for calcium. On the other hand, magnesium acts as an antagonist to calcium, with both electrolytes playing essential roles in the human body, and this electrolyte can also be influenced by viral infection, with low magnesium levels facilitating viral infection, inflammatory response, or cytokine storm. According to this study, survival was not statistically significantly influenced by the serum levels of these electrolytes in hospitalized patients, but rather by the mild and moderate forms of COVID-19. Thus, our study revealed that serum levels of calcium and magnesium at the time of admission for COVID-19 infection were not statistically significantly influenced by the association with type 2 diabetes, although most patients presented hypocalcemia and normal magnesium levels. In the group of diabetic patients, serum total calcium was statistically significantly correlated only with total serum proteins. Meanwhile, ionic calcium was statistically significantly correlated with uric acid (inverse correlation), urea (inverse correlation), and total cholesterol (direct correlation), and not statistically significantly correlated with total lipids. Overall, the magnesium level significantly correlated with lipids (triglycerides, total lipids) and inflammatory (fibrinogen, ESR) biomarkers. Other statistically significant correlation was observed between serum total calcium and D-dimers with the transfer to the intensive care unit.

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Abbreviations

In this manuscript, the following abbreviations are used:

SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
COVID-19	Coronavirus disease
CRP	C-reactive protein
RT-PCR	Reverse Transcription Polymerase Chain Reaction
CT	Computed tomography
Mg	Serum magnesium
Ca	Calcium
ATP	Adenosine triphosphatase
ROS	Reactive oxygen species
TMPRSS2	Transmembrane serin protease 2
INR	International normalized ratio
ESR	Erythrocyte sedimentation rate
VLDL	Very Low-Density cholesterol
HDL	High-density cholesterol
LDL	Low-density cholesterol

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