https://doi.org/10.48047/AFJBS.7.2.2025.487 -508

African Journal of Biological Sciences

Journal homepage: http://www.afjbs.com

Research Paper Open Access

The relationships between serum calcium, magnesium, and lipid metabolism in type 2 diabetic patients from northwestern Algeria: a cross-sectional study

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Volume 7, Issue 2, Feb 2025

Received: 05 Jan 2025

Accepted: 29 Jan 2025

Published: 09 Feb 2025

doi:10.48047/AFJBS.7.2.2025.487 -508

Abstract

Objective: This study aimed to explore the relationships between serum calcium, magnesium levels, and their ratio with lipid profiles in patients with type 2 diabetes.

Material and Methods: This cross-sectional study involved 116 diabetic patients from northwestern Algeria. Fasting blood samples were collected to assess serum calcium, magnesium, and lipid levels. Participants were categorized into quartiles based on their serum calcium, magnesium, and Ca/Mg ratio. Associations between serum minerals and lipid parameters were evaluated using ANOVA, Fisher's test, and bivariate correlation analysis. Linear regression was conducted to examine unbiased associations between lipid ratios and serum mineral levels.

Results: The sample consisted predominantly of women (91 women *vs.* 25 men), with a mean age of 67.41 ± 10.12 years. Higher quartiles of serum calcium were correlated with increased LDL (p=0.012), blood glucose (p=0.004), and systolic blood pressure (p<0.001). The third quartile of magnesium levels was associated with lower total cholesterol (p=0.015) and triglycerides (p=0.004). The Ca/Mg ratio impacted only triglyceride levels (p=0.009). Heatmap analysis showed weak associations between lipid ratios and the minerals.

Conclusion: The relationships between serum calcium, magnesium levels, and the Ca/Mg ratio with lipid profiles in T2D patients may be considered as crucial factors in predicting cardiovascular risk.

Keywords: Type 2 diabetes; Serum calcium; Serum magnesium; Lipid profile.

Introduction

Type 2 Diabetes (T2D) is a metabolic circumstance that is characterized by insulin resistance and an impaired ability to adjust blood glucose ranges.[1] Wordily, T2D is considered the biggest public health problem with considerable human and socio-economic impacts.[2] Estimably, there may be 642 million sufferers of diabetes in the world by 2040 against 415 million patients (8.8%) in the year of 2015, with a highest exchange predicted in the metropolitan populations of low- and middle-income countries. It has been reported that more than 90% of patients with T2D reside in urban areas and about 10% in rural areas.[3]

Minerals such as zinc, potassium (K), calcium (Ca), and magnesium (Mg) are known to be essential for the control of glucose metabolism.[4] Calcium and magnesium are important minerals that actively participate in many physiological processes, including glucose metabolism and lipid homeostasis. Alterations in serum levels of these two minerals have been pronounced in individuals with T2D, suggesting a specific role for these minerals in the improvement of diabetes profile and its complications.[5] Numerous studies have examined the association between serum calcium levels and T2D, with conflicting results. Similarly, investigations have indicated inconclusive effects regarding the relation between serum magnesium levels and T2D, with some studies finding reduced magnesium levels in diabetic subjects.[6]

In the same context, people with T2D regularly present abnormalities of lipid metabolism.[7] Dyslipidemia, characterized by low levels of high-density lipoprotein (HDL) and high levels of triglycerides and LDL, is a well-established risk factor for cardiovascular complications in diabetic patients.[8]

The present cross-sectional study is dedicated to explore the interactions between serum calcium and magnesium levels as well as the calcium-to-magnesium (Ca/Mg) ratio, with lipid metabolism, particularly lipid ratios, which are regarded as indicators of potential cardiovascular complications, in patients with T2D residing in northwestern Algeria.

Materials and Methods

Study Design and Participants

This study utilized a cross-sectional design, which deemed appropriate for comprehending the relationships between serum calcium, magnesium levels, their ratio, and lipid metabolism in patients with T2D. The cross-sectional approach allowed us to obtain a snapshot of these associations at a specific point in time, making it possible to explore the links between these variables within a defined patient group. We recruited 116 patients with T2D

from the Larbi Ben M'Hidi Diabetic Center in Sidi-Bel-Abbes city, located in northwestern Algeria, between December 2023 and May 2024. All participants provided written informed consent; a confidentiality was ensured.

The inclusion criteria for the study were as follows: (1) Subjects with T2D, (2) age of 40 years or older, (3) Be willing to participate in the study and provide informed consent. Exclusion criteria included: (1) Individuals with other types of diabetes, (2) Individuals with a history of kidney or liver disease, (3) Pregnant or breastfeeding women, (4) Subjects receiving medications known to affect calcium, magnesium, or lipid metabolism.

Ethical approval

The study was conducted in compliance with the ethical principles outlined in the Helsinki Declaration and the protocol of the study was approved by the Ethics Committee of CHU of Sidi Bel Abbes (No: 27, Date: December 2nd, 2023).

Sample Size Calculation

A power analysis was used to determine our sample size based for assessing the associations between serum calcium, magnesium, their Ca/Mg ratio, and lipid metabolism. A traditional impact length of 0.3, was selected for the sample size calculation, with a statistical strength of 0.80, and a significance level of 0.05. Following these parameters, the analysis indicated that a minimum of 115 participants was necessary to achieve reliable results.

Data Collection and Blood Analyses

Data collection was performed by trained research assistants following a standardized protocol. A comprehensive questionnaire was used to collect demographic information including age, gender, address, marital status, education level, and medical history.

Anthropometric parameters, such as weight, height, and waist circumference, were acquired using standardized methods. Body mass index (BMI) was calculated as dividing weight (in kilograms) by height (in meters) squared. Blood pressure was measured using a calibrated sphygmomanometer with participants in a seated position after 5 minutes of rest.

Blood samples were collected in heparinized tubes from each diabetic patient in the morning after an overnight fast of at least eight (8) hours. Blood samples were immediately centrifuged at 3500 for 5 minutes rpm and stored at -80 °C until further analysis. Glycemic and lipid parameters, as well as total cholesterol, triglycerides, LDL-c and HDL-c, were accomplished by enzymatic colorimetric methods. While, glycated hemoglobin (HbA1c) levels were measured using a high-performance liquid chromatography (HPLC) method.

Serum calcium and magnesium levels were quantified using a *Selectra Pro M: Automatic Biochemistry Analyzer*. ELITechGroup. Calibration of the analyzer was performed regularly using calibration standards to ensure the accuracy of the serum measurements.The Ca/Mg ratio was calculated based on serum calcium and magnesium levels.

Ethical approval

The study was conducted in compliance with the ethical principles outlined in the Helsinki Declaration and the protocol of the study was approved by the Ethics Committee of CHU of Sidi Bel Abbes (No: 27, Date: December, 2, 2023).

Statistical analyses

Statistical analysis was performed using SPSS software version 27.0 (IBM Corp., Armonk, NY, USA, 2020). Descriptive statistics were executed to summarize the baseline characteristics of the patients. Continuous variables, they were presented as mean ± standard deviation or median and quartiles, according to their distribution. The association between serum calcium, magnesium, Ca/Mg ratio and lipid parameters was assessed using ANOVA, Fisher's test and bivariate correlation analysis. In addition, linear regression analysis was performed to capture the unbiased association between lipid ratios and serum mineral levels. Statistical significance was set at $p \leq 0.05$.

Results

Table 1 summarizes the main characteristics of the 116 T2D patients who were involved in the study, with a majority of women (91 women *vs.* 25 men). The mean age of the participants was 67.41±10.12 years (range: 41-90 years). The average duration of diabetes was 19.95±8.80 years. Participants had a mean weight of 75.80 kg (range: 48-128 kg), a mean height of 1.63 meters, and a mean body mass index (BMI) of 27.71 kg/m² (range: 16.85-40.40), indicating a general tendency towards overweight and obesity. Waist circumference averaged 107.57±10.84 cm, suggesting a potential prevalence of abdominal obesity.

Regarding the lipid profile, the mean levels of total cholesterol were 1.72±0.38 g/L, HDL-c 0.44±0.13 g/L, LDL-c 1.02±0.33 g/L, and triglycerides 1.35±0.52 g/L, all of which suggest potential cardiovascular risk. The mean blood glucose level was 1.38 g/L (range: 0.60-2.22 g/L), with a mean HbA1c of 7.93%, reflecting average glycemic control over the past 2 to 3 months. Blood pressure measurements showed a mean systolic pressure of 13.06 cmHg (range: 9.00-18.00 cmHg) and mean diastolic pressure of 7.03 cmHg (range: 4.00-10.00 cmHg). Concerning serum micronutrients, the mean serum calcium level was 2.514 mmol/L (range: 2.253-2.738 mmol/L), and the mean magnesium level was 0.849±0.127 mmol/L.

Participants were divided into four groups based on quartiles of serum calcium levels (Table 2). Age and diabetes duration showed non-significant differences between groups (p=0.787 and p=0.429, respectively), while other anthropometric parameters exhibited greater variation. Participants in the fourth quartile of calcium had a slightly higher mean age (68.72 years) compared to those in the lowest quartile (66.07 years). However, no statistically significant differences were observed in weight, BMI, or waist circumference between the four groups. Notably, a substantial increase in LDL-c levels was indicated (p=0.012) from the first (0.87 g/L) to the third quartile (1.14 g/L), suggesting a potential correlation between increased LDL-C and higher serum calcium levels. Participants in the fourth quartile of calcium also had higher blood glucose levels (1.56 g/L) compared to those in the first quartile (1.23 g/L) (p=0.004). Additionally, systolic blood pressure was significantly higher (p<0.001) in the fourth quartile (14.48 cmHg) compared to the first quartile (12.32 cmHg), suggesting that high blood pressure may be related to higher serum calcium levels. No significant variation in HbA1c levels was found between quartiles (p=0.398).

Table 3 shows results of the participants divided based on quartiles of serum magnesium levels. No significant differences were found in age (p=0.624) or diabetes duration (p=0.479) between quartiles. However, weight (82.81±15.28 kg) and height (1.67±0.10 m) were significantly higher in the third quartile of magnesium compared to the other quartiles (p=0.027 and p=0.011, respectively). Total cholesterol was lower in the third quartile (1.57 g/L) compared to the others quartiles (p=0.015), similarly for triglycerides which were also significantly lower in the third quartile (1.19 g/L) (p=0.004). HDL (p=0.215) and LDL (p=0.139) levels demonstrated that there were no differences. Blood glucose and HbA1c levels remained stable across quartiles (p=0.217 and p=0.696, respectively), while systolic (p=0.436) and diastolic (p=0.530) blood pressure, did not present significant variations. Serum calcium levels remained consistent across quartiles (p=0.556), while the Ca/Mg ratio revealed higher significant variations (p<0.001) between quartiles.

Participants were further categorized into quartiles based on their Ca/Mg ratio (Table 4). Significant variations were observed in weight (F=3.080, p=0.030) and height (F=3.539, p=0.017) across the quartiles. However, no huge variations were found in age (F=0.052, p=0.984), duration of diabetes (F=0.582, p=0.628), BMI (F=1.080, p=0.761), waist circumference (F=1.547, p=0.206), and overall LDL cholesterol levels (F=1.802, p=0.151). In contrast, triglyceride levels exhibited a significant variation (p=0.009) between the quartiles of the Ca/Mg ratio.

Scatterplots and linear regression between different lipid ratios, calcium, magnesium and Ca/Mg ratio are shown in Fig 1. Fig 1 (A) illustrates the TC/HDL ratio and its relationships with Ca (A1), Mg (A2) and Ca/Mg ratio (A3), respectively. Fig 1 (B) displays the LDL/HDL ratio and its relationships with Ca (B1), Mg (B2) and Ca/Mg ratio (B3), respectively, and finally, Fig 1 (C) presents the TG/HDL ratio and its associations with Ca (C1), Mg (C2) and Ca/Mg ratio (C3), respectively. The findings in figures A1 and B1 indicate that the CT/HDL and LDL/HDL ratios are positively correlated with serum calcium levels. An approaching statistical relevance for TC/HDL (p=0.055) and reaching statistical significance for LDL/HDL (p=0.018).

In Fig 1 (C3), the TG/HDL ratio shows a potential correlation with the Ca/Mg ratio; however, this relationship does not reach statistical significance (p=0.153, R^2=0.018). Fig 1 (C2) indicates a weak inverse correlation between serum TG/HDL levels and magnesium levels (p=0.343). Regarding the Ca/Mg ratio, no discernible correlation was revealed between the TC/HDL ratio and the Ca/Mg ratio (R^2=0.000) (Fig 1 (A3)), similarly for the LDL/HDL ratio (R^2=0.000) (Fig1 (B3)).

The heatmap correlation analysis (Fig 2) reveals several relationships between serum calcium (Ca), magnesium (Mg), the Ca/Mg ratio (Ca_Mg_Ratio), and various lipid profile parameters. Serum calcium and magnesium exhibit very weak correlation with each other (0.071). In contrast, the Ca/Mg ratio shows a strong inverse correlation with serum magnesium levels (-0.95) and a weak positive correlation with calcium levels (0.17).

Total cholesterol (TC) levels exhibit a weak positive association with serum calcium levels (0.24), very weak inverse correlation with serum magnesium levels (-0.009), and very weak positive correlation with the Ca/Mg ratio (0.11). Triglycerides (TG) levels, show an extremely weak positive correlation with serum calcium levels (0.098), Ca/Mg ratio (0.23), and an inverse association with serum magnesium (-0.16). HDL-c levels display very weak positive correlation with the Ca/Mg ratio (0.083), and inverse correlations with both calcium (-0.055) and magnesium (-0.097).

The heatmap correlation analysis (Fig 3) reveals several associations between Ca, Mg, Ca/Mg ratio and lipid ratios. Serum calcium and magnesium levels show very weak positive correlation with each other (0.071). The Ca/Mg ratio demonstrates a strong inverse correlation with magnesium (-0.95) and a weak positive association with calcium levels (0.17). The TC/HDL lipid ratio (TC_HDL_Ratio) displays a weak positive association with calcium (0.18) and magnesium (0.063) levels, along with very weak positive correlation with the Ca/Mg ratio (Ca_Mg_Ratio) (0.011). Similarly, the LDL/HDL ratio shows a weak positive correlation with

calcium (0.22), and very weak positive correlation with both magnesium (0.051) and Ca/Mg ratio (0.022).

The TG/HDL ratio (TG_HDL_Ratio) shows very weak positive correlations with calcium (0.063) and with the Ca/Mg ratio (0.13), alongside a weak negative correlation with magnesium (-0.089). Additionally, lipid ratios TC/HDL, LDL/HDL, and TG/HDL showed strong to moderate positive associations with each other, ranging from 0.530 to 0.893.

Discussion

The prevalence of dyslipidemia among individuals with T2D is widely recognized as a serious concern, due its impact on cardiovascular health. This cross-sectional study, aimed to examine the associations between serum calcium, magnesium levels, and their Ca/Mg ratio with classical lipid parameters and their ratios as major indicators of cardiovascular risk in patients with T2D in northwestern Algeria. The results provide insight into the complex interplay between mineral metabolism, lipid profiles, and cardiovascular risk in the context of T2D.

In the present study, a significant positive association was observed between elevated serum calcium levels and increased LDL-c concentrations (R^2=0.069, p=0.012). Participants in the third calcium quartile had a mean LDL-c of 1.14 g/L compared with 0.87 g/L in the first quartile. These findings are consistent with several recent studies. Al-Daghri *et al.* (2023) reported a positive correlation between serum calcium and LDL-c (R^2=0.234, p<0.001) in T2D patients,[9] similarly, a meta-analysis by Zhang *et al.* (2022) found that every 1 mg/dL increase in serum calcium was associated with a 0.020 mmol/L (0.77 mg/dL) increase in LDL-c (95% CI: 0.011–0.029, p<0.001).[10] Bakr *et al.* (2016) in Egypt, reported that higher calcium levels were correlated with increased total cholesterol and LDL-c in individuals with T2D.[11] Mechanisms underlying this association may include the impact of calcium on lipid synthesis, absorption, and vascular function.[12] Calcium has been shown to influence cholesterol synthesis in the liver by regulating the activity of HMG-CoA reductase, a fundamental enzyme in cholesterol biosynthesis.[13] High calcium levels may contribute to an increase in this enzyme, leading to an overproduction of cholesterol and high LDL-c levels. Additionally, high calcium levels have been associated with alterations in bile acid metabolism, potentially reducing bile acid excretion and promoting cholesterol retention in the liver.[14]

Regarding lipid ratios, our results indicate positive correlations between calcium levels and TC/HDL and LDL/HDL ratios, which are well-established as markers of cardiovascular risk in T2D subjects (p=0.05 and p=0.018, respectively). These results support the hypothesis that calcium homeostasis may play a crucial role in lipid metabolism and cardiovascular disease risk in the context of T2D, as also suggested by Ghosh *et al.* (2017) in Saudi women with T2D.[15]

Calcium stability has been proven to play a crucial role in insulin secretion and sensitivity.[16] In diabetics, calcium balance is impaired and leads to imperfect cellular control in cardiac muscles, platelets, skeletal muscles, and erythrocytes. This alerted homeostasis is worrisome because it can be an important complementary factor in controlling proper insulin action and secretion, and different vascular complications can be affected by this altered balance.[17] Furthermore, a study claimed that in recent times, the severity of atherosclerosis has been counted by the coronary artery calcium score, this score signifies the amount of calcium in the coronary arteries. A high score signifies a high cardiovascular risk. There is a close relationship between coronary artery calcium score and serum calcium.[18] Serum calcium levels may impact cardiovascular disease risk through various processes.[19]

Interestingly, Higher serum magnesium levels were inversely associated with total cholesterol (p=0.015) and triglycerides (p=0.004). The third quartile of magnesium exhibited the most pronounced reductions in these lipids (total cholesterol: 1.57 g/L *vs.* 1.72 g/L in the overall study population; triglycerides: 1.19 g/L *vs.* 1.35 g/L in the overall study population). Participants in the third quartile of magnesium had significantly lower triglyceride levels (1.19±0.39 g/L) compared with those in the first quartile (1.64±0.55 g/L). These findings are supported by a systematic review and meta-analysis by Li *et al.* (2023), which demonstrated that magnesium supplementation reduced total cholesterol by -0.17 mmol/L (95% CI: -0.28 to -0.06, p=0.003), LDL-c by -0.12 mmol/L (95% CI: -0.21 to -0.02, p=0.02), and triglycerides by -0.23 mmol/L (95% CI: -0.36 to -0.09, p=0.001) in T2D patients.[20]

Our results are consistent with the study published by Ben-Salem *et al.* (2018) in Tunisia, which showed that high magnesium levels were associated with lower total cholesterol and LDL-c levels in T2D patients.[21] The positive effects of magnesium on lipid metabolism may be explained by its role in inhibiting enzymes involved in lipid synthesis and activating those involved in fatty acid oxidation.[22]

The inverse relationship between high serum magnesium levels and low total cholesterol and triglyceride levels may be attributed to the pleiotropic effects of magnesium on metabolic health. Magnesium plays a crucial role in insulin signaling, and its deficiency is often associated with insulin resistance, a key pathophysiological feature of T2D.[23] Improved insulin sensitivity may lead to better glucose uptake by cells, reducing the need for lipolysis and thereby lowering triglyceride levels. Magnesium also has anti-inflammatory properties and can modulate the activity of enzymes involved in lipid metabolism, such as lipoprotein lipase and HMG-CoA reductase, contributing to favorable changes in the lipid profile.[12]

It has been confirmed that magnesium deficiency is considered the most prevalent, as this macroelement seems to play a fundamental role in a multitude of diseases, such as metabolic syndrome, T2D, obesity, high blood pressure, with Piuri *et al.* (2021) classifying it as the most prevalent mineral imbalance in high-income communities.[24] In another study published by Randall *et al.* (2008), 1318 healthy subjects involved in their study showed significant positive relationships between Mg and TC, HDL-c, LDL-c, and TG.[25] A disorder of magnesium metabolism and aberrant dietary magnesium deficiency may play a crucial role as risk markers for acute myocardial infarction and ischemic heart disease, especially in hypertensive heart disease, diabetic vascular disease, insulin resistance, atherosclerosis, and vasospasms. The crucial role of magnesium in these risk markers is evaluated by trials, epidemiological and clinical evaluations.[26]

Magnesium deficiency has been associated with changes in blood lipids and blood sugar, atherosclerosis, T2D, high blood pressure, myocardial infarction, kidney stones, and mental disorders.[27] Atherosclerosis is the result of oxidation and excess lipids; this disease affects the large arteries. This chronic inflammatory disease has been the leading cause of morbidity and mortality in the cardiovascular complex.[28] In addition, the correlation between low magnesium intake and atherosclerosis has been suggested by many epidemiological survey results. However, the Atherosclerosis Risk in Communities (ARIC) study showed that magnesium deficiency can lead to the pathogenesis of coronary atherosclerosis.[29] Another research published by Abbott *et al.* (2003) revealed additional evidence suggesting that a reduced risk of coronary heart disease is associated with dietary magnesium intake.[30] Investigations have shown that T2D and metabolic syndrome are the most studied regarding their correlation with magnesium. This micronutrient plays an essential role in insulin and glucose metabolism, mainly through its effect on the activity of insulin receptor tyrosine kinase, by transmitting ATP phosphate to proteins. In addition, magnesium can impact the activity of phosphorylase B kinase by releasing glucose-1-phosphate from glycogen and this micronutrient can influence the function of glucose transport protein 4 (GLUT4) and improve glucose translocation into the cell.[31] Magnesium is considered a cofactor for enzymes involved in glucose metabolism and may act as a protective function against diabetes by relying on insulin efficacy and its impact on glucose homeostasis. The autophosphorylation process of protein kinases in insulin signaling is stimulated by magnesium ion.[32]

Our study demonstrated a significant correlation between Ca/Mg ratio and triglycerides levels (R^2=0.050, p=0.009), with participants in the highest quartile of Ca/Mg ratio having a mean triglyceride level of 1.65 g/L compared to 1.28 g/L in the lowest quartile. This result is

consistent with the research of Cai *et al.* (2022), who reported that a higher Ca/Mg ratio was independently associated with an increased risk of dyslipidemia (OR=1.31, 95% CI: 1.15-1.49, $p<0.001$) in the general population.[33] Thus, the correlation between the Ca/Mg ratio and triglycerides levels suggests that an imbalance in these minerals may contribute to dyslipidemia. An increased Ca/Mg ratio may exacerbate insulin resistance and impair glucose metabolism, leading to increased lipolysis and elevated triglyceride levels.[12] Furthermore, an altered Ca/Mg ratio may have effects on vascular function by increasing inflammation consequently leading to a detrimental influence on lipid metabolism.[33]

The Ca/Mg ratio was found to be significantly associated with several metabolic parameters in our study. Participants in the highest quartile of the Ca/Mg ratio had higher weight and systolic blood pressure than those in the lowest quartile. In addition, the TG/HDL ratio showed a positive correlation with the Ca/Mg ratio, suggesting that an imbalance in the Ca/Mg ratio may negatively impact lipid metabolism and contribute to components of the metabolic syndrome in patients with T2D. These findings are supported by previous research by Zghal *et al.* (2017) in Tunisia, who found that a higher Ca/Mg ratio was associated with poorer glycemic control in patients with T2D.[34] Other research has demonstrated that a decrease in serum Mg levels or an increase in Ca levels can pathologically lead to cardiovascular risk. The serum Ca/Mg ratio may be more revealing of homeostasis than the assessment of the serum magnesium profile.[35]

The residual plot with linear regression of TC/HDL and LDL/HDL ratios show random scatter around the horizontal axis, suggesting a linear relationship between serum calcium levels and these lipid ratios. Specifically, higher calcium levels were associated with increased TC/HDL (R^2=0.032, p=0.055) and LDL/HDL (R^2=0.048, p=0.018) ratios. This result is consistent with previous studies linking hypercalcemia to impaired lipid metabolism and increased cardiovascular risk in patients with T2D.[36]

Residual plots for magnesium levels show random scatter for all three lipid ratios, supporting linear associations. Lower magnesium levels were significantly associated with higher TG/HDL ratio (R^2=0.008, p=0.343). These results are consistent with existing literature demonstrating the protective role of magnesium in lipid metabolism and its inverse association with cardiovascular disease risk in diabetic populations.[2]

The residual plots for the Ca/Mg ratio reveal a non-significant linear trend with the TC/HDL and LDL/HDL ratios, (TC/HDL: R^2=0.000, p=0.907; LDL/HDL: R^2=0.000, p=0.812), suggesting that while no significant relationship was observed, higher Ca/Mg ratios

may still influence lipid risk markers. However, the plots of TG/HDL ratio, suggests a potential linear relationship. This highlights the importance of considering the balance between calcium and magnesium in influencing lipid metabolism and cardiovascular risk.

Limitations and Future Directions

While this cross-sectional study provides valuable information on the associations between mineral levels and metabolic parameters in patients with T2D in Algeria, it does not allow for the establishment of causality. Although the sample size was sufficient for the analysis, the study's scope may limit the generalizability of the findings to broader populations. Future longitudinal studies with larger and more diverse cohorts from various Arab and African countries are needed to confirm these associations and better understand the underlying causal mechanisms.

Furthermore, our results suggest that, even if serum calcium and magnesium levels may play a role in lipid metabolism, they do not demonstrate a direct correlation with glycemic control in this population. The relationship between glycemic control and lipid levels may be affected by multiple factors.

Nevertheless, this study offers valuable insights into the role of mineral balance in metabolic health, underscoring the need for further research to investigate its clinical implications for T2D management, especially in regions with prevalent mineral deficiencies.

Figures

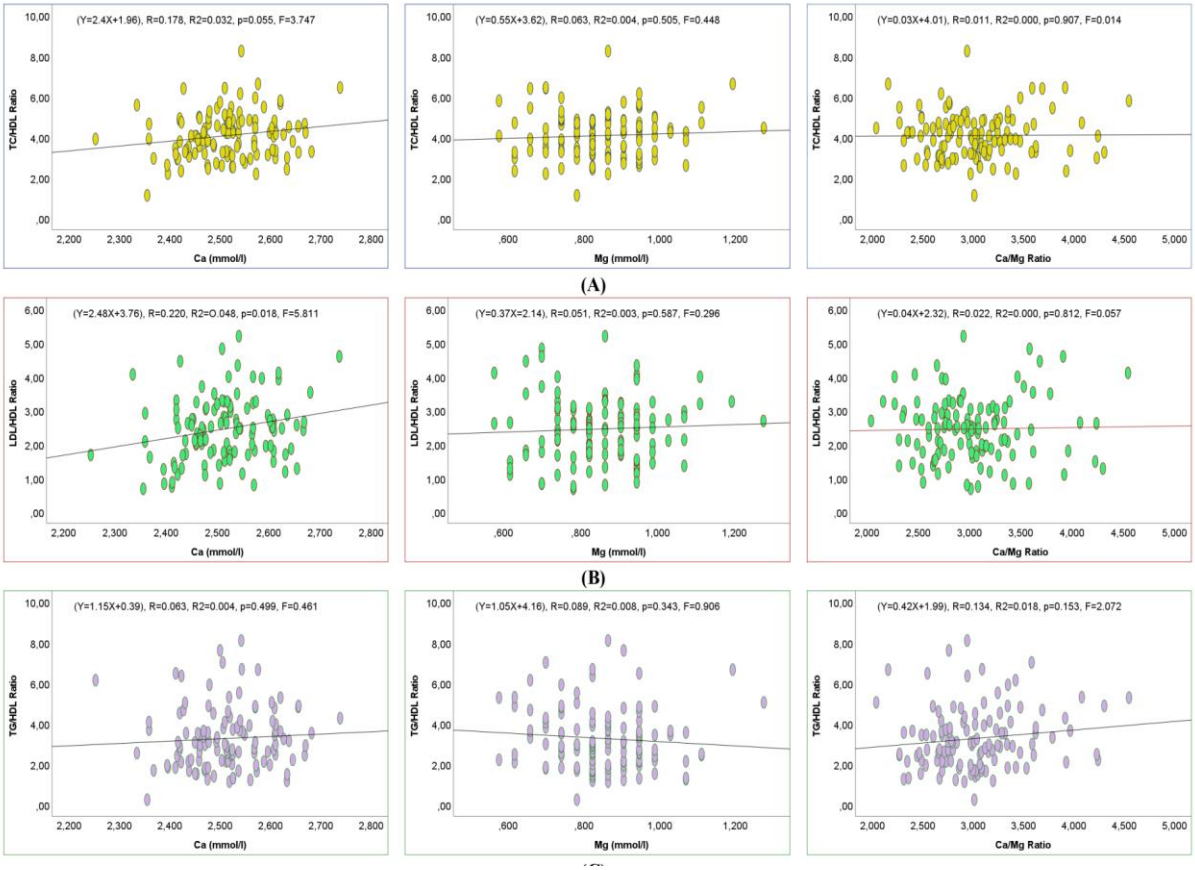
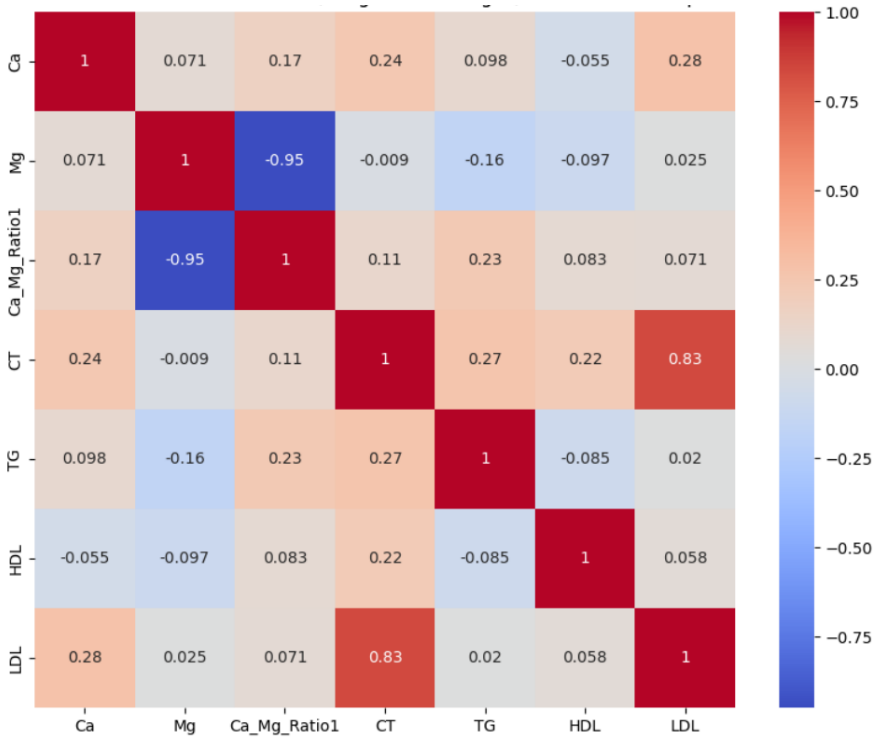
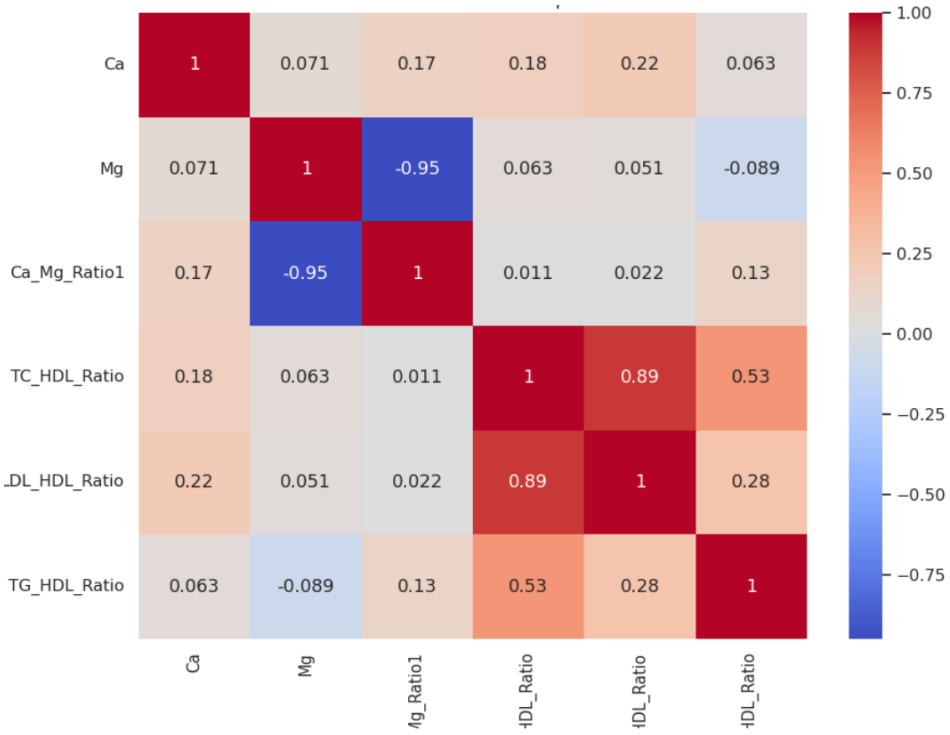


Fig 1. Residual plots of the linear regression between lipid ratios (A) TC/HDL, (B) LDL/HDL, (C) TG/HDL and serum mineral levels.



Ca: calcium; Mg: Magnesium; Ca_Mg_Ratio: Ratio Ca/Mg; TC: Total Cholesterol; TG: Triglycerides; HDL: High Density Lipoprotein; LDL; Low Density Lipoprotein.

Fig 2. Heatmap of correlations between Ca, Mg, Ca/Mg ratio and lipid profile parameters.



Ca: calcium; Mg: Magnesium; Ca_Mg_Ratio: Ratio Ca/Mg; TC_HDL_Ratio; Ratio TC/HDL; LDL_HDL_Ratio: Ratio LDL/HDL; TG_HDL_Ratio: Ratio TG/HDL.

Fig 3. Heatmap of correlations between Ca, Mg, Ca/Mg ratio and lipid ratios.

Tables

Table 1. Baseline Characteristics of the 116 type 2 diabetic patients.

Variables (N=116; M=25/F=91)	**Mean±S.D.**	**Min.-Max.**	**Median**	**P_{25}**	**P_{75}**
Age (years)	67.41±10.12	41-90	68.50	60	75
Diabetes duration (years)	19.95±8.80	1-50	20	14	25
Anthropometric parameters					
Weight (kg)	75.80±14.55	48-128	74	66	85
Height (m)	1.63±0.09	1.47-1.90	1.61	1.57	1.68
BMI (kg/m^2)	28.48±4.84	16.85-40.40	27.71	24.91	32.04
Waist circumference (cm)	107.57±10.84	78.00-139	105.00	100.00	113.00
Blood lipids					
Total Cholesterol (g/L)	1.72±0.38	1-2.67	1.67	1.44	1.95
High density lipoprotein (g/L)	0.44±0.13	0.20-1.37	0.43	0.36	1.49
Low density lipoprotein (g/L)	1.02±0.33	0.29-1.93	1.00	0.81	1.17
Triglycerides (g/L)	1.35±0.52	0.35-3.16	1.31	0.99	1.69
Blood glucose					
Glycemia (g/L)	1.38±0.35	0.60-2.22	1.40	1.12	1.56
Glycated Hemoglobin (%)	7.93±1.07	5.56-12.70	7.80	7.22	8.50
Lipids ratios					
TC/HDL	4.08±1.11	1.14-8.25	4.06	3.24	4.79
LDL/HDL	2.45±0.93	0.69-5.20	2.48	1.77	3.03
TG/HDL	3.27±1.50	0.26-8.10	2.98	2.15	4.08
Blood Pressure					
Systolic blood pressure (cmHg)	13.06±1.76	9.00-18.00	13.00	12.00	14.00
Diastolic blood pressure (cmHg)	7.03±1.22	4.00-10.00	7.00	6.00	8.00
Serum micronutrients					
Ca (mmol/L)	2.514±0.082	2.253-2.738	2.515	2.459	2.569
Mg (mmol/L)	0.849±0.127	0.576-1.275	0.822	0.750	0.946
Ca/Mg	3.025±0.472	2.041-4.548	2.995	2.693	3.268

BMI: Body Mass Index; TC: Total Cholesterol; HDL: Hight Density Lipoprotein; LDL: Low Density Lipoprotein; TG: Triglycerides; Ca: Calcium; Mg: Magnesium; P_{25}: 25^{th} percentile; P_{75}: 75^{th} percentile.

Table 2. Baseline Characteristics of the 116 type 2 diabetic patients classified according to quartiles of serum calcium.

Variables, mean±S.D.	**Quartile 1**	**Quartile 2**	**Quartile 3**	**Quartile 4**	**F**	**R^2**	***p****
Age (years)	66.07±12.49	67.79±8.77	67.03±7.08	68.72±11.55	0.354	0.006	0.787
Diabetes duration (years)	21.79±10.71	19.07±6.78	18.28±8.37	20.66±8.92	0.929	0.003	0.429
Anthropometric parameters							
Weight (kg)	79.72±15.31	75.37±16.21	75.86±12.18	72.26±13.98	1.293	0.029	0.281
Height (m)	1.62±0.07	1.63±O.11	1.63±0.10	1.62±0.07	0.113	0.000	0.952
BMI (kg/m^2)	30.21±5.10	28.11±4.78	28.42±4.46	27.19±4.73	2.023	0.041	0.115
Waist circumference (cm)	110.21±10.40	108.06±11.34	106.58±10.20	105.35±11.37	1.064	0.027	0.367
Blood lipids							
Total Cholesterol (g/L)	1.58±0.35	1.68±0.39	1.81±0.36	1.80±0.41	2.546	0.055	0.060
High density lipoprotein (g/L)	0.45±0.19	0.42±0.10	0.44±0.10	0.44±0.11	0.374	0.000	0.772
Low density lipoprotein (g/L)	0.87±0.30	1.00±0.34	1.14±0.29	1.08±0.34	3.803	0.069	**0.012**
Triglycerides (g/L)	1.25±0.53	1.33±0.56	1.39±0.490.10	1.43±0.49	0.678	0.017	0.567
Blood glucose							
Glycemia (g/L)	1.23±0.31	1.35±0.33	1.38±0.35	1.56±0.33	4.740	0.104	**0.004**
Glycated Haemoglobin (%)	7.78±1.01	8.00±0.97	7.75±0.92	8.18±1.31	0.995	0.010	0.398
Lipids ratios							
TC/HDL	3.71±1.08	4.10±0.99	4.29±1.20	4.22±1.14	1.580	0.030	0.198
LDL/HDL	2.07±0.94	2.47±0.87	2.69±0.87	2.57±0.94	2.470	0.043	0.066
TG/HDL	3.05±1.55	3.29±1.52	3.37±1.65	3.38±1.31	0.306	0.007	0.821
Blood Pressure							
Systolic blood pressure (cmHg)	12.32±0.90	12.79±1.83	12.67±1.60	14.48±1.78	10.784	0.162	**<0.001**
Diastolic blood pressure (cmHg)	6.94±1.12	6.93±1.38	6.77±1.32	7.46±0.96	1.784	0.016	0.154
Serum micronutrients							
Mg (mmol/L)	0.8129±.115	0.858±0.121	0.8796±0.111	0.848±0.154	1.393	0.013	0.249
Ca/Mg	3.026±0.449	2.954±0.418	2.931±0.386	3.190±0.590	1.814	0.012	0.149

(*): Comparison between quartiles using ANOVA test; BMI: Body Mass Index; TC: Total Cholesterol; HDL: Hight Density Lipoprotein; LDL: Low Density Lipoprotein; TG: Triglycerides; Ca: Calcium; Mg: Magnesium; F: Fisher Test; R^2: Regression coefficient for statistical models with quartiles as independent variables.

Table 3. Baseline Characteristics of the 116 type 2 diabetic patients classified according to quartiles of serum magnesium.

Variables, mean±S.D.	**Quartile 1**	**Quartile 2**	**Quartile 3**	**Quartile 4**	**F**	**R^2**	***p****
Age (years)	67.45±11.54	68.52±8.74	65.34±10.94	68.31±9.20	0.588	0.000	0.624
Diabetes duration (years)	19.31±8.12	22.03±9.70	19.90±9.73	18.55±7.53	0.833	0.003	0.479
Anthropometric parameters							
Weight (kg)	73.85±14.57	73.52±13.25	82.81±15.28	73.03±13.44	3.174	0.003	**0.027**
Height (m)	1.60±0.07	1.62±0.08	1.67±0.10	1.62±0.09	3.881	0.017	**0.011**
BMI (kg/m^2)	28.77±5.24	27.84±4.54	29.43±4.69	27.88±4.92	0.716	0.001	0.544
Waist circumference (cm)	108.37±9.29	105.57±9.10	110.62±11.27	105.75±12.96	1.428	0.001	0.239
Blood lipids							
Total Cholesterol (g/L)	1.85±0.42	1.64±0.34	1.57±0.27	1.81±0.44	3.637	0.003	**0.015**
High density lipoprotein (g/L)	0.45±0.09	0.47±0.19	0.40±0.11	0.436±0.10	1.512	0.009	0.215
Low density lipoprotein (g/L)	1.09±0.41	0.96±0.27	0.93±0.24	1.09±0.36	1.866	0.000	0.139
Triglycerides (g/L)	1.64±0.55	1.25±0.50	1.19±0.39	1.32±0.51	4.790	0.050	**0.004**
Blood glucose							
Glycemia (g/L)	1.40±0.36	1.29±0.31	1.36±0.39	1.48±0.32	1.507	0.010	0.217
Glycated Haemoglobin (%)	7.90±1.32	7.80±0.92	8.13±0.94	7.88±1.05	0.481	0.001	0.696
Lipids ratios							
TC/HDL	4.26±1.22	3.66±0.87	4.14±1.23	4.25±1.05	1.891	0.002	0.135
LDL/HDL	2.58±1.16	2.15±0.65	2.49±0.95	2.58±0.85	1.401	0.002	0.246
TG/HDL	3.76±1.39	2.94±1.53	3.27±1.72	3.11±1.26	1.645	0.015	0.183
Blood Pressure							
Systolic blood pressure (cmHg)	13.20±1.71	12.62±1.84	13.10±1.63	13.34±1.87	0.916	0.003	0.436
Diastolic blood pressure (cmHg)	7.00±1.14	6.77±1.11	7.10±1.16	7.24±1.45	0.741	0.009	0.530
Serum micronutrients							
Ca (mmol/L)	2.508±0.106	2.508±0.074	2.507±0.085	2.533±0.060	0.697	0.011	0.556
Ca/Mg	3.653±0.354	3.097±0.094	2.823±0.168	2.527±0.202	130.484	0.753	**<0.001**

(*): Comparison between quartiles using ANOVA test; BMI: Body Mass Index; TC: Total Cholesterol; HDL: Hight Density Lipoprotein; LDL: Low Density Lipoprotein; TG: Triglycerides; Ca: Calcium; Mg: Magnesium; F: Fisher Test; R^2: Regression coefficient for statistical models with quartiles as independent variables.

Table 4. Baseline Characteristics of the 116 type 2 diabetic patients classified according to quartiles of Ca/Mg ratio.

Variables, mean±S.D.	**Quartile 1**	**Quartile 2**	**Quartile 3**	**Quartile 4**	**F**	**R^2**	***p****
Age (years)	67.86±10.64	66.90±10.32	67.66±8.46	67.21±11.34	0.052	0.000	0.984
Diabetes duration (years)	18.83±9.88	20.62±9.05	21.38±8.90	18.97±7.39	0.582	0.000	0.628
Anthropometric parameters							
Weight (kg)	71.28±13.22	82.26±16.26	74.59±12.89	75.09±14.08	3.080	0.001	**0.030**
Height (m)	1.61±0.09	1.67±0.11	1.63±0.06	1.60±0.07	3.539	0.011	**0.017**
BMI (kg/m^2)	27.36±4.85	29.26±4.78	28.07±4.65	29.24±5.04	1.080	0.011	0.761
Waist circumference (cm)	105.08±12.15	110.06±11.70	105.83±9.37	109.37±9.52	1.547	0.008	0.206
Blood lipids							
Total Cholesterol (g/L)	1.74±0.44	1.64±0.30	1.65±0.35	1.84±0.41	1.802	0.009	0.151
High density lipoprotein (g/L)	0.43±0.10	0.40±0.10	0.47±0.19	0.45±0.09	1.618	0.013	0.189
Low density lipoprotein (g/L)	1.03±0.36	1.00±0.27	0.96±0.29	1.09±0.40	0.705	0.002	0.551
Triglycerides (g/L)	1.28±0.55	1.25±0.37	1.24±0.48	1.65±0.55	4.064	0.050	**0.009**
Blood glucose							
Glycemia (g/L)	1.40±0.34	1.42±0.37	1.31±0.34	1.39±0.35	0.619	0.003	0.604
Glycated Haemoglobin (%)	7.90±0.89	8.04±1.06	7.83±0.99	7.94±1.32	0.199	0.000	0.897
Lipids ratios							
TC/HDL	4.12±1.07	4.29±1.20	3.71±0.96	4.20±1.18	1.537	0.001	0.209
LDL/HDL	2.46±0.89	2.64±0.89	2.17±0.73	2.53±1.13	1.376	0.011	0.254
TG/HDL	3.06±1.42	3.40±1.67	2.93±1.45	3.70±1.38	1.594	0.012	0.195
Blood Pressure							
Systolic blood pressure (cmHg)	12.93±1.85	13.03±1.54	12.96±1.78	13.34±1.93	0.325	0.006	0.808
Diastolic blood pressure (cmHg)	7.10±1.51	7.05±1.13	6.93±1.09	7.03±1.15	0.094	0.001	0.960
Serum micronutrients							
Ca (mmol/L)	2.497±0.063	2.518±0.074	2.533±0.080	2.509±0.107	0.984	0.005	0.403
Mg (mmol/L)	1.004±0.088	0.889±0.040	0.812±0.028	0.692±0.056	149.27	0.795	**<0.001**

(*): Comparison between quartiles using ANOVA test; BMI: Body Mass Index; TC: Total Cholesterol; HDL: Hight Density Lipoprotein; LDL: Low Density Lipoprotein; TG: Triglycerides; Ca: Calcium; Mg: Magnesium; F: Fisher Test; R^2: Regression coefficient for statistical models with quartiles as independent variables.

Conclusion

Our findings suggest that maintaining an optimal balance of calcium and magnesium is a critical strategy for enhancing metabolic health in this population. However, further research is required to elucidate the underlying mechanisms and to explore the clinical implications of these associations in larger, more diverse cohorts.

Acknowledgments

Sincere appreciation to all the staff of the diabetes center of Sidi-Bel-Abbes.

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