Drug and Alcohol Dependence 245 (2023) 109822

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

journal homepage: www.elsevier.com/locate/drugalcdep

Associations of hypomagnesemia in patients seeking a first treatment of alcohol use disorder

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ARTICLE INFO

Keywords:
Alcohol use disorder
Magnesium deficiency
Oxidative stress
Electrolyte disturbances

ABSTRACT

Introduction: Hypomagnesemia (hypoMg) has not yet been extensively studied in alcohol use disorder (AUD) . We hypothesize that chronic, excessive alcohol consumption favors oxidative stress and pro-inflammatory alterations that may be exacerbated by hypoMg. The objective of this study was to analyze the prevalence and associations of hypoMg in AUD.

Patients and Methods: Cross-sectional study in patients admitted for a first treatment of AUD in six tertiary centers between 2013 and 2020. Socio-demographic, alcohol use characteristics, and blood parameters were ascertained at admission.

Results: 753 patients (71% men) were eligible; age at admission was 48 years [IQR, 41–56 years]. Prevalence of hypoMg was 11.2%, higher than that observed for hypocalcemia (9.3%), hyponatremia (5.6%), and hypokalemia (2.8%). HypoMg was associated with older age, longer duration of AUD, anemia, higher erythrocyte sedimentation rate, gamma-glutamyl transpeptidase, glucose levels, advanced liver fibrosis (FIB-4 $\geq$3.25) and estimated glomerular filtration rate (eGFR) $<$ 60 mL/min. In multivariate analysis, advanced liver fibrosis (OR, 8.91; 95% CI, 3.3–23.9) and eGFR $<$ 60 mL (OR, 5.2; 95% CI, 1.0–26.2) were the only factors associated with hypoMg.

Conclusions: Mg deficiency in AUD is associated with liver damage and glomerular dysfunction suggesting that both comorbidities should be assessed in the course of serum hypoMg.

1. Introduction

Magnesium (Mg) is the second most abundant intracellular cation in humans and plays a key physiological role as a cofactor and activator of enzymes involved in vital cellular processes (de Baaij et al., 2015; Fiorentini et al., 2021). Mg is crucial for muscle function, nervous system, bone development, and blood glucose homeostasis and pressure control, among other roles (de Baaij et al., 2015; Fiorentini et al., 2021).

Abbreviations: ALF, advanced liver fibrosis; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AUD, alcohol use disorder; CI, confidence interval; eGFR, estimted glomerular filtration rate; ESR, erythrocyte sedimentation rate; FIB4, fibrosis-4 index; GGT, gamma glutamyl transpeptidase; HUGTP, Hospital Universitari Germans Trias i Pujol; hypoCa, hypocalcemia; hypoK, hypokalemia; hypoMg, hypomagnesemia; hypoNa, hyponatremia; IQR, interquartile range; Mg, magnesium; OR, odds ratio; SDU, standard drink units.

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https://doi.org/10.1016/j.drugalcdep.2023.109822
Received 4 October 2022; Received in revised form 15 February 2023; Accepted 16 February 2023
Available online 24 February 2023

It is present in all types of human cells and is widely distributed in the body (Romani, 2013). In addition, 99% of the Mg in the body is found in the bone, muscle, and soft tissues, and 1% in the serum (de Baaij et al., 2015).

Mg participates in carbohydrate, lipid, protein, and nucleic acid metabolism, ion transportation, cell proliferation, signal transduction, and particularly, in all reactions involving adenosine triphosphate production and use (Laires et al., 2004). Therefore, abnormal Mg levels can negatively impact almost every organ and contribute to or worsen pathological conditions (Al Alawi et al., 2018).

The metabolism of Mg primarily involves the intestine and kidneys; 80% of dietary magnesium is absorbed in the intestine, and 70–80% of serum Mg is filtered by the kidneys, with only 1–3% being excreted.

Clinically, severe hypomagnesemia (hypoMg) is characterized by the onset of neuromuscular and neuropsychiatric alterations (i.e., tremor, tetany, seizures, muscle weakness, delirium, and coma), electrocardiogram manifestations, and arrhythmias, although the last may be related to other electrolyte disturbances associated with serum hypoMg.

In addition to serious complications, hypoMg is associated with oxidative stress, insulin resistance, systemic inflammation and increased risk of cardiometabolic outcomes (Ford et al., 2007; Guerrero-Romero et al., 2016; Kass et al., 2012; Liu and Dudley, 2020; Palmer and Clegg, 2015) including arterial hypertension and type 2 diabetes mellitus. In turn, increasing the dietary content of Mg has been associated with a lower risk of developing stroke, heart failure, diabetes mellitus, and mortality from any cause (Fang et al., 2016).

Up to a third of patients with alcohol use disorder (AUD) are estimated to be deficient in Mg (Vanoni et al., 2021), but most studies are old and focus on patients with acute intercurrent illnesses. Although excessive alcohol consumption is one of the main health risk factors in the Western countries, the prevalence of hypoMg among individuals with AUD who seek treatment remains unknown.

We hypothesize that chronic, excessive alcohol consumption favors oxidative stress and pro-inflammatory alterations that may be exacerbated by hypoMg. Moreover, malnutrition, decreased gastrointestinal absorption, and excessive renal losses due to ethanol-induced tubular dysfunction stand out among the pathophysiological mechanisms involved in hypoMg in AUD (Grochowski et al., 2019). Hypomagnesemia is occasionally associated with severe AUD complications after correcting metabolic acidosis or administering glucose solutions for promoting insulin secretion and increasing intracellular magnesium levels (Palmer and Clegg, 2017). A recent systematic review and meta-analysis on magnesium and alcohol concluded that renal function played a key role in magnesium homeostasis (Vanoni et al., 2021).

The objective of this study was to characterize serum hypoMg in patients seeking a first treatment for AUD, to analyze the frequency of other simultaneous electrolyte alterations, and to identify factors associated with Mg deficiency.

2. Methods

This was a multicenter cross-sectional study with patients admitted to their first treatment for AUD (CohRTA Study) in six hospital-based treatment units, from 2013 to November 2020. The patients requested for the AUD treatment on their own initiative in the participating centers, all part of the Spanish public healthcare system: Hospital Universitari de Bellvitge, L'Hospitalet de Llobregat; Hospital Universitari Son Espases, Palma de Mallorca; Parc de Salut Mar, Barcelona; Hospital Clínic Provincial, Barcelona; Hospital Universitario 12 de Octubre, Madrid; and Hospital Universitari Germans Trias i Pujol (HUGTP), Badalona.

The study was approved by the Clinical Research Ethics Committee of the coordinating center (HUGTP – approval number PI-13–031) and participating centers. The patients signed an informed consent form for the transfer of clinical data and biological samples. The methods used in this study complied with the ethical standards for medical research and the principles of good clinical practice established in the Declaration of Helsinki.

The CohRTA multicenter study protocol included a clinical history and physical examination performed by internists and psychiatrists specialized in addiction medicine. The following data were collected on alcohol consumption: age at onset of alcohol use, age at onset of regular alcohol consumption, amount of alcohol intake in Standard Drink Units (SDUs), and history of alcohol intoxication (i.e., lifetime and last year prevalence) requiring medical attention. For the purposes of this study one SDU was defined as equivalent to 10 g of alcohol. All patients were diagnosed with AUD according to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (American Psychiatric Association, 2013).

A fasting blood sample was collected for complete blood count and biochemistry (sodium, potassium, magnesium, calcium, aspartate aminotransferase [AST], alanine aminotransferase [ALT], gamma glutamyl transpeptidase [GGT], total cholesterol, albumin, total bilirubin, and creatinine) were measured with standard enzymatic methods using multichannel automatic analyzers; specifically, the enzymatic colorimetric method was used to assess magnesium levels. More details of the CohRTA study protocol have been published previously (Sanvisens et al., 2018).

Of the 967 patients recruited, 753 (77.8%) were included in this study, that is, only those whose serum Mg levels were determined in the baseline blood tests (Fig. 1). Hypomagnesemia was defined as Mg < 1.7 mg/dL (Pham et al., 2014), and clinical records of patients with hypoMg were reviewed to gather data on prescribed pharmacological treatments.

The analytical alterations were defined based on the reference values determined by the laboratories. The clinical chemistry and hematology laboratories complied with the UNE-EN-ISO9001:2015 standards and were accredited in their respective areas.

Renal function was assessed by the estimated Glomerular Filtration Rate (eGFR), calculated using creatinine, age, sex, and ethnicity through the Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI) (Levey et al., 2009) and was stratified into three levels: ≥ 90, 60–89 and < 60 mL/min/1.73 m^2.

Patients were evaluated for liver fibrosis using the fibrosis-4 (FIB-4) index, according to the following equation (Sterling et al., 2006):

$$FIB-4 = \frac{Age[years] \times AST[U/L]}{Platelet[10^9/L] \times \sqrt{ALT[U/L]}}$$

FIB-4 values above 3.25 were considered to reflect advanced liver fibrosis (ALF) (Sterling et al., 2006).

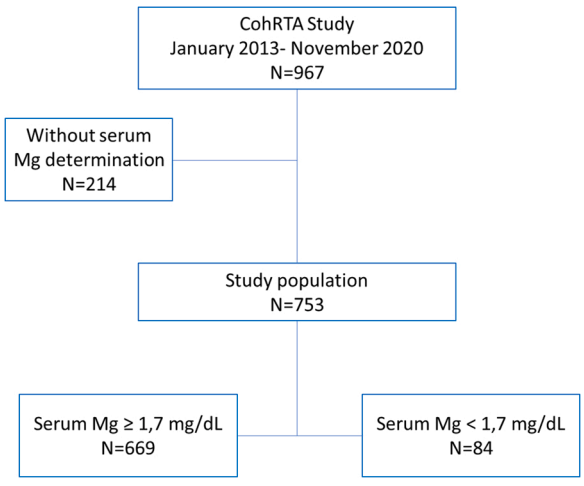

Fig. 1. Flowchart of AUD patients included in the study.

2.1. Statistical analysis

Descriptive analyses were performed. Continuous variables were detailed using the median and interquartile range (IQR) and categorical variables using relative frequencies. Bivariate analyses were performed to establish differences between patients with and without serum hypoMg using Chi-squared, F-Fisher, and Mann-Withney U, where appropriate.

Logistic regression models were used to establish associations with serum hypoMg. In these analyses, variables related to alcohol consumption and blood tests were included, and 18 patients with hypoMg attributable to hypoalbuminemia (<35 g/L) were excluded (Liamis et al., 2013). Variables with statistically significant differences in the univariate analysis were included in the multivariate analysis. A sensitivity analysis was performed with serum Mg < 1.5 mg/dL as cut-off threshold.

P values < 0.05 were considered statistically significant. Statistical analysis was performed using the Stata software (version 11.0; College Station, Texas, USA).

3. Results

A total of 753 patients (71% men) with a median age of 48 years [IQR, 41–56 years] were included in this study, 84% of whom were born in Spain. The median age at onset of alcohol use was 15 years [IQR, 14–17 years] and the median age at onset of regular alcohol consumption was 21 years [IQR, 17–30 years]; alcohol intake was 15 SDU/day [IQR, 10–24 SDU/day].

The overall prevalence of serum hypoMg was 11.2% (n = 84), with no sex differences. Serum Mg < 1.2 mg/L was observed in only six of the 84 (7.1%) patients; 36.6% (n = 31) of the patients with hypoMg had been prescribed treatment with proton pump inhibitors and 14.6% (n = 13) with diuretics. Table 1 outlines sociodemographic and alcohol use characteristics at study entry based on the presence or absence of serum hypoMg.

In terms of blood parameters, median hemoglobin was 14.3 g/dL [IQR, 13.2–15.4 g/dL], total cholesterol was 198 mg/dL [IQR, 168–232 mg/dL), albumin was 42.8 g/L [IQR, 39.9–45.1 g/L], and total bilirubin was 0.7 mg/dL [IQR, 0.4–1.0 mg/dL).

With respect to renal function, 16.5% of the patients had an eGFR < 90 mL/min/1.73 m^2, and 19.1% of the patients met the criteria for ALF (FIB-4 ≥ 3.25).

In terms of serum electrolyte levels, the median serum magnesium was 2.0 mg/dL [IQR, 1.8–2.1 mg/dL], with 140 mEq/L sodium [IQR, 138–142 mEq/L), 9.4 mg/dL calcium [IQR, 9.1–9.7 mg/dL], and 4.3 mEq/L potassium [IQR, 4.1–4.6 mEq/L]. Tables 2 and 3 outlines the analytical parameters (i.e., blood count, biochemistry), eGFR, and baseline FIB-4 of patients with or without hypoMg.

3.1. Simultaneous electrolyte disturbances

The overall prevalence of hypocalcemia (hypoCa), hyponatremia (hypoNa), and hypokalemia (hypoK) were 9.3%, 5.6%, and 2.8%, respectively, and were significantly (*P* < 0.001) higher in patients with hypoMg than in those with normal serum Mg levels. Fig. 2 shows the frequency of hypoCa, hypoNa, and hypoK in AUD patients with and without hypoMg.

The odds ratio (OR) of hypoMg was higher in patients with hypoNa, hypoK, and hypoCa (OR, 5.15 (95% confidence interval (CI), 2.5–10.7); OR, 4.5 (95% CI, 1.5–13.2); and OR, 1.88 (95% CI, 0.88–4.02), respectively). In addition, the odds of patients with hypoMg presenting hypoCa was 13.5 times higher than that of those presenting hypoK (95% CI, 1.87–97.6; *P* = 0.010).

Table 1
Sociodemographic and alcohol use characteristics in AUD 753 patients with and without serum hypoMg.

	Total N = 753 n (%)	No hypoMg N = 669 n (%)	HypoMg N = 84 n (%)	*P* value
Men	534 (70.9)	472 (70.5)	62 (73.8)	0.536
Age (years) (n = 752), *median [IQR]*	48 [41–56]	48 [40–55]	54.5 [47–60]	< 0.001
Born in Spain	632 (84.0)	557 (83.3)	75 (89.3)	0.156
BMI (kg/m^2) (n = 525), *median [IQR]*	25.1 [22.4–28.4]	25.1 [22.4–28.4]	25.2 [22.5–30.3]	0.445
Type of accommodation (n = 731)				
House/flat/ apartment	686 (93.8)	610 (93.7)	76 (95.0)	0.649
Other	45 (6.2)	41 (6.3)	4 (5.0)	
Educational level (n = 724)				
Does not know how	9 (1.2)	7 (1.1)	2 (2.5)	0.481
to read or write	166 (22.9)	150 (23.3)	16 (19.7)	
Primary education	437 (60.4)	384 (59.7)	53 (65.4)	
Secondary education	112 (15.5)	102 (15.9)	81 (11.2)	
University student				
Cohabitation (n = 739)				
Living alone	177 (23.9)	153 (23.2)	24 (29.6)	0.634
With partner and/	351 (47.5)	315 (47.9)	36 (44.4)	
or children	147 (19.9)	133 (20.2)	14 (17.3)	
With family origin	64 (8.7)	57 (8.7)	7 (8.6)	
Other situations				
Alcohol-related variables				
Age at the start of alcohol consumption (n = 727), *median [IQR]*	15 [14–17]	15 [14–17]	16 [14–18]	0.110
Age at the start of regular alcohol consumption (n = 748), *median [IQR]*	21 [17–30]	21 [17–30]	21.5 [18–30]	0.156
Duration of alcohol consumption (n = 726), *median [IQR]*	32 [24–40]	32 [24–40]	37 [31–45]	< 0.001
Amount of alcohol consumption (SDU/day), *median [IQR]*	15 [10–24]	15 [10–24.3]	15 [8–22]	0.572
Alcohol intoxication				
Lifetime (n = 688)	202 (29.4)	179 (29.2)	23 (30.3)	0.855
Last year (n = 682)	126 (18.5)	111 (18.3)	15 (19.7)	0.764
Prescribed pharmacological treatment				
Proton pump inhibitors	NA	NA	31 (36.6)	-
Diuretics	NA	NA	13 (14.6)	-

BMI: body mass index, IQR: interquartile range, NA: not available, SDU: standard drink unit

3.2. Associations of serum hypoMg

Patients with hypoMg were older (54.5 vs. 48 years, *P* < 0.001) and had been drinking alcohol for a longer period (37 vs. 32 years; *P* < 0.001) than those with normal serum Mg levels. HypoMg was associated with higher erythrocyte sedimentation rate (ESR) (*P* < 0.001), total bilirubin (*P* < 0.001), glucose (*P* < 0.001), AST and ALT (*P* < 0.001), and a higher prevalence of ALF (*P* < 0.001) and altered renal function (*P* = 0.004) (Table 2). In addition, higher

Table 2
Blood parameters and prevalence of alterations in 753 AUD patients with and without serum hypomagnesemia.

	Total N = 753 Median [IQR]	No hypoMg N = 669 Median [IQR]	HypoMg N = 84 Median [IQR]	*P* value
Hematology				
Leukocytes (x10^9/L) (n = 747)	7.0 [5.7–8.6]	7.1 [5.9–8.7]	6.2 [4.8–8.0]	0.001
< 4.0, n (%)	41 (5.5)	30 (4.5)	11 (13.1)	0.001
Hemoglobin (g/dL) (n = 746)	14.3 [13.2–15.4]	14.5 [13.4–15.6]	13.4 [11.9–14.4]	< 0.001
men < 13 g/dL; women < 12, n (%)	108 (14.5)	83 (12.5)	25 (30.1)	< 0.001
Platelets (x10^9/L) (n = 742)	225 [177–276]	229 [182–281]	181 [117–226]	< 0.001
< 150 × 10^9/L, n (%)	110 (14.8)	81 (12.3)	29 (34.9)	< 0.001
Lymphocytes (x10^9/L) (n = 737)	2.1 [1.6–2.7]	2.2 [1.6–2.8]	1.8 [1.4–2.3]	< 0.001
< 1.2, n (%)	60 (8.1)	43 (6.6)	17 (20.7)	< 0.001
ESR (mm/h) (n = 697)	9 [6–21]	9 [5–19]	22 [11–42]	< 0.001
> 20, n (%)	186 (26.7)	145 (23.3)	41 (54.7)	< 0.001
Biochemistry				
Total cholesterol (mg/dL) (n = 746)	198 [168–232]	199 [168.5–233]	193.5 [161–223]	0.125
> 220 mg/dL, n (%)	261 (35.0)	238 (35.8)	23 (28.0)	0.163
Triglycerides (mg/dL) (n = 745)	118 [81–189]	117 [80–90]	122.5 [87–173]	0.346
> 150 mg/dL, n (%)	267 (35.8)	238 (35.9)	29 (35.4)	0.925
Albumin (g/L) (n = 739)	42.8 [39.9–45.1]	43 [40–45.5]	40.4 [35.2–43]	< 0.001
< 35.0, n (%)	49 (6.6)	31 (4.7)	18 (21.7)	< 0.001
Glucose (mg/dL) (n = 743)	93 [84–105]	92 [84–103]	100 [87–124]	< 0.001
> 110, n (%)	142 (19.1)	108 (16.4)	34 (40.9)	< 0.001
Total bilirubin (mg/dL) (n = 710)	0.7 [0.4–1.0]	0.67 [0.4–1.0]	0.9 [0.6–1.3]	< 0.001
> 1.2, n (%)	101 (14.2)	76 (12.1)	25 (30.1)	< 0.001
AST (U/L) (n = 688)	34 [22–65]	33 [21.5–61]	48.5 [29–108]	< 0.001
> 37 U/L, n (%)	309 (44.9)	260 (42.8)	49 (61.2)	0.002
ALT (U/L) (n = 711)	29 [18–53]	29 [18–53]	33 [18–50]	0.538
> 41 U/L, n (%)	238 (33.5)	209 (33.2)	29 (35.4)	0.700
GGT (U/L) (n = 751)	77 [33–241]	68 [31–211]	254.5 [66–498]	< 0.001
> 50, n (%)	458 (61.0)	392 (58.8)	66 (78.6)	< 0.001
Liver fibrosis and renal function				
FIB-4 (n = 671)	1.3 [0.8–2.6]	1.2 [0.8–2.2]	3.6 [1.7–6.6]	< 0.001
< 1.5, n (%)	354 (52.8)	340 (57.2)	14 (18.2)	< 0.001
1.5–3.25, n (%)	189 (28.2)	170 (28.6)	19 (24.7)	
≥ 3.25, n (%)	128 (19.1)	84 (14.1)	44 (57.1)	
Creatinine (mg/dL) (n = 745)	0.76 [0.68–0.85]	0.76 [0.68–0.85]	0.75 [0.65–0.85]	0.390
> 1.2 mg/dL, n (%)	16 (2.1)	10 (1.5)	6 (7.3)	< 0.001
eGFR mL/min/1.73 m^2 (n = 744)	105.4 [95.7–112.6]	105.7 [96.4–112.8]	102.4 [89.5–110.6]	0.012
≥ 90, n (%)	14 (1.9)	560 (84.6)	61 (74.4)	0.004
60–89, n (%)	109 (14.6)	93 (14.0)	16 (19.5)	
< 60, n (%)	621 (83.5)	9 (1.4)	5 (6.1)	

ALT: alanine aminotransferase, AST: aspartate aminotransferase: eGFR: estimated glomerular filtration rate, ESR: erythrocyte sedimentation rate, FIB-4: fibrosis-4 index, GGT: gamma glutamyl transpeptidase, IQR: interquartile range

Table 3
Logistic regression model for the associations of serum hypomagnesemia in AUD patients.

	Univariate OR (95% CI); *P value*	Multivariate OR (95% CI); *P value*
Age (years)	**1.06 (1.04–1.09); < 0.001**	1.05 (0.98–1.11); 0.136
Duration of alcohol consumption (years)	**1.04 (1.02–1.07); 0.001**	0.98 (0.93–1.03); 0.520
Leukopenia < 4.0 × 10^9/L	2.11 (0.84–5.27); 0.110	–
Anemia (Hb<13 g M, <12 g W)	**1.92 (1.02–3.62); 0.044**	0.97 (0.40–2.34); 0.946
Lymphopenia (x10^9/L) < 1.2	2.03 (0.91–4.54); 0.083	–
ESR > 20 mm/h	**3.29 (1.92–5.64); < 0.001**	1.61 (0.80–3.22); 0.181
Glucose > 110 mg/dL	**2.99 (1.73–5.16); < 0.001**	1.39 (0.65–2.94); 0.396
Total bilirubin > 1.20 mg/dL	1.78 (0.93–3.41); 0.084	–
Calcium < 8.8 mg/dL	1.88 (0.88–4.02); 0.102	–
Sodium < 136.0 mEq/L	**5.15 (2.48–10.7); < 0.001**	2.08 (0.73–5.93); 0.169
Potassium < 3.50 mEq/L	**4.5 (1.53–13.2); 0.006**	0.35 (0.04–2.97); 0.335
GGT > 50 U/L	**2.38 (1.31–4.33); 0.004**	0.69 (0.29–1.64); 0.400
FIB-4		
< 1.5	**1**	1
1.5–3.25	**3.09 (1.42–6.74); 0.005**	2.23 (0.85–5.82); 0.102
≥ 3.25	**11.4 (5.51–23.6);< 0.001**	**8.91 (3.32–23.9); < 0.001**
eGFR (mL/min/1.73 m^2)		
≥ 90	1	1
60–89	1.66 (0.87–3.20); 0.125	1.18 (0.49–2.82); 0.707
< 60	**6.62 (2.13–20.5); 0.001**	**5.24 (1.04–26.2); 0.044**

CI: confidence interval, eGFR: glomerular filtration rate, ESR: erythrocyte sedimentation rate, FIB-4: fibrosis-4 index, GGT: gamma glutamyl transpeptidase, Hb: hemoglobin, M: men, OR: odds ratio, W: women

prevalence of anemia ($P < 0.001$), leukopenia ($P < 0.001$), lymphopenia ($P < 0.001$), and thrombocytopenia ($P < 0.001$) were found in patients with hypoMg (Table 2).

Two independent factors associated with serum hypoMg were ALF (FIB-4 ≥ 3.25) and eGFR < 60 mL/min/1.73 m^2, as shown by multivariate analysis (Table 3). Patients with FIB-4 ≥ 3.25 were nine times more likely to present with hypoMg (OR, 8.91; 95% CI, 3.32–23.9) than those without fibrosis (FIB-4 <1.5). Patients with eGFR < 60 mL/min/1.73 m^2 were up to five times more likely (OR, 5.24; 95% CI, 1.04–26.2) to present with serum hypoMg than those with normal renal function.

The sensitivity analysis taking serum Mg < 1.5 mg/dL as a reference, showed that ALF (FIB-4 ≥ 3.25) was associated with serum hypoMg.

4. Discussion

This multicenter study shows that prevalence of serum hypomagnesemia among patients admitted to the first treatment of AUD is lower than that reported in AUD patients hospitalized for serious illnesses. In this sense, the characteristics of those seeking their first treatment of AUD could differ from hospitalized patients with alcohol-associated serious medical complications. A recent systematic review and meta-analysis on hypomagnesemia and AUD reported a prevalence of 27%; however, most reviewed studies were conducted more than three decades ago, with few cases, and in the clinical context of patients with severe complications (Vanoni et al., 2021). A case-control study concludes that 53% of AUD patients had a lower level of ionized Mg in

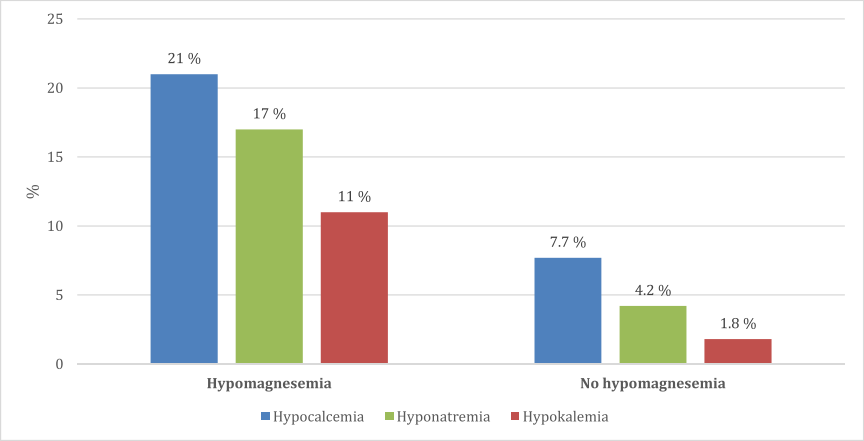

Fig. 2. Prevalence of hypocalcemia, hyponatremia, and hypokalemia in AUD patients with and without serum hypomagnesemia.

erythrocytes and 34% had decreased total Mg concentrations, almost twice less frequent than observed in the control group (Ordak et al., 2017).

Several pathophysiological mechanisms are involved in excessive alcohol consumption that may explain Mg deficiency. First, unhealthy alcohol use has been associated with malnutrition and chronic diarrhea, which can alter intestinal absorption of Mg. Second, a redistribution/translocation of extracellular to intracellular Mg has been described during alcohol withdrawal. Third, ethanol favors renal Mg loss by causing reversible tubular dysfunction (Rondón-Berríos, 2006).

Serum hypoMg in this series is the most common electrolyte disturbance, surpassing hypoCa, hypoNa, and hypoK. In addition to being the most frequent alteration, hypoMg is more likely to occur among patients with hypoNa or hypoK. Based on these findings, monitoring electrolyte abnormalities when starting AUD treatment may help prevent severe dyselectrolytemia. In hypoMg, the onset of hypoCa has been related to a decrease in parathyroid hormone (PTH) secretion and vitamin D deficiency (Palmer and Clegg, 2017). Conversely, in the context of hypoMg, hypoK has been associated with changes in renal excretion of both electrolytes, albeit also attributed to the intrinsic properties of renal outer medullary potassium 1 (ROMK1) channels in Mg redistribution (Huang and Kuo, 2007).

In this study, ALF and impaired renal glomerular filtration rate are independent factors associated with hypoMg, suggesting that both comorbidities should be evaluated when serum Mg deficiency is detected. Avoiding the progression of liver damage and renal impairment are key aspects of clinical care for patients with AUD.

Different pathophysiological mechanisms could explain the association of liver and kidney damage with hypoMg. Among them, oxidative stress stands out as a mediator of the relationship between Mg deficiency and liver fibrosis and impaired kidney function. Alcohol metabolism through the Cytochrome P450 Family 2 Subfamily E Member 1 (CYP2E1) system increases the production of reactive oxygen species (ROS)/reactive nitrogen species (RNS), induces endoplasmic reticulum stress, activates stress proteins, and alters autophagy, thus causing mitochondrial damage and hepatocellular death. The oxidative environment produced by ethanol metabolism weakens the cellular antioxidant system and reduces glutathione (GSH) levels (Das and Vasudevan, 2007). In turn, Mg deficiency is accompanied by an increase in oxidative stress markers, such as DNA, protein, and lipid oxidation, given the clear relationship between Mg deficiency, a weakened antioxidant defense, and the onset of oxidative stress (Zheltova et al., 2016). Mechanisms related to hypoMg and oxidative stress include inflammation and endothelial dysfunction, as well as cellular changes (i.e., mitochondrial dysfunction, increased fatty acid production, and reduced GSH) (Townsend et al., 2003). In addition, alcohol contributes to the onset of oxidative stress through mechanisms such as hypoxia, presence of endotoxins, cytokine release (Sergent et al., 2001), and micronutrient deficiency, including Mg (Adachi and Brenner, 2006).

The liver is the main organ involved in alcohol metabolism and most susceptible to damage caused by oxidative stress (Cederbaum et al., 2009). In fact, ROS/RNS production and oxidative stress in hepatocytes is the main underlying mechanism of alcohol-related liver disease (Adachi and Brenner, 2006; Cederbaum et al., 2009; Das and Vasudevan, 2007; Sergent et al., 2001). Accordingly, some studies have shown the association between Mg and liver disease (Fengler et al., 2021; Liu et al., 2019; Romani, 2008; Tao and Fulda, 2021), but not in the context of patients seeking treatment for AUD. The association of hypoMg and liver damage has been recently described in 48 AUD patients. The authors suggest that a proinflammatory environment through the activation of Lipopolysaccharide binding-protein and the Tumor necrosis factor-α may have a role in the observed association (Winrich et al., 2022).

The kidney plays a key role in magnesium homeostasis (Laires et al., 2004; Vanoni et al., 2021). In AUD, an inappropriately high Mg excretion has been described in patients with hypoMg, with impaired kidney Mg handling playing a critical role in the development of Mg deficiency (Vanoni et al., 2021). Indeed, preclinical studies suggest that ethanol has a deleterious effect on the kidney, which should be recognized as a separate entity (that is, alcoholic kidney injury) (Varga et al., 2017). This new entity may be closely related to ethanol-induced oxidative stress and pro-inflammatory alterations. As previously mentioned, one of the ROS production mechanisms related to alcohol consumption is the CYP2E cytochrome enzymatic pathway, found in the liver and kidney, albeit more robustly in the latter. Massive CYP2E1 induction in the kidneys leads to oxidative stress, which modifies phospholipids in cell membranes (Lu and Cederbaum, 2008; Varga et al., 2017). Interactions between the kidney and other organs, such as the liver, are difficult to establish given the complex association of oxidative stress with alcohol-induced pro-inflammatory changes. In fact, liver disease favors changes in the kidney (kidney-liver axis), and both conditions have been associated with magnesium deficiency. The results from this study suggest that patients with excessive alcohol consumption, liver fibrosis, and kidney dysfunction should be tested for hypoMg.

4.1. *Strengths and limitations*

This study has several limitations. First, the cross-sectional design prevented us from drawing conclusions on the causality of the findings. Second, we lacked data on the dietary and eating habits that determine the Mg intake of the patients. Third, having no information on the prescribed pharmacological treatment of those with normal Mg precluded us from making comparisons when analyzing the role of proton pump inhibitors and/or diuretics in Mg levels. Finally, results from this

study in AUD patients cannot be generalized to individuals with moderate alcohol consumption. However, the main strength of the study lies in the fact that, to our knowledge, this is the largest series of patients admitted for AUD treatment in whom serum Mg levels and their association with other electrolyte abnormalities have been analyzed.

5. Conclusions

Mg deficiency in AUD patients is associated with liver damage and glomerular dysfunction thus suggesting that both comorbidities should be assessed in the context of serum hypoMg. Moreover, patients with serum hypoMg are more likely to suffer other electrolyte alterations.

Future directions

Future studies may help to clarify the underlying pathophysiology of hypoMg in organ damage and providing new directions in the treatment of electrolyte alterations that could prevent liver disease and renal dysfunction.

Role of Funding Sources

The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Data statement

The datasets during and/or analyzed during the current study available from the corresponding author on reasonable request.

Author contributions

Conceptualization, AHR, AS and RM; Data curation, AHR, RB, LM, MT, GR, FB, PZ and DF; Formal analysis, AS and RM; Funding acquisition, AS and RM; Investigation, AHR, AS, LBT and RM; Methodology, AS and RM; Project administration, FRF, MF and RM; Resources, RB, LM, MT, GR, FB, PZ, DF, FRF and MF; Writing – original draft, AHR, AS and LBT; Writing – review & editing, AS and RM. All the authors contributed to the discussion section and revised and approved the final manuscript.

Conflict of interest statement

None.

Acknowledgements

Funders: This work was supported by the Ministry of Science, Innovation and Universities, Carlos III Health Institute (ISCIII), European Fund for Regional Development (FEDER), Network for Cooperative Research in Health (RETICS) and Results-oriented Cooperative Research Networks in Health (RICORS), Spain [grant numbers RD21/0009/0004, RD16/0017/0003, PI20/00883]; the Ministry of Health, Social Services and Equality, National Plan on Drugs (PNSD), Spain [grant numbers 2018/020 and 2020/024]; and the Agency for Management of University and Research Grants, Government of Catalonia [grant number 2017SGR316].

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