"IMPACT OF SERUM MAGNESIUM LEVELS ON CLINICAL OUTCOME OF CRITICALLY ILL PATIENTS - A ONE YEAR PROSPECTIVE STUDY"

REG NO. BG0111007

Dissertation

Submitted to the
KLE University, Belgaum, Karnataka

In Partial Fulfillment
of the requirements for the degree of

M. D.
in
GENERAL MEDICINE

DEPARTMENT OF MEDICINE,
JAWAHARLAL NEHRU MEDICAL COLLEGE,
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ENDORSEMENT

This is to certify that the dissertation entitled "**IMPACT OF SERUM MAGNESIUM LEVELS ON CLINICAL OUTCOME OF CRITICALLY ILL PATIENTS - A ONE YEAR PROSPECTIVE STUDY"** is a bonafide research work done by **THE CANDIDATE REG NO. BG0111007**.

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LIST OF ABBREVIATIONS USED

≈	-	Approximately equals
°C	-	Degree centrigrade
AAS	-	Atomic absorption spectroscopy
A_B	-	Absorbance of Blank
ALI	-	Acute lung injury
APACHE	-	Acute Physiology and Chronic Health Evaluation
ARDS	-	Acute respiratory distress syndrome
A_S	-	Absorbance of Standard
A_T	-	Absorbance of Test
ATP	-	Adenosine triphosphate
BUN	-	Blood urea nitrogen
$C_6H_6O_7Mg$	-	Magnesium citrate
Ca	-	Calcium
COPD	-	Chronic obstructive pulmonary disease
DBP	-	Diastolic blood pressure
DNA	-	Deoxyribonucleic acid
g	-	Gram
GCS	-	Glasgow coma score
GI	-	Gastrointestinal
GTP	-	Guanosine triphosphate
HAP	-	Hydroxyapatite
Hb	-	Haemoglobin
i.e.	-	That is
ICU	-	Intensive care unit

Kg	-	Kilogram
L	-	Litre
mEq/L	-	Milli equivalent per liter
Mg	-	Magnesium
mg	-	Milligram
$Mg(OH)_2$	-	Magnesium hydroxide
mg/dL	-	Milligram per deciliter
$MgCl_2$	-	Magnesium chloride
$MgCO_3$	-	Magnesium carbonate
$MgSO_4$	-	Magnesium sulphate
min	-	Minute
mm Hg	-	Millimeter of mercury
Mmol	-	Millimole
MV	-	Mechanical ventilation
n	-	Total number
OP	-	Organophosphorous
p	-	Probability
RBCs	-	Red blood cells
RNA	-	Ribonucleic acid
SBP	-	Systolic blood pressure
SD	-	Standard deviation
SOFA	-	Sequential Organ Failure Assessment
U.S.	-	United States
UTI	-	Urinary tract infection
vs	-	Versus

WBC	-	White blood cells
μmol/L	-	Micromole per liter

ABSTRACT

Background and objectives

Hypomagnesemia is an emerging electrolyte disturbance in hospitalized patients; especially in the critically ill ones and it has been shown to predict mortality in the ICU. This study was aimed to find the impact of admission serum magnesium levels and patient outcome considering, mortality , need and duration of ventilatory support, length of stay in ICU and APACHE II Score.

Methodology

The present one year prospective study was conducted under the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum on critically ill patients. A total of 90 patients from January 2012 to December 2012 were studied. Patients were divided as hypomagnesemics and normomagnesemics.

Results

In the present study in 64.44% in hypomagnesemics and 75.56% in normomagnesemics were males. In hypomagnesemics 48.89% of patients each were aged more than 60 years whereas normomagnesemics, 28.89% were aged between 31 t 45 and 46 to 60 years ($p=0.008$). 17.78% of patients with magnesium levels < 1.8 mg/dL had APACHE II score of > 30. 53.33% patients hypomagnesemia expired compared to 28.89% with normomagnesemia ($p=0.018$). Significantly higher number of patients with hypomagnesemia required ventilation (88.89%) compared to patient with normomagnesemia (51.11%) ($p<0.001$).

Conclusion and interpretation

Overall, the present study showed that, patients with hypomagnesemia at admission are significantly at high risk of mortality, requirement of ventilation, prolonged ventilatory support and longer duration of hospital stay and also predict higher APACHE II scores.

Keywords

APACHE II scores; Critically ill patients; Hypomagnesemia; Ventilatory support;

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Chapter 1

Introduction

INTRODUCTION

Magnesium (Mg) is essential for normal cellular functions and is the second most abundant intracellular cation. It serves as a co-factor for several enzymes required for electrolyte homeostasis and is also necessary for membrane stability, cell division, and generation of action potentials.[1] Magnesium is pivotal in the transfer, storage, and utilization of energy as it regulates and catalyzes >300 enzyme systems.[2]

In general, Mg deficiency has been associated with a number of clinical manifestations such as atrial and ventricular arrhythmias, cardiac insufficiency, coronary spasm, sudden death, skeletal and respiratory muscle weakness, bronchospasm, tetany, seizures, and other neuromuscular abnormalities and a number of electrolyte abnormalitites, including hypokalemia, hypocalcemia, hyponatremia, and hypophosphatemia.[3-5]

Further, Mg has been directly implicated in hypokalemia, hypocalcemia, tetany, and dysrhythmia. Moreover, Mg may play a role in acute coronary syndromes, acute cerebral ischemia, and asthma.[6]

Its deficiency results primarily from gastrointestinal or urinary Mg losses, but malnutrition and decreased dietary Mg intake may hasten the development of Mg depletion.[7]

As Mg regulates hundreds of enzyme systems by regulating enzymes controlling intracellular calcium, Mg affects smooth muscle vasoconstriction, important to the underlying pathophysiology of several critical illnesses.[6]

Magnesium deficiency is common in critical illnesses[6,7] and correlates with higher mortality rate and worse clinical outcome in the intensive care unit patients.[6,8] Hypomagnesemia is one of the most common electrolyte disturbances in hospitalized patients, especially in the critically ill. Various changes in Mg can occur during the perioperative period. Plasma concentrations are decreased after abdominal,[9] heart,[10] or orthopedic surgery.[11] Hypomagnesemia is often overlooked, although it carries prognostic significance.[12]

The Prevalence of hypomagnesemia (measuring total serum magnesium) has a wide range (11% to 61%), and considerable controversy exists regarding its effects on morbidity and mortality.[13-15] Hypomagnesemia occurs in 40% of hospitalized patients,[16] approximately 60% of postoperative patients,[14] 65% of medical ICU patients,[17] and up to 90% of surgical ICU patients.[18] Hypomagnesemia has been implicated in the development of cardiovascular dysfunction and the systemic inflammatory response syndrome in ICU patients.[19]

The severity of hypomagnesemia can be assessed using subjective clinical evaluation and biochemical markers of organ dysfunction. Objective scoring systems such as, the Acute Physiology and Chronic Health Evaluation (APACHE) II and Sequential Organ Failure Assessment (SOFA) scores, are also commonly used to assess severity of illness and to predict outcome in other groups of critically ill patients.[20,21] The scoring systems may identify high-risk groups among the critically ill, to whom therapeutic interventions may be directed in order to reduce morbidity and mortality, and comparisons may be made of the benefit of such interventions.[21]

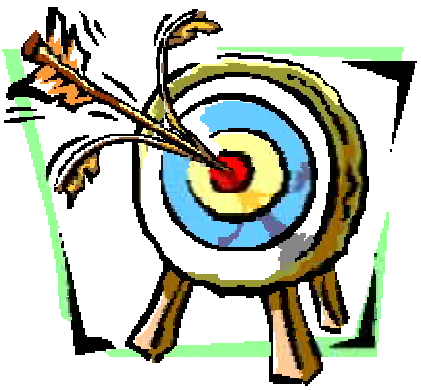
In the general population with hypomagnesemia, the predictive abilities of APACHE II and SOFA have not been evaluated. The APACHE II score incorporates 12 physiologic variables, age, and an assessment of chronic diseases in individual patients.[21] The SOFA score was developed through a consensus process[22] and afterwards validated in a larger population of 1449 critically ill patients.[23] SOFA is composed of scores from six organ systems (respiratory, cardiovascular, hepatic, coagulation, renal, and neurological) graded from 0 to 4 according to the degree of dysfunction/failure.[23]

Malnutrition in the intensive care unit (ICU) patients is a widely acknowledged problem that may intensify underlying illnesses and increase the risk of complications. Nutritional assessment upon admission to the ICU is necessary to identify patients at risk and to guide nutritional support during ICU stay.[1]

However, there is a paucity of data evaluating serum magnesium at admission as a predictor of morbidity or mortality especially in Indian context. Hence the present study was undertaken to determine the usefulness of admission serum magnesium levels with regards to patient outcome considering mortality, need and duration of ventilatory support, length of stay in ICU and APACHE 2 Score.

Chapter 2

Objectives



OBJECTIVES

The objectives of the study were to study impact of serum magnesium levels on outcome of critically ill patients considering the following parameters

- Mortality.
- Need for ventilatory support.
- Duration of ventilatory support.
- Length of stay in ICU.
- APACHE II Score.

Chapter 3

Review of Literature

REVIEW OF LITERATURE

Since the first intensive care units (ICUs) were established in the United States in the 1960s, there has been a gradual growth in the appreciation of the importance and magnitude of critical illness. The frequency of critical illness and the provision of critical care services have now reached what can be considered epidemic proportions. Of the 38 million annual U.S. hospital admissions of children and adults,[24] nearly 6 million, or 2% of the U.S. population, are admitted to an ICU.[25] The disease burden of the disorders and conditions that constitute critical illness is of sufficient scale so that efforts to prevent and treat critical illness have implications for overall public health.[26]

Critical illness consists of a heterogeneous group of conditions and disorders that share a risk of organ dysfunction, long-term morbidity, and mortality. However, the syndromes that mostly requires critical care include sepsis, acute respiratory distress syndrome [ARDS] / acute lung injury [ALI], and even organ failure.[26]

The provision of mechanical ventilation (MV) for acute respiratory failure was a major motivating factor in the development of ICUs and is one of the hallmarks of critical care.[26]

The clinical epidemiology of critical illness is vital to inform clinical care, meaningful patient-oriented research, and health policy in critical care. Describing the natural history of disease informs the development of treatments to improve outcomes and the care delivered at the bedside. Understanding the burden of disease influences the prioritization of research efforts and the

allocation of health care resources. Knowledge of risk factors for disease aids in prevention of disease, timely intervention to treat it, and selection of study populations.[26]

Critically ill patients have been defined as those that by dysfunction or failure of one or more organs/systems requiring interventions for monitoring and therapy.[27] They may require immediate requirement for any form of organ support, (intubation, ventilation, inotropes) or is likely to suffer acute cardiac, respiratory or neurological deterioration requiring such support.[28]

ICUs are the units with the highest mortality in hospital. Mortality rates in ICUs ranges between 16% and 67% depending on the patient characteristics. Critically ill patients have a high prevalence of electrolyte disorders because of the presence of multiple causative factors. Early diagnosis and treatment is necessary. Clinicians should be cautious about electrolyte homeostasis and the underlying pathophysiology of electrolyte disorders to provide optimal therapy for patients.[29]

Magnesium deficiency is common in ICU patients and it correlates with higher mortality rate and worse clinical outcome.[30] Hypomagnesemia is known to cause muscle weakness and respiratory failure, it is one of the factor causing difficulty in weaning the patient from the ventilator.[31]

Magnesium

Magnesium is the eighth most common element in the crust of the Earth and is mainly tied up within mineral deposits, for example as magnesite

(magnesium carbonate [$MgCO_3$]) and dolomite.The most plentiful source of biologically available magnesium, however, is the hydrosphere. In the sea, the concentration of magnesium is ≈ 55 mmol/L and in the Dead Sea as an extreme example the concentration is reported to be 198 mmol/L magnesium and has steadily increased over time.[32,33]

Magnesium salts dissolve easily in water and are much more soluble than the respective calcium salts. As a result, magnesium is readily available to organisms. Magnesium plays an important role in plants and animals alike. In plants, magnesium is the central ion of chlorophyll. In vertebrates, magnesium is the fourth most abundant cation and is essential, especially within cells, being the second most common intracellular cation after potassium, with both these elements being vital for numerous physiological functions. Traditionally, magnesium salts are used as antacids or laxatives in the form of magnesium hydroxide [$Mg(OH)_2$], magnesium chloride ($MgCl_2$), magnesium citrate ($C_6H_6O_7Mg$) or magnesium sulphate ($MgSO_4$).[32]

Chemical characteristics

Magnesium is a Group 2 (alkaline earth) element within the periodic table and has a relative atomic mass of 24.305 Da, a specific gravity at 20°C of 1.738, a melting point of 648.8°C and a boiling point of 1090°C.[32]

In the dissolved state, magnesium binds water tighter than calcium, potassium and sodium. Thus, the hydrated magnesium cation is hard to dehydrate. Its radius is ≈ 400 times larger than its dehydrated radius. This difference between the hydrated and the dehydrated state is much more

prominent than in sodium (≈25-fold), calcium (≈25-fold) or potassium (4-fold).[34] Consequently, the ionic radius of dehydrated magnesium is small but biologically relevant.[32]

This simple fact explains a lot of magnesium's peculiarities, including its often antagonistic behaviour to calcium, despite similar chemical reactivity and charge. For instance, it is almost impossible for magnesium to pass through narrow channels in biological membranes that can be readily traversed by calcium because magnesium cannot be easily stripped of its hydration shell.[35]

Steric constraints for magnesium transporters are also far greater than for any other cation transport system:[34] proteins transporting magnesium are required to recognize the large hydrated cation, strip off its hydration shell and deliver the bare (i.e. dehydrated) ion to the transmembrane transport pathway through the membrane.[34] There are obvious chemical similarities between calcium and magnesium but in cell biology, major differences often prevail.

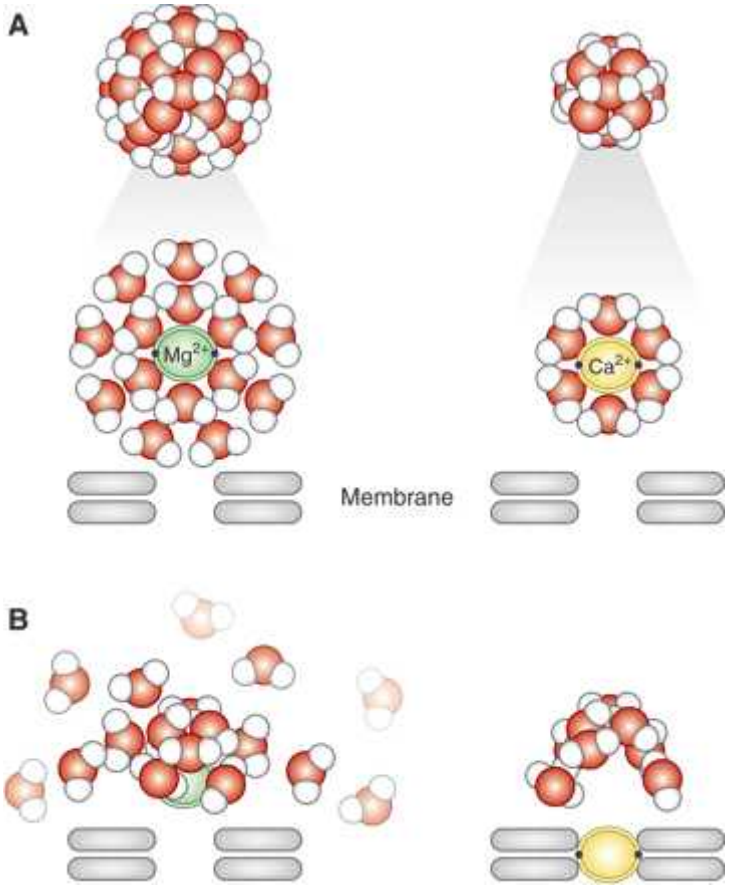


Figure 1. Magnesium - (A and B) Magnesium (top left) is surrounded by two hydration shells, whereas calcium (top right) has just one layer. If elements need to fit into a structure (transporter or membrane 'pore'), calcium (below right) simply sheds its hydration shell and its dehydrated ion will fit. Magnesium (below left), on the other hand, first has to get rid of two layers, which is highly energy consuming (simplified model).[32]

Comparison of magnesium and calcium differences and similarities[32]

	Magnesium	Calcium
Chemical aspects		
Name (symbol)	Magnesium (Mg)	Calcium (Ca)
Element category	Alkaline earth metal	Alkaline earth metal
Abundance	Eighth most abundant element in the crust of the Earth	Fifth most abundant element in the crust of the Earth
Atomic number	12	20
Valence	2	2
Crystal structure	Hexagonal	Face-centered cubic
Atomic radius	0.65 Å	0.94 Å
Atomic weight	24.305 g/mol	40.08 g/mol
Specific gravity	1.738 (20°C)	1.55 (20°C)
Number of hydration shells	Two layers	One layer
Radius after hydration	≈400 × larger than its dehydrated form	≈25 × larger than its dehydrated form
Isotopes	Magnesium naturally exists in three stable isotopes:	Calcium has five stable isotopes:
	$^{[24]}$Mg (most abundant isotope)	$^{[40]}$Ca (most abundant isotope)
	$^{[25]}$Mg	$^{[42]}$Ca
	$^{[26]}$Mg	$^{[43]}$Ca
	$^{[28]}$Mg radioactive, β-decay	$^{[44]}$Ca
		$^{[46]}$Ca
Physiological aspects		
Availability in the human body	Normal serum concentration range: 0.65–1.05 mmol/L, divided into three fractions:	Normal serum concentration range: 2.2–2.6 mmol/L, divided into three fractions:
	Free, ionized (ultrafilterable fraction): 55–70%	Free, ionized (ultrafilterable fraction): 47.5–50%
	Protein-bound (non-ultrafilterable): 20–30%	Protein-bound (non-ultrafilterable): 42–46%
	Complexed (citrate, bicarbonate, phosphate): 5–15%	Complexed (citrate, bicarbonate, phosphate): 6.0–6.5%
Total body content in adults	≈24 g	≈1000 g
Function with respect to cell death	Anti-apoptotic	Pro-apoptotic
Information attained by serum level	Serum level does not represent total body content	Serum level does not represent total body content

Physiological role of magnesium in the body

The body of most animals contains ≈ 0.4 g magnesium/kg.[34] The total magnesium content of the human body is reported to be ≈ 20 mmol/kg of fat-free tissue. In other words, total magnesium in the average 70 kg adult with 20% (w/w) fat is ≈ 1000 to 1120 mmol or ≈ 24 g.[32,34,36] These values should be interpreted with caution, however, as analytical methods differ considerably throughout the years. In comparison, the body content of calcium is ≈ 1000 g (i.e. 42 times greater than the body content of magnesium).[37]

Distribution in the human body

About 99% of total body magnesium is distributed in bone, muscles and non-muscular soft tissue.[38]

Distribution of magnesium in the adult human being, molar mass of magnesium = 24.305 g/mol;[32]

issue	Body weight (kg wet weight)	Concentration (mmol/kg wet weight)	Content (mmol)	% of total body magnesium
Serum	3.0	0.85	2.6	0.3
Red blood cells	2.0	2.5	5.0	0.5
Soft tissue	22.7	8.5	193.0	19.3
Muscle	30.0	9.0	270.0	27.0
Bone	12.3	43.2	530.1	52.9
Total	70.0	64.05	1000.7	100.0

Approximately 50–60% of magnesium resides as surface substituents of the hydroxyapatite mineral component of bone.[32,39] An illustration of bioapatite is shown below.

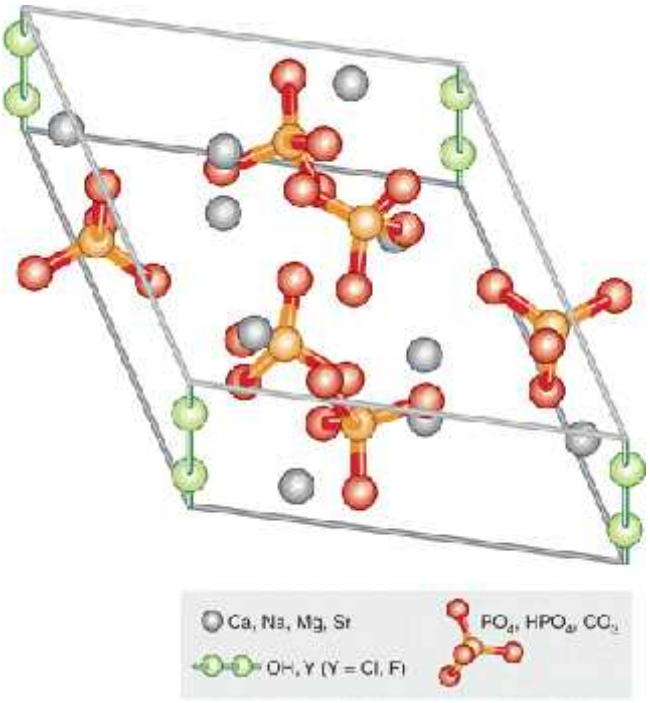


Figure 2. Hydroxyapatite crystal unit. Enamel apatite contains the lowest concentrations of carbonate and magnesium ions, and is rich in fluoride F. Dentin and bone have the highest levels of carbonate and magnesium ions, but have low fluoride content. Fluoride decreases solubility and increases chemical stability, carbonate, chloride and especially magnesium all increase solubility of the otherwise very insoluble mineral. Chemically the mineral comprises a highly substituted carbonated calcium hydroxyapatite (HAP). In the absence of exact compositional analysis the biogenic forms of this mineral are collectively alluded to as "bioapatite". Ca, calcium; Na, sodium; Mg, magnesium; Sr, strontium; OH, hydroxide; Cl, chloride; F, fluoride; PO_4, HPO_4, phosphate; CO_3, carbonate.[32]

Most of the remaining magnesium is contained in skeletal muscle and soft tissue. The magnesium content of bone decreases with age, and magnesium stored in bones is not completely bioavailable during magnesium deprivation. Nonetheless, bone provides a large exchangeable pool to buffer acute changes in serum magnesium concentration. Overall, one third of skeletal magnesium is exchangeable, serving as a reservoir for maintaining physiological extracellular magnesium levels.[32,34]

Intracellular magnesium concentrations range from 5 to 20 mmol/L; 1–5% is ionized, the remainder is bound to proteins, negatively charged molecules and adenosine triphosphate (ATP).[32]

Extracellular magnesium accounts for ≈ 1% of total body magnesium which is primarily found in serum and red blood cells (RBCs). Serum magnesium can just like calcium be categorized into three fractions. It is either free/ionized, bound to protein or complexed with anions such as phosphate, bicarbonate and citrate or sulphate. Of the three fractions in plasma, however, ionized magnesium has the greatest biological activity.[32,40,41]

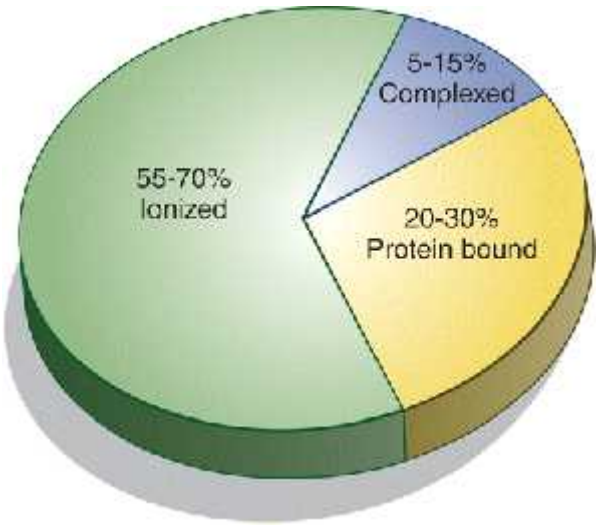


Figure. 3. Total serum magnesium is present in three different states. Because of different measurement methods, results published for each state of serum magnesium vary considerably. Therefore, a range for every state is provided.[32]

Magnesium is primarily found within the cell where it acts as a cofactor for the energy-rich ATP and nuclear acids. Magnesium is a cofactor in >300 enzymatic reactions. Magnesium critically stabilizes enzymes, including many ATP-generating reactions. ATP is required universally for glucose utilization, synthesis of fat, proteins, nucleic acids and coenzymes, muscle contraction, methyl group transfer and many other processes, and interference with magnesium metabolism also influences these functions.[32]

Thus, one should keep in mind that ATP metabolism, muscle contraction and relaxation, normal neurological function and release of neurotransmitters are all magnesium dependent. It is also important to note that magnesium contributes to the regulation of vascular tone, heart rhythm, platelet-activated thrombosis and bone formation.[32,43]

Magnesium has numerous functions in the body, for example, serving as a cofactor in enzymatic reactions.[32]

Enzyme function

- Enzyme substrate (ATP-Mg, GTP-Mg)
- Kinases B
- Hexokinase
- Creatine kinase
- Protein kinase
- ATPases or GTPases
- Na^+ /K^+-ATPase
- Ca^{2+}-ATPase
- Cyclases
- Adenylate cyclase
- Guanylate cyclase
- Direct enzyme activation
- Phosphofructokinase
- Creatine kinase
- 5-Phosphoribosyl-pyrophosphate synthetase
- Adenylate cyclase
- Na^+/ K^+-ATPase

Membrane function

- Cell adhesion
- Transmembrane electrolyte flux

Calcium antagonist

- Muscle contraction/relaxation
- Neurotransmitter release
- Action potential conduction in nodal tissue

Structural function

- Proteins
- Polyribosomes
- Nucleic acids
- Multiple enzyme complexes
- Mitochondria

In muscle contraction, for example, magnesium stimulates calcium re-uptake by the calcium-activated ATPase of the sarcoplasmic reticulum. Magnesium further modulates insulin signal transduction and cell proliferation and is important for cell adhesion and transmembrane transport including transport of potassium and calcium ions. It also maintains the conformation of nucleic acids and is essential for the structural function of proteins and mitochondria.[32]

It has long been suspected that magnesium may have a role in insulin secretion owing to the altered insulin secretion and sensitivity observed in magnesium-deficient animals.[44]

Epidemiological studies have shown a high prevalence of hypomagnesaemia and lower intracellular magnesium concentrations in diabetics. Benefits of magnesium supplementation on the metabolic profile of diabetics have been observed in some, but not all, clinical trials, and so larger prospective studies are needed to determine if dietary magnesium supplementation is associated with beneficial effects in this group.[45]

Recent epidemiological studies have suggested that a relatively young gestational age is associated with magnesium deficiency during pregnancy, which can lead to congenital problems in fetus.[46]

There is also evidence that magnesium and calcium compete with one another for the same binding sites on plasma protein molecules. It was shown that magnesium antagonizes calcium-dependent release of acetylcholine at motor endplates.[32] Thus, magnesium may be considered a natural ‘calcium antagonist’.

While calcium is a powerful 'death trigger',[47] magnesium inhibits calcium-induced cell death.[48] It antagonizes calcium-overload-triggered apoptosis. Magnesium is important in health and disease.[49]

Regulation of magnesium influx and efflux

There is considerable variation in the plasma/tissue exchange of magnesium between various organs of an animal and also between animal species. These observations indicate that various cell types handle magnesium quite differently, which is again different from calcium.[32]

Myocardium, kidney parenchyma, fat tissue, skeletal muscle, brain tissue and lymphocytes exchange intracellular and extracellular magnesium at different rates. In mammalian heart, kidney and adipocytes, total intracellular magnesium is able to exchange with plasma magnesium within 3–4 h.[32]

In humans, equilibrium for magnesium among most tissue compartments reaches very slowly. About 85% of the whole body magnesium, measured as $^{[28]}Mg$ is either non-exchangeable or exchanges very slowly with a roughly estimated biological half-life of ≈ 1000 h.[32]

Magnesium consumption

Humans need to consume magnesium regularly to prevent magnesium deficiency, but as the recommended daily allowance for magnesium varies, it is difficult to define accurately the exact optimal intake of magnesium. Values of ≥300 mg are usually reported with adjusted dosages for age, sex and nutritional status. The Institute of Medicine recommends 310–360 mg and 400–420 mg for

adult women and men, respectively. Other recommendations in the literature suggest a lower daily minimum intake of 350 mg for men and 280–300 mg magnesium for women (355 mg during pregnancy and lactation).[32,35]

While drinking water accounts for ≈ 10% of daily magnesium intake,[50] chlorophyll (and thus green vegetables) is the major source of magnesium. Nuts, seeds and unprocessed cereals are also rich in magnesium.[36] Legumes, fruit, meat and fish have an intermediate magnesium concentration. Low magnesium concentrations are found in dairy products.[32]

It is noteworthy that processed foods have a much lower magnesium content than unrefined grain products and that dietary intake of magnesium in the western world is decreasing owing to the consumption of processed food.[32,51]

With the omnipresence of processed foods, boiling and consumption of de-mineralized soft water, most industrialized countries are deprived of their natural magnesium supply. On the other hand, magnesium supplements are very popular food supplements, especially in the physically active.

Magnesium absorption and excretion

Magnesium homeostasis is maintained by the intestine, the bone and the kidneys. Magnesium just like calcium is absorbed in the gut and stored in bone mineral, and excess magnesium is excreted by the kidneys and the faeces.

Magnesium is mainly absorbed in the small intestine,[32,40] although some is also taken up via the large intestine.[35] Two transport systems for magnesium in the gut are known.[52] The majority of magnesium is absorbed in the small

intestine by a passive paracellular mechanism, which is driven by an electrochemical gradient and solvent drag. A minor, yet important, regulatory fraction of magnesium is transported via the transcellular transporter transient receptor potential channel melastatin members TRPM 6 and TRPM7—members of the long transient receptor potential channel family—which also play an important role in intestinal calcium absorption.[32]

Of the total dietary magnesium consumed, only about 24–76% is absorbed in the gut and the rest is eliminated in the faeces.[32] It is noteworthy that intestinal absorption is not directly proportional to magnesium intake but is dependent mainly on magnesium status. The lower the magnesium level, the more of this element is absorbed in the gut, thus relative magnesium absorption is high when intake is low and vice versa. When intestinal magnesium concentration is low, active transcellular transport prevails, primarily in the distal small intestine and the colon.[52]

The kidneys are crucial in magnesium homeostasis as serum magnesium concentration is primarily controlled by its excretion in urine. Magnesium excretion follows a circadian rhythm, with maximal excretion occurring at night.[32]

Under physiological conditions, ≈ 2400 mg of magnesium in plasma is filtered by the glomeruli. Of the filtered load, ≈95% is immediately reabsorbed and only 3–5% is excreted in the urine,[32,35] i.e. ≈100 mg.

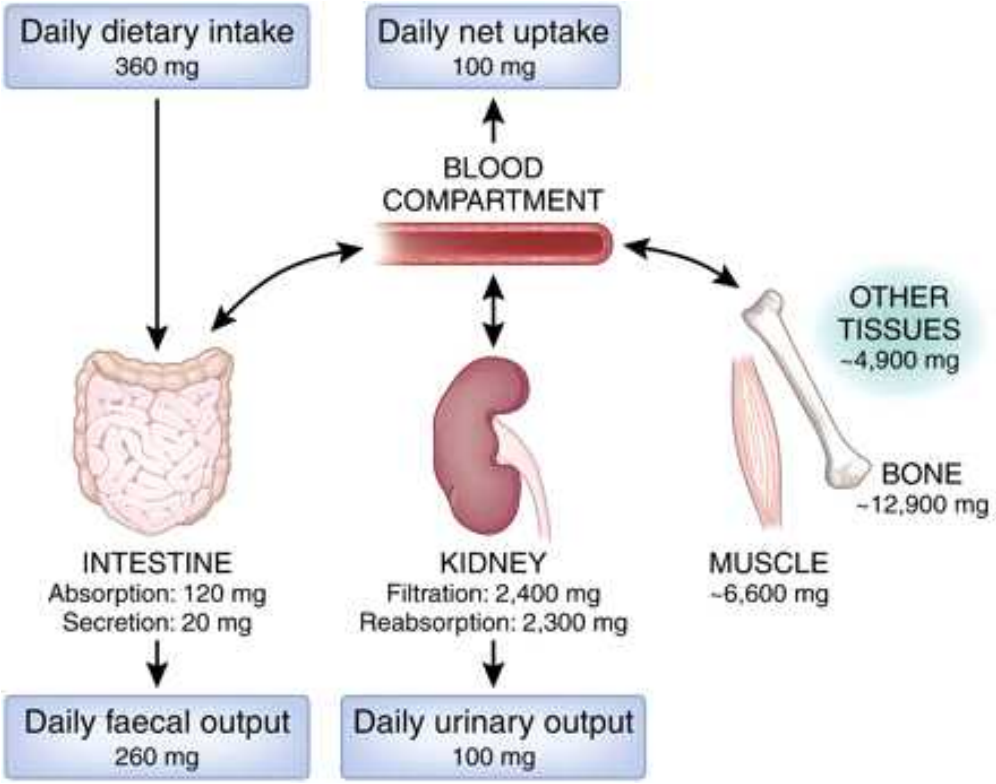


Figure 4. Magnesium balance. Values as indicated based on The conversion factor from milligrams to millimole is 0.04113.[32]

It is noteworthy that magnesium transport differs from that of the most other ions since the major re-absorption site is not the proximal tubule, but the thick ascending limb of the loop of Henle. There, 60–70% of magnesium is reabsorbed, and another small percentage (≈10%) is absorbed in the distal tubules. The kidneys, however, may lower or increase magnesium excretion and re-absorption within a sizeable range: renal excretion of the filtered load may vary from 0.5 to 70%. On one hand, the kidney is able to conserve magnesium during magnesium deprivation by reducing its excretion; on the other hand, magnesium might also be rapidly excreted in cases of excess intake.[32]

While reabsorption mainly depends on magnesium levels in plasma, hormones play only a minor role (e.g. parathyroid hormone, anti-diuretic hormone, glucagon, calcitonin), with oestrogen being an exception to this rule.

- Magnesium is essential for man and has to be consumed regularly and in sufficient amount to prevent deficiency.
- It is a cofactor in more than 300 enzymatic reactions needed for the structural function of proteins, nucleic acids and mitochondria.
- Absorption is complex, depending on the individual's magnesium status, and excretion is controlled primarily by the kidneys.

Assessment of magnesium status

Serum magnesium concentration

To date, three major approaches are available for clinical testing. The most common test for the evaluation of magnesium levels and magnesium status in patients is serum magnesium concentration,[40,53] which is valuable in clinical medicine, especially for rapid assessment of acute changes in magnesium status.[38]

Magnesium assessment[32]

Magnesium in:

- Serum
- Red blood cells[a]
- Leucocytes[b]
- Muscle[c]

Metabolic assessment via:

- Balance studies
- Isotopic analyses
- Renal excretion of magnesium
- Retention of magnesium, following acute administration

Free magnesium levels with:

- Fluorescent probes[d]
- Ion-selective electrodes[e]
- Nuclear magnetic resonance spectroscopy[fg]
- Metallochrome dyes

a) Red blood cell magnesium concentration does not seem to correlate well with total body magnesium status.

b) Magnesium content of mononuclear cells may be a better predictor of skeletal and cardiac muscle magnesium content.

c) Muscle is an appropriate tissue for the assessment of magnesium status but it is an invasive and expensive procedure requiring special expertise.

d) Intracellular free magnesium concentration can be determined by using fluorescent probes. Application of fluorescent dyes, however, is limited because the major fluorescent dye for magnesium (mag-fura 2) has a higher affinity for calcium than for magnesium.

e) Ion-specific microelectrodes can be used to measure the internal free ion concentration of cells and organelles. Major advantages are that readings can be made over long time spans. In contrast to dyes, very little extra ion buffering capacity has to be added to the cells, and direct measurement of the ion flux across the membrane of a cell is possible with every ion passing across the membrane contributing to the result. Nonetheless, ion-selective electrodes for magnesium are not entirely selective for ionized magnesium. A correction is applied based on the ionized calcium concentration.

f) Total magnesium content of a biological sample can be determined by using flame atomic absorption spectroscopy (AAS). However, this technique is destructive and, for optimal accuracy, sample volume has to add up to ≈ 2 mL with a concentration ranging from 0.1 to 0.4 µmol/L. With this technique, only content, not uptake, can be quantified.

g) Nuclear magnetic resonance may be used to measure intracellular free magnesium concentration.

However, serum magnesium concentration does not correlate with tissue pools, with the exception of interstitial fluid and bone. It also does not reflect total body magnesium levels.[38,54] Only 1% of total body magnesium is present in extracellular fluids, and only 0.3% of total body magnesium is found in serum, and so serum magnesium concentrations are poor predictors of intracellular/total body magnesium content.[32]

This situation is comparable to assessing total body calcium by measuring serum calcium, which, too, does not adequately represent total body content. As with many reference values, laboratory parameters will also vary from laboratory to laboratory resulting in slightly varying ranges for the 'healthy' populations evaluated. What is considered the 'normal level' might actually be slightly too low, representing a mild magnesium deficit present in the normal population.[38]

In addition, there are individuals in particular those with a subtle chronic magnesium deficiency whose serum magnesium levels are within the reference range but who still may have a deficit in total body magnesium. And vice versa: some people though very few have low serum magnesium levels but a physiological magnesium body content.[38]

Moreover, serum magnesium might be higher in vegetarians and vegans than in those with omnivorous diets. The same applies to levels after short periods of maximal exercise as lower serum levels are observed after endurance exercises and also during the third trimester of pregnancy. There is also intra-individual variability. Moreover, measurements are strongly affected by haemolysis and by bilirubin in serum.[32]

In healthy individuals, magnesium serum concentration is closely maintained within the physiological range. This reference range is 0.65–1.05 mmol/L for total magnesium concentrations in adult blood serum and 0.55–0.75 mmol/L for ionized magnesium.[32]

According to Graham et al.,[55] blood plasma concentration in healthy individuals is similar to serum, ranging from 0.7 to 1.0 mmol/L.

Magnesium concentration in RBCs is generally higher than its concentration in serum[55] (i.e. 1.65–2.65 mmol/L).[56] The magnesium concentration is even higher in 'young' RBCs, which might be particularly relevant in patients receiving erythropoietin. Thus, when measuring magnesium serum levels, it is important to avoid haemolysis to prevent misinterpretation,[32,38]

Although some limitations may apply, serum magnesium concentration is still used as the standard for evaluating magnesium status in patients. It has proven helpful in detecting rapid extracellular changes. In addition, measuring serum magnesium is feasible and inexpensive and should become more common in clinical routine.[32]

Twenty-four-hour excretion in urine

Another approach for the assessment of magnesium status is urinary magnesium excretion. This test is cumbersome, especially in the elderly, since it requires at least a reliable and complete 24-h time frame.[32]

As a circadian rhythm underlies renal magnesium excretion, it is important to collect a 24-h urine specimen to assess magnesium excretion and

absorption accurately. This test is particularly valuable for assessing magnesium wasting by the kidneys owing to medication or patients' physiological status.[32]

The results will provide aetiological information: while a high urinary excretion indicates renal wasting of magnesium, a low value suggests an inadequate intake or absorption.[32]

Magnesium retention test—'loading test'

A further refinement is the magnesium retention test. This 'loading test' may serve for identification of patients with hypomagnesaemic and normomagnesaemic magnesium deficiencies. Retention of magnesium following acute oral or parenteral administration is used to assess magnesium absorption, chronic loss and status. Changes in serum magnesium concentration and excretion following an oral magnesium load reflect intestinal magnesium absorption.[32]

Magnesium retained during this test is retained in bone. Thus, the lower the bone magnesium content the higher the magnesium retention in this test. The percentage of magnesium retained is increased in cases of magnesium deficiency and is inversely correlated with the concentration of magnesium in bone. This test quantifies the major exchangeable pool of magnesium, providing a more sensitive index of magnesium deficiency than simply measuring serum magnesium concentration. A urinary excretion of >60–70% of the magnesium load suggests that magnesium depletion is unlikely. Standardization of this test, however, is lacking.[32]

Pathophysiology

Hypomagnesaemia

The definition of magnesium deficiency seems simpler than it is, primarily because accurate clinical tests for the assessment of magnesium status are still lacking. Evaluation of serum magnesium concentration and collection of a 24-h urine specimen for magnesium excretion are at present the most important laboratory tests for the diagnosis of hypomagnesaemia. The next step would be to perform a magnesium retention test.[32]

In the literature, patients with serum magnesium concentrations ≤0.61 mmol/L (1.8 mg/dL)[32,57] , respectively, were considered hypomagnesaemic.[32]

Hypomagnesaemia is common in hospitalized patients, with a prevalence ranging from 9 to 65%. A particularly high incidence of hypomagnesaemia is observed in intensive care units. Furthermore, a significant association has been reported between hypomagnesaemia and esophageal surgery. In these severely ill patients, nutritional magnesium intake was probably insufficient. Certain drugs have been associated with magnesium wasting (although the relationship between these factors remains unclear), putting the afflicted patients at an increased risk for acute hypomagnesaemia. Such medications include aminoglycosides, cisplatin, digoxin, furosemide, amphotericin B and cyclosporine A. Moreover, it was observed that in patients with severe hypomagnesaemia, mortality rates increase. Therefore, assessment of magnesium status is advised, particularly in those who are critically ill. When hypomagnesaemia is detected, one should

address if identifiable—the underlying pathology to reverse the depleted status.[32,58]

Hypomagnesaemia has been linked to poor condition (malignant tumours, cirrhosis or cerebrovascular disease) and a number of other ailments. Magnesium deficiencies can occur from reduced intake caused by poor nutrition or parenteral infusions lacking magnesium, from reduced absorption and increased gastrointestinal loss, such as in chronic diarrhoea, malabsorption or bowel resection/bypass.[32,59]

Deficiencies might also be triggered by increased magnesium excretion in some medical conditions such as diabetes mellitus, renal tubular disorders, hypercalcaemia, hyperthyroidism or aldosteronism or in the course of excessive lactation or use of diuretics. Compartmental redistribution of magnesium in illnesses such as acute pancreatitis might be another cause of acute hypomagnesaemia.

Settings in which symptomatic hypomagnesaemia might occur[32]

Decreased dietary intake:

- Malnutrition
- Parenteral infusions without magnesium
- Gastrointestinal malabsorption and loss
- Severe or prolonged chronic diarrhoea
- Increased renal loss
- Congenital or acquired tubular defects

Drug induced:

- Loop diuretics[a]
- Aminoglycosides
- Amphotericin B
- Cyclosporine and tacrolimus
- Cisplatin
- Cetuximab
- Omeprazole
- Pentamidine
- Foscarnet

Endocrine causes:

- Primary and secondary hyperaldosteronism
- Hungry bone syndrome, e.g. after surgery of primary hyperparathyroidism[b]
- Syndrome of inappropriate anti-diuretic hormone hypersecretion
- Diabetes mellitus
- Stress

Other causes:

- Chronic alcoholism[c]
- Excessive lactation, heat, prolonged exercise
- Severe burns
- Cardiopulmonary bypass surgery
- Iatrogenic

[a]Loop diuretics such as furosemide, torasemide, ethacrynic acid, bumethanide and piretanide cause an increased urinary excretion. Thiazide diuretics, acting on the early distal tubule, might lead to magnesium loss only in the long run. In contrast, potassium-sparing diuretics, such as triamterene and amiloride acting on the late distal tubule, contribute to magnesium conservation by the kidneys. Osmotic agents such as mannitol or glucose hamper tubular re-absorption and augment magnesium excretion.

[b]Hypomagnesaemia—due to deposition of magnesium in the calcium- and magnesium-depleted bone—occurs in one third of the patients after surgical correction of primary hyperparathyroidism.

[c]It was observed that chronic alcohol consumption goes along with a significant increase of urinary magnesium excretion and a reduced muscle magnesium content. Thus, empiric use of magnesium replacement therapy was suggested as part of the therapeutic alcohol withdrawal syndrome regimen.

In addition, several inherited forms of renal hypomagnesaemia exist.[60] These genetic changes led to the detection of various transporters.[52]

Chronic hypomagnesaemia

Diagnosis of chronic hypomagnesaemia is difficult as there may be only a slightly negative magnesium balance over time. There is equilibrium among certain tissue pools, and serum concentration is balanced by magnesium from bone. Thus, there are individuals with a serum magnesium concentration within the reference interval who have a total body deficit for magnesium. Magnesium levels in serum and 24-h urine samples may be normal, and so parenteral administration of magnesium with assessment of retention should be considered if in doubt.[32]

Chronic latent magnesium deficiency has been linked to atherosclerosis, myocardial infarction, hypertension, malignant tumours, kidney stones, alteration in blood lipids, premenstrual syndrome and psychiatric disorders.[32]

Clinical signs of hypomagnesaemia

Clinical signs of hypo- and hypermagnesaemia overlap often and are rather non-specific. Manifestations of hypomagnasaemia might include tremor, agitation, muscle fasciculation, depression, cardiac arrhythmia and hypokalaemia.[35]

Early signs of magnesium deficiency include loss of appetite, nausea, vomiting, fatigue and weakness. As magnesium deficiency worsens, numbness, tingling, muscle contractions, cramps, seizures, sudden changes in behaviour

caused by excessive electrical activity in the brain, personality changes, abnormal heart beat and coronary spasms might occur. Severe hypomagnesaemia is usually accompanied by other imbalances of electrolytes such as low levels of calcium and potassium in the blood.[52] However, even in patients with severe hypomagnesaemia, clinical signs associated with magnesium deficiency may be absent.[32]

In addition, there seems to be a greater likelihood of clinical symptoms with a rapid decrease in serum magnesium concentration compared with a more gradual change. Therefore, physicians should not wait for clinical signs to occur before checking serum magnesium levels.[32]

Clinical and laboratory manifestations of hypomagnesaemia[32]

Neuromuscular	Cardiac	Central nervous system	Metabolic
Weakness	Arrhythmias	Depression	Hypokalaemia
Tremor	ECG changes	Agitation	Hypocalcaemia
Muscle fasciculation		Psychosis	
Positive Chvostek's sign[b]		Nystagmus	
Positive Trousseau's sign[c]		Seizures	
Dysphagia			

- a ECG, electrocardiogram.
- b Sign of tetany, an abnormal reaction (i.e. facial twitching) seen as a reaction to the tapping of the facial nerve.
- c Characteristic spasm of muscles of the hand and forearm seen following occlusion of the brachial artery.

Hypermagnesaemia

As the kidneys play a crucial role in magnesium homeostasis, in advanced chronic kidney disease, the compensatory mechanisms start to become inadequate and hypermagnesaemia may develop.[42]

Symptomatic hypermagnesaemia may be caused by excessive oral administration of magnesium salts or magnesium-containing drugs such as some laxatives[61] and antacids, particularly when used in combination in the elderly and when renal function declines.[32,62]

In addition, hypermagnesaemia may be iatrogenic, when magnesium sulphate is given as an infusion for the treatment of seizure prophylaxis in eclampsia[63] or erroneously in high doses for magnesium supplementation.[64]

Prevalence of mostly undiagnosed hypermagnesaemia in hospitalized patients is reported, varying from 5.7%[65] to 7.9% and 9.3%.[32] In intensive care patients, the prevalence of total hypermagnesaemia was reported as being 13.5%, whereas ionized hypermagnesaemia was 23.6%.[66]

These studies did not specify whether hypermagnesaemia in hospitalized patients was a pathological consequence of severe disease, or if it was iatrogenic, perhaps reflecting excessive magnesium supplementation in intensive care.

Case reports exist of pre-term babies with extreme hypermagnesaemia magnesium levels of 17.5 mmol/L[67] and 21.5 and 22.5 mmol/L[64] which, in one case, was the result of a malfunctioning total parenteral nutrition mixing device. All three infants survived. There are other reports about affected neonates whose

mothers had gestational toxicosis and who had been treated with magnesium sulphate because of eclamptic convulsion.[32]

Excessive magnesium ingestion and intoxication was also reported in association with drowning in the Dead Sea. The average serum magnesium concentration in 48 adults who 'nearly drowned' in the Dead Sea was 3.16 mmol/L, with one patient recorded at 13.57 mmol/L.[68]

Clinical signs of hypermagnesaemia

Serum magnesium concentrations, as reported in the literature, vary widely among patients with similar signs and symptoms. In the beginning, no immediate clinical signs may be present and hypermagnesaemia might stay undetected for sometime. For example, increased magnesium concentrations (>1.07 mmol/L) were found in sera from 7.9% of 6252 patients, but no description of symptoms was noted in 80% of clinical charts, also not in patients with values >1.6 mmol/L (0.8%).[32]

Moderately elevated serum magnesium levels may be associated with hypotension, cutaneous flushing, nausea and vomiting, but these symptoms mostly occur only upon infusion of magnesium sulphate. At higher concentrations, magnesium might lead to neuromuscular dysfunction, ranging from drowsiness to respiratory depression, hypotonia, areflexia and coma in severe cases. Cardiac effects of hypermagnesaemia may include bradycardia; uncharacteristic electrocardiogram findings such as prolonged PR, QRS and QT intervals, complete heart block, atrial fibrillation and asystole. However, these findings are neither diagnostic nor specific for this metabolic abnormality.[67]

Clinical manifestations of hypermagnaesemia[32]

Serum Mg (mmol/L)	Symptoms		
	Neurological	**Circulatory–respiratory–gastrointestinal**	**ECG**
2.1–2.4		Paralytic ileus	Bradycardia
2.5–4.0	Deep tendon reflexes depressed, muscle weakness, slurred speech, lethargy	Hypotension, nausea, flushing, decreased uterine tone upon magnesium infusion; gastrointestinal paralysis	Tachycardia, T-wave abnormalities; prolonged QT-time
3.7–4.9	Confusion, loss of deep tendon reflexes, neuromuscular blockade, quadriparesis	Hypotension	
5.0–6.95	Lethargy, slurred speech, profound muscle weakness	Hypotension, increased respiratory rate; respiratory arrest	Atrial fibrillation; QT prolongation sinus tachycardia, 1st degree AV-block, bradycardia
Up to ≤7.65 and 7.3	Paralysis of the limbs	No respiratory arrest, slight decrease of blood pressure	Sinus arrhythmia, slight alterations in ventricular action (T-wave, ST, R abnormalities, prolonged PR interval)
>8.9–10.65	'Coma', pseudocomatose state, central brain-stem herniation syndrome, non-fatal neuromuscular blockade	Profound hypotension, cardiopulmonary non-fatal arrest, cardiovascular collapse at 25 mg/dL (10.3 mmol)	Prolonged QT interval, bradycardia
Up to 13. 5; 16.9; 17.8; 21.5 and 22.5		Respiratory depression, apnoea, cardiopulmonary arrest	Non-fatal refractory bradycardia

· a The table demonstrates a certain difficulty to link clinically distinct symptoms to specific serum magnesium levels. However, neurological symptoms, such as depression/loss of deep tendon reflexes, unequivocally occur at serum levels greater than 3.7 to 4.0 mmol/L.

· b Symptom also used for monitoring purposes in eclampsia [109]

· AV, atrio-ventricular; Mg, magnesium; $MgSO_4$, magnesium sulphate; PD, peritoneal dialysis.

Absence of deep tendon reflexes might help diagnose excess magnesium levels. Deep tendon reflexes may be diminished at serum magnesium concentrations >2.5 mmol/L and will vanish when levels exceed 5 mmol/L. At these levels, severe muscle weakness has also been observed.[32]

Treatment of hypo- and hypermagnesaemia

In cases of mild hypomagnesaemia in otherwise healthy individuals, oral magnesium administration is used successfully. Acute and chronic oral magnesium supplementation has been described as well tolerated with a good safety profile.[70,71] Intravenous administration of magnesium, mostly as magnesium sulphate, should be used when an immediate correction is mandatory as in patients with ventricular arrhythmia and severe hypomagnesaemia.[71]

Treatment of patients with symptomatic hypermagnesaemia includes discontinuation of magnesium administration, use of supportive therapy and administration of calcium gluconate. Treatment of severe, symptomatic hypermagnesaemia may require haemodialysis.[32]

- Mild hypo- and hypermagnesaemia are quite common, especially in hospitalized patients, and may not be associated with clinical symptoms.
- Severe hypo- and hypermagnesaemia show partially overlapping symptoms, making diagnosis difficult without assessment of serum magnesium concentration.

Role of admission magnesium levels among critically ill patients

Hypomagnesemia is one of the most common electrolyte disturbances in hospitalized patients, especially in the critically ill. The Prevalence of hypomagnesemia (measuring total serum magnesium) has a wide range (11% to 61%), and considerable controversy exists regarding its effects on morbidity and mortality.[13-15]

Magnesium deficiency commonly occurs in critical illnesses[6,7] and correlates with higher mortality rate and worse clinical outcome in the intensive care unit patients.[6,8] Magnesium has been directly implicated in hypokalemia, hypocalcemia, tetany, and dysrhythmia. Moreover, Mg may play a role in acute coronary syndromes, acute cerebral ischemia, and asthma. Magnesium regulates hundreds of enzyme systems. By regulating enzymes controlling intracellular calcium, Mg affects smooth muscle vasoconstriction, important to the underlying pathophysiology of several critical illnesses.[6] Its deficiency results primarily from gastrointestinal or urinary Mg losses, but malnutrition and decreased dietary Mg intake may hasten the development of Mg depletion.[6]

Magnesium therapy is supported by clinical trials in the treatment of symptomatic hypomagnesemia and preeclampsia and is recommended for torsade de pointes.[6] Hypomagnesemia occurs in 40% of hospitalized patients,[16] approximately 60% of postoperative patients,[14] 65% of medical ICU patients,[17] and up to 90% of surgical ICU patients.[18] Hypomagnesemia has been implicated in the development of cardiovascular dysfunction and the systemic inflammatory response syndrome in ICU patients.[19]

Various changes in Mg can occur during the perioperative period. Plasma concentrations are decreased after abdominal,[9] heart,[10] or orthopedic surgery.[11] This disorder is often overlooked, although it should probably be searched for systematically because of its significance for the prognosis of patients.[12]

The severity of hypomagnesemia can be assessed using subjective clinical evaluation and biochemical markers of organ dysfunction. Objective scoring systems such as, the Acute Physiology and Chronic Health Evaluation (APACHE) II and Sequential Organ Failure Assessment (SOFA) scores, are also commonly used to assess severity of illness and to predict outcome in other groups of critically ill patients.[20,21]

The scoring systems may identify high-risk groups among the critically ill, to whom therapeutic interventions may be directed in order to reduce morbidity and mortality, and comparisons may be made of the benefit of such interventions[15]. In the general population with hypomagnesemia, the predictive abilities of APACHE II and SOFA have not been evaluated. The APACHE II score incorporates 12 physiologic variables, age, and an assessment of chronic diseases in individual patients.[20] The SOFA score was developed through a consensus process[22] and afterwards validated in a larger population of 1449 critically ill patients.[23] SOFA is composed of scores from six organ systems (respiratory, cardiovascular, hepatic, coagulation, renal, and neurological) graded from 0 to 4 according to the degree of dysfunction/failure.[23]

However, there is a paucity of data evaluating serum magnesium at admission as a predictor of morbidity or mortality.

A prospective, observational study was conducted in 1993 to test the hypothesis that the mortality rate of acutely ill patients admitted to a medical ward or medical ICU is higher for those patients who present with hypomagnesemia than for those patients who do not present with hypomagnesemia. A total of 381 consecutive acutely ill patients were enrolled. Serum magnesium concentrations and other metabolic variables were measured on admission from the Emergency Department. Acute Physiology and Chronic Health Evaluation (APACHE II) scores were computed for all patients, and mortality rates were determined for hypomagnesemic and normomagnesemic groups. Hypomagnesemic and normomagnesemic groups had comparable APACHE II scores and other variables. However, the mortality rates of the hypomagnesemic ward and medical ICU groups were approximately twice ($p<0.01$) the rate of the normomagnesemic groups. Additionally, the duration of hospital survival in those patients who died was approximately 8 days less for hypomagnesemia than normomagnesemia, but not for ward admissions. Other associated metabolic abnormalities were frequently observed in both hypomagnesemic and normomagnesemic groups, including hypokalemia and hypocalcemia. Study showed that, hypomagnesemia detected at the time of admission of acutely ill medical patients is associated with an increased mortality rate for both ward and medical ICU patients.[72]

Another prospective observational study in 2003 to define the prevalence of ionized hypomagnesemia in critically ill patients and to evaluate its relationship with organ dysfunction, length of stay, and mortality at a medical-surgical, university hospital ICU enrolled 446 consecutive patients admitted to

the ICU over 3-month period. The ionized magnesium level (normal value, 0.42-0.59 mmol/L) was measured at admission and then every day until discharge from the ICU. At admission, 18% of patients had ionized hypomagnesemia, 68% had normal ionized magnesium levels, and 14% had ionized hypermagnesemia. There was no significant difference in the length of stay or in the mortality rate between these three groups of patients. Hypomagnesemic patients more frequently had total and ionized hypocalcemia, hypokalemia, and hypoproteinemia. A total of 23 patients developed ionized hypomagnesemia during their ICU stay; these patients had higher Acute Physiology And Chronic Health Evaluation II (14.9 +/- 5.4 vs. 11.0 +/- 6.2) and Sequential Organ Failure Assessment (SOFA; 7.1 +/- 5.4 vs. 3.9 +/- 2.8) scores at admission ($p < .01$ for both), a higher maximum SOFA score during their ICU stay (10.0 +/- 5.6 vs. 4.4 +/- 3.2, $p < .01$), a higher prevalence of severe sepsis and septic shock (57 vs. 11%, $p < .01$), a longer ICU stay (15.4 +/- 15.5 vs. 2.8 +/- 4.7 days, $p < .01$), and a higher mortality rate (35% vs. 12%, $p < .01$) than the other patients. The major risk factors for developing hypomagnesemia during the ICU stay were a prolonged ICU stay, treatment with diuretics, and sepsis. Study concluded that, development of ionized hypomagnesemia during an ICU stay is associated with a worse prognosis. It is often associated with the use of diuretics and the development of sepsis. Monitoring of ionized magnesium levels may have prognostic, and perhaps therapeutic, implications.[73]

In 2007, a retrospective study was conducted in Iran on 100 patients > or =16 years old, admitted to the medical-surgical intensive care unit (ICU) at the University Hospital over 2 years period. Study aimed to define the prevalence of

admission hypomagnesemia in critically ill patients and to evaluate its relationship with organ dysfunction, length of stay, and mortality. Observations were made on admission total serum magnesium level, a variety of lab tests related to magnesium, need for ventilator, duration of mechanical ventilation, hospital/ICU lengths of stay, and general patient demographics. The serum magnesium level (normal value, 1.3-2.1 mEq/L) was measured at admission. At admission, 51% of patients had hypomagnesemia, 49% had normal magnesium levels. There was significant difference in mortality rate (55% vs 35%), the length of hospital (15.29 +/- 0.66 vs 12.81 +/- 0.91), or ICU (9.16 +/- 0.53 vs 5.71 +/- 0.55) stay between these two groups of patients ($p < 0.05$ for all). Hypomagnesemic patients more frequently had total hypocalcemia, hypokalemia, and hyponatremia. A total of 51 patients developed hypomagnesemia during their ICU stay; these patients had higher Acute Physiology And Chronic Health Evaluation II (APACHE II) (14.16 +/- 1.03 vs 10.80 +/- 0.94) and Sequential Organ Failure Assessment (SOFA; 10.89 +/- 0.90 vs 7.58 +/- 5.01) scores at admission ($p < 0.01$ for both), a higher maximum SOFA score during their ICU stay (14.75 +/- 0.73 vs 8.08 +/- 0.52, $p < 0.01$), a more need to ventilator (58.6% vs 41.4%, $p < 0.05$), and longer duration of mechanical ventilation (7.2 vs 4.7 day, $p < 0.01$) than the other patients. The ROC curve of SOFA score in the hypomagnesemia yields significantly better results than APACHE II. An increase of 5 units in the APACHE II or SOFA measured on admission increase relative probability of hypomagnesemia by a factor of 0.12 and 0.16 respectively. Authors concluded that, development of hypomagnesemia during an ICU stay is

associated with guarded prognosis and recommended that, monitoring of serum magnesium levels may have prognostic, and perhaps therapeutic, implications.[74]

In an observational study conducted by Limaye et al[31] on hypomagnesemia in critically ill medical patients, it was found that on admission to MICU, 52% had hypomagnesemia. Patients with hypomagnesemia had higher mortality rates (57.7% vs. 31.7%), more frequent need for ventilatory support (73% vs. 53%), longer duration of mechanical ventilation (4.27 vs. 2.15 days), more frequently had sepsis (38% vs. 19%), hypocalcemia (69% vs. 50%) and hypoalbuminemia (80.76% vs. 70.8%). Patients with diabetes mellitus had hypomagnesemia more frequently (27% vs. 14%).

Another historical cohort study to determine the prevalence of abnormalities in serum magnesium concentrations in critically ill patients upon admission to the ICU and the association of serum magnesium level with prognosis was conducted in the medical ICU of Hazrat-e-Rasool Hospital and 273 critically ill patients were enrolled in this study. Binary logistic regression analyses were performed to identify significant independent risk factors of mortality in the ICU. The mortality rate was 53.8% in the understudy subjects. One-hundred forty-seven subjects (53.8%) had normal serum magnesium levels, whereas, 126 subjects (46.2%) had abnormal values (hyper- or hypomagnesemia). Patients with lower total serum magnesium level had longer length of mechanical ventilation and ICU stay. The mortality rate was higher in patients who had abnormal magnesium levels. Age, serum Mg and mechanical ventilation were three risk factors that independently predicted probability of mortality in the ICU patients. Authors concluded that, monitoring of serum

magnesium levels may have prognostic, and perhaps therapeutic, implications and physicians should be alert to the high incidence of magnesium deficiency in critically ill patients.[1]

A recent study aimed to evaluate the probable significance of hypomagnesemia in patients' clinical outcome evaluated 216 patients admitted to intensive care units of Imam Khomeini university hospital in Urmia. A test of serum magnesium was performed at time of admission to ICU and patients were followed during their hospitalization both in ICU and hospital wards. Duration of hospital stay, need for mechanical ventilation and its possible effect on morbidity and mortality were evaluated. Out of 216 patients, 79 patients (36.58%) had normal serum magnesium levels. 69 patients (31.94%) and 68 patients (31.48%) had low and high levels of serum magnesium respectively. There was no statistically significant relationship between magnesium serum level and length of hospital stay, need for mechanical ventilation and mortality. Findings of the study indicated, magnesium deficiency could be documented in patients admitted to intensive care units and low level of blood magnesium is not related to increased mortality and morbidity or poor clinical outcome.[75]

Chapter 4

Methodology

METHODOLOGY

The present study was conducted under the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum on critically ill patients.

Study design

The study design was one year prospective study.

Study period and duration

The study was conducted for one year from January 2012 to December 2012.

Place

This study was done among the patients admitted in intensive care units under the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum a teaching hospital attached to Jawaharlal Nehru Medical College, Belgaum.

Source of Data

Patients admitted in intensive care units under the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum during the study period were included in the study.

Sample size

A total of 90 patients admitted in intensive care units were selected for the study.

Sampling procedure

A study has reported mortality rate in hypomagnesemics as 57.7 % and in normomagnesemics as 31.7(Considering mortality as important outcome) .Based on these findings mortality rates among hypomagnesemics was twice as in the normomagnesemics. Hence the sample size was calculated by applying these values in following formula.

$$n = 2 (Z_a + Z_b)^2 \times p \times q / (P_0 - P_1)^2$$

Where,

n	=	Sample size
p	=	Mean of mortality rate in both hypomagnesemics and normomagnesemics group (44.7)
P_0	=	Mortality rate in hypomagnesemics (57.7).
P_1	=	Mortality rate in normomagnesemics (31.3).
q	=	100 – p = 55.3
z_a & z_b	=	Constants
a	=	0.5
b	=	0.2 or power =80%
z_a	=	1.65
z_b	=	0.84

Based on these values, the sample size was calculated as 90 patients that is, 45 in each group.

Selection criteria

Inclusion

- All patients with APACHE 2 score of more than 20 or less than 6 admitted in ICU.
- Patients aged more than 18 years.

Exclusion

- Patients who had received magnesium prior to admission.
- Patients receiving magnesium preparations at time of admission.
- Patients who have received blood transfusions prior to ICU admission
- Patients with chronic alcoholism.
- Patients receiving diuretics, aminoglycosides
- Pregnant women with eclamptic seizures, receiving $MgSO_4$
- Patients receiving cisplatin, amphotericin.

Ethical clearance

Prior to the commencement, the ethical clearance was obtained from Institutional Ethics Committee, Jawaharlal Nehru Medical College, Belgaum.

Informed Consent

The patients fulfilling selection criteria were explained about the nature of the study and in case if the patient was unconscious, the nature of study was informed to the relatives. Those who expressed their willingness to participate in

the study were enrolled after obtaining a written informed consent either from patient or from relative (Annexure I).

Method of collection of data

Demographic data such as age and sex were recorded. Patients were assessed for presenting complaints, history of other diseases and habits through an interview with the patients or care giver. Further these patients underwent a thorough clinical examination for vitals (pulse rate, blood pressure and respiratory rate) and other clinical signs including Glasgow coma score (GCS) followed by systemic examination. These findings were recorded on a predesigned and pretested proforma (Annexure II). Patients was followed up for the outcomes such as mortality , need of ventilator support , duration of I.C.U stay , and APACHE 2 Score.

Investigations

The selected patients underwent the following investigations.

- Haemoglobin (Hb).
- Total white blood cell (WBC) count.
- Haematocrit.
- Platelet count.
- Blood urea nitrogen (BUN).
- Serum creatinine
- Serum sodium
- Serum potassium

- Serum calcium
- Serum bilirubin
- Serum albumin
- Arterial blood gases
- Serum Magnesium

Estimation of serum magnesium

At time of admission to medical ICU, serum magnesium levels were tested.

Calmagite dye method for quantitative estimation of serum magnesium[76]

Test principle

Under alkaline conditions, magnesium ions react with calmagite dye to produce a red complex which is measured spectrophotometrically at 530 nm. Intensity of the colour produced is directly proportional to magnesium concentration in the serum. To eliminate the interference of calcium during estimation, EGTA is included in the reagent. Heavy metal interference is prevented by the presence of cyanide and a surfactant system is included to prevent protein interference.

Test procedure

Three test tubes labeled Blank, Standard and Test are prepared as in table.

In test tubes	Blank	Standard	Test
Calmagite reagent	1.0 ml	1.0 ml	1.0 ml
Standard sample	-	10 ml	-
Patient's sample	-	-	10 ml
Distilled water	10 ml	-	-

There test tubes are incubated at room temperature (22-28ºC). The absorbance of Test (A_T), Standard (A_S) and Blank (A_B) are read at 530nm in spectrophotometer. Magnesium concentration is calculated by the following formula.

Magnesium concentration (mEq/L) = $(A_T\text{-}A_B / A_S\text{-}A_B) \times 2$

Serum magnesium concentration is expressed in mg/dl by linearity of 1 mEq/L = 1.2 mg/dl.

Subsequently patients were divided into three groups based on their serum magnesium concentrations defined as follows:

- Normal, 1.8 to 2.4 mg/dL
- Low <1.8mg/dL
- High >2.4 mg/dL.

Outcome variables

Patients were assessed for the following parameters.

APACHE II Score

APACHE II ("Acute Physiology and Chronic Health Evaluation II") is a severity-of-disease classification system[20,21] one of several ICU scoring systems. It is applied within 24 hours of admission of a patient to an intensive care unit (ICU): an integer score from 0 to 71 is computed based on several measurements; higher scores correspond to more severe disease and a higher risk of death. APACHE II score was calculated for each patient at admission to medical ICU.

Physiologic Variable	**High Abnormal Range**				**Low Abnormal Range**					
	+4	+3	+2	+1	0	+1	−2	−3	−4	Points
Temperature - rectal (°C)	≥41°	39 to 40.9°		38.5 to 38.9°	36 to 38.4°	34 to 35.9°	32 to 33.9°	30 to 31.9°	≤29.9°	
Mean Arterial Pressure - mm Hg	>160	130 to 159	110 to 129		70 to 109		50 to 69		≤49	
Heart Rate (ventricular response)	≥180	140 to 179	110 to 139		70 to 109		55 to 69	40 to 54	≤39	
Respiratory Rate (non-ventilated or ventilated)	≥50	35 to 49		25 to 34	12 to 24	10 to 11	6 to 9		≤5	
Oxygenation: A-aDO2 or PaO2 (mm Hg) a. FIO2 ≥0.5 record A-aDO2 b. FIO2 <0.5 record PaO2	>500	350 to 499	200 to 349		<200 PO2 >70	PO2 61 to 70		PO2 55 to 60	PO2 < 55	
Arterial pH (preferred) Serum HCO3 (venous mEq/l) (not preferred, but may use in the ABCs)	≥7.7 ≥52	7.6 to 7.69 41 to 51.9		7.5 to 7.59 32 to 40.9	7.33 to 7.49 22 to 31.9		7.25 to 7.32 18 to 21.9	7.15 to 7.24 15 to 17.9	<7.15 <15	
Serum Sodium (mEq/l)	≥180	160 to 179	155 to 159	150 to 154	130 to 149		120 to 129	111 to 119	≤110	
Serum Potassium (mEq/l)	≥7	6 to 6.9		5.5 to 5.9	3.5 to 5.4	3 to 3.4	2.5 to 2.9		<2.5	
Serum Creatinine (mg/dl) Double point score for acute renal failure	≥3.5	2 to 3.4	1.5 to 1.9		0.6 to 1.4		<0.6			
Hematocrit (%)	≥60		50 to 59.9	46 to 49.9	30 to 45.9		20 to 29.9		<20	
White Blood Count (total/mm3) (in 000s)	≥40		20 to 39.9	15 to 19.9	3 to 14.9		1 to 2.9		<1	
Glasgow Coma Score (GCS) Score = 15 minus actual GCS										
A. Total Acute Physiology Score (sum of 12 above points)										
B. Age points (years) ≤44=0; 45 to 54=2; 55 to 64=3; 65 to 74=5; ≥75=6										
C. Chronic Health Points (see below)										
Total APACHE II Score (add together the points from A+B+C)										

Ventilatory support

Ventilatory support was assessed as number patients requiring ventilation and duration of ventilator support in days.

Length of stay in ICU

Length of stay in ICU was noted.

Mortality

Patients were evaluated for the outcome and evaluated as improved or expired.

Statistical analysis

The data obtained was coded and entered into Microsoft Excel Worksheet (Annexure III). The categorical data was expressed as rates, ratios and proportions and comparison was done using chi-square test. The continuous data was expressed as mean ± standard deviation (SD) and comparison was done by student 't' test. A probability value ('p' value) of less than or equal to 0.05 was considered as statistically significant.

Chapter 5

Results

RESULTS

This one year prospective study was conducted under the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum on critically ill patients.

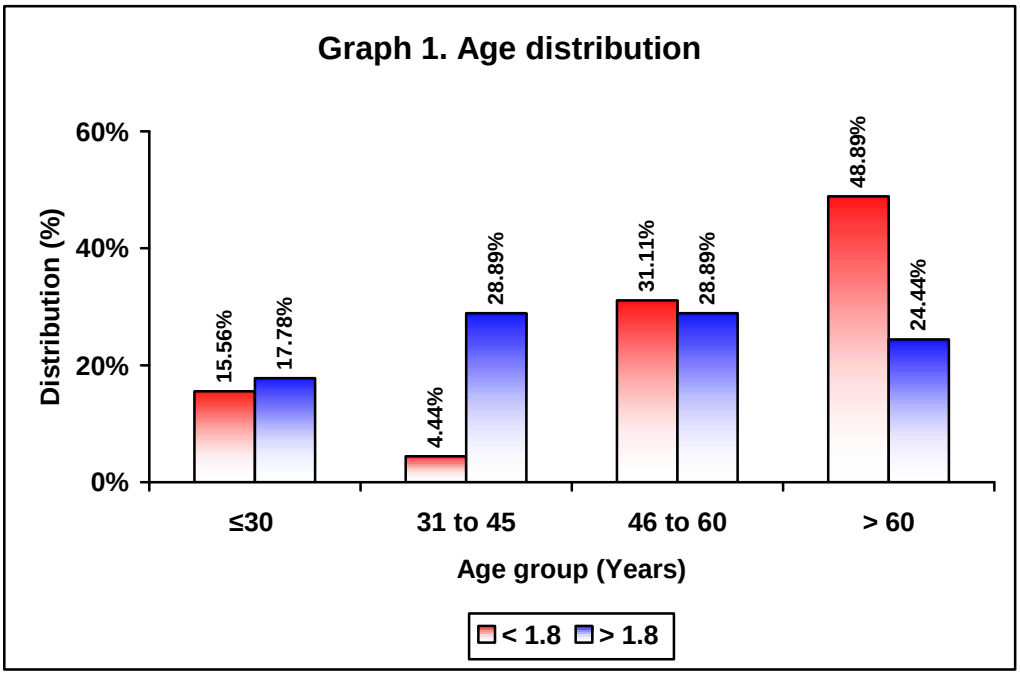
A total of 90 patients with admitted in intensive care units under the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum from January 2012 to December 2012 were studied. Patients were divided into two groups based on magnesium levels that is, magnesium levels < 1.8 (hypomagesemics; n=45) and > 1.8 (normomagnesemics; n=45).

The data obtained was coded and entered into Microsoft excel spread sheet. The data was analysed and the final results and observations were tabulated as below.

Table 1. Age distribution

Age group (years)	Serum magnesium levels (mg/dL)			
	< 1.8		> 1.8	
	No	%	No	%
≤ 30	7	15.56	8	17.78
31 to 45	2	4.44	13	28.89
46 to 60	14	31.11	13	28.89
> 60	22	48.89	11	24.44
Total	**45**	**100.00**	**45**	**100.00**

p = 0.008

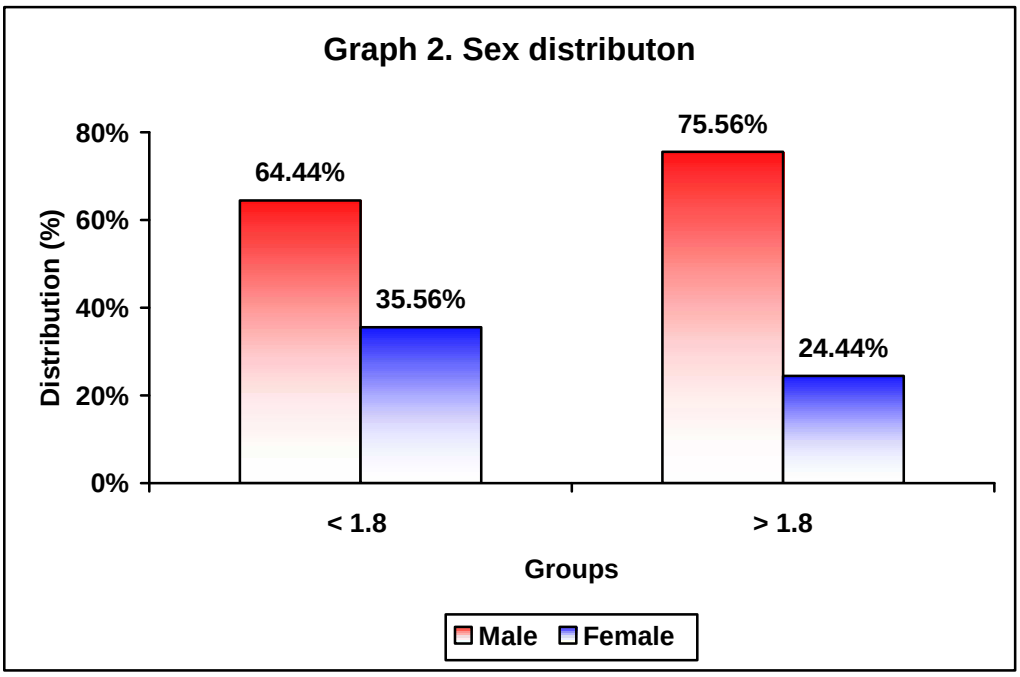


In this study among the patients with magnesium levels < 1.8 mg/dL, 48.89% of patients were aged more than 60 years as compare to 24.44% in patients with magnesium levels > 1.8 mg/dL. This difference was statistically significant (p=0.008).

Table 2. Sex distribution

Sex	Serum magnesium levels (mg/dL)			
	< 1.8		> 1.8	
	No	%	No	%
Male	29	64.44	34	75.56
Female	16	35.56	11	24.44
Total	**45**	**100.00**	**45**	**100.00**

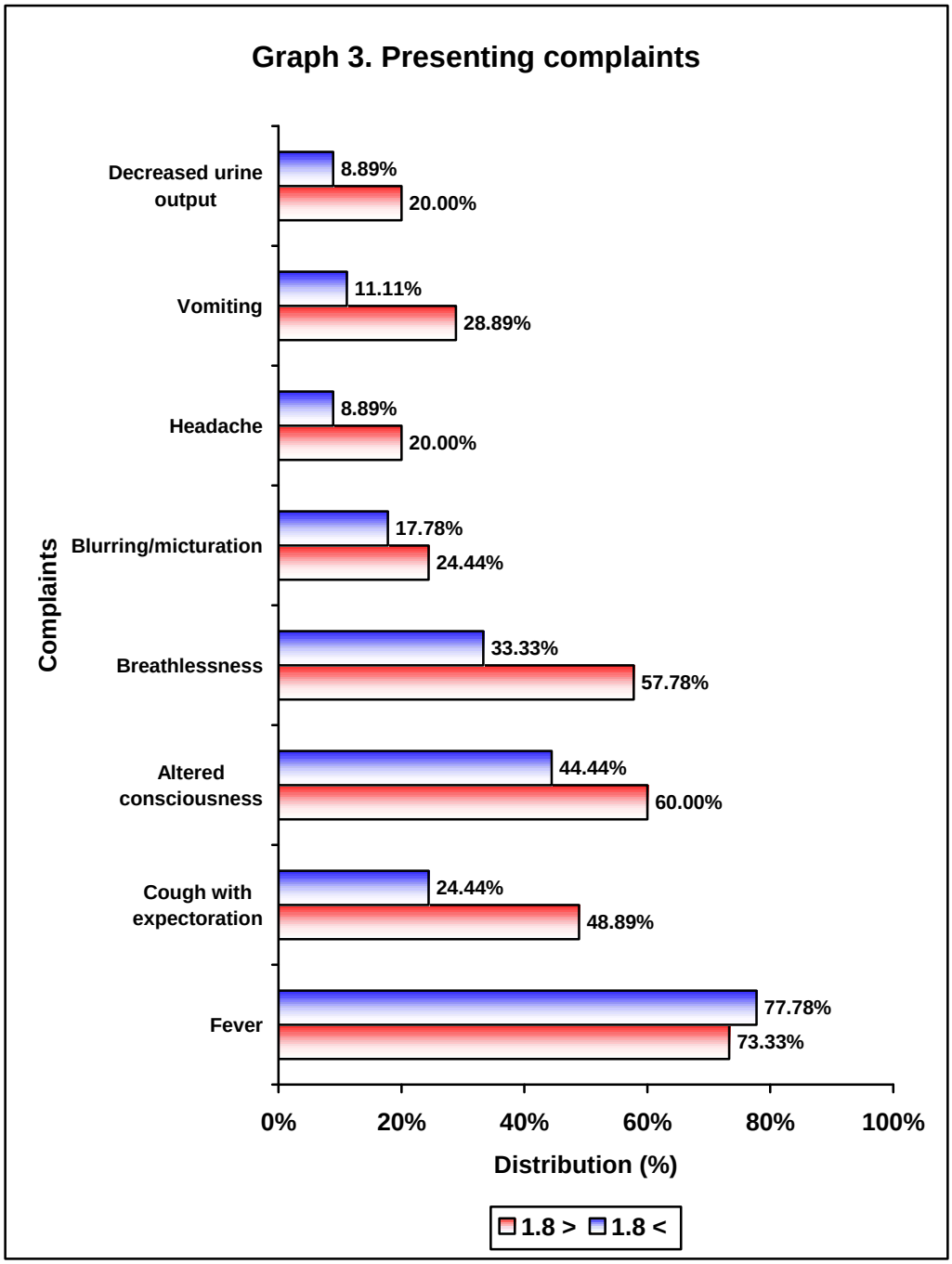
p = 0.250



In the present study among patients with magnesium levels < 1.8 mg/dL, 64.44% were males and 35.56% were females and male to female ratio 1.8:1 while in those with magnesium levels ≥ 1.8 mg/dL, 75.56% were males and 24.44% females with male to female ratio of 3.09:1. However this difference was statistically not significant (p=0.250).

Table 3. Presenting complaints

Complaints	Serum magnesium levels (mg/dL)			
	< 1.8		> 1.8	
	No	**%**	**No**	**%**
Fever	33	73.33	35	77.78
Cough with expectoration	22	48.89	11	24.44
Breathlessness	26	57.78	15	33.33
Blurring / micturation	11	24.44	8	17.78
Headache	9	20.00	4	8.89
Vomiting	13	28.89	5	11.11
Altered consciousness	27	60.00	20	44.44
Abdominal pain	15	33.33	7	15.56
Decreased urine output	9	20.00	4	8.89



In the present study fever was the commonest symptom in both the groups (77.78% in normomagnesemics and 73.33% in hypomagnesemics). However, among the patients with magnesium levels < 1.8 mg/dL, altered consciousness, breathlessness and cough with expectoration were noted in 60.00%, 57.78% and 48.89% of patients respectively.

Table 4. Past history

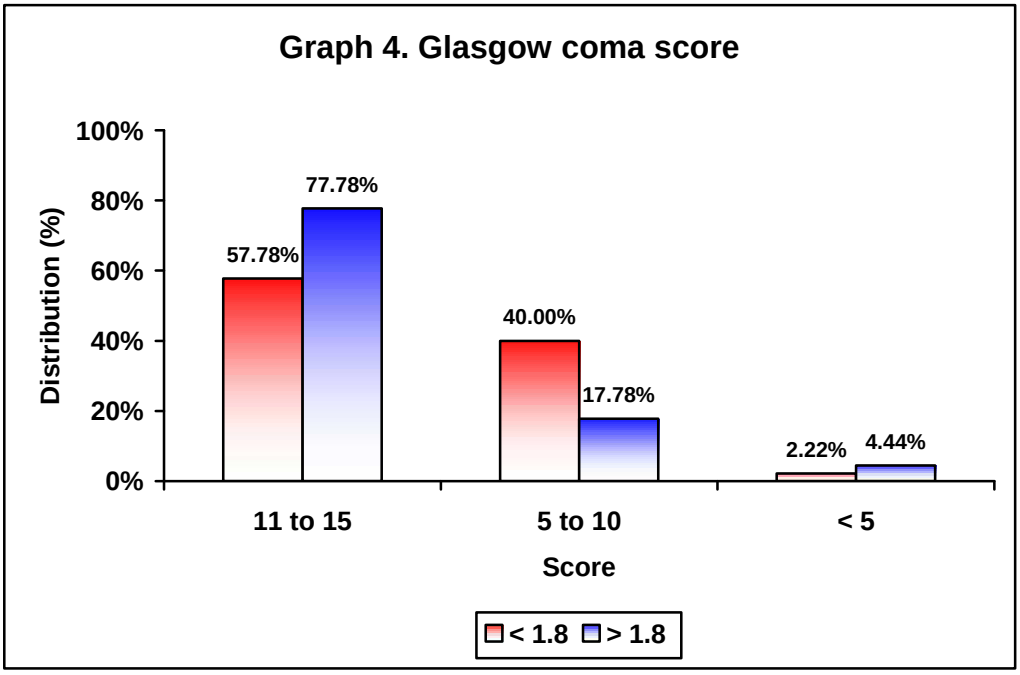
History	Serum magnesium levels (mg/dL)			
	< 1.8		> 1.8	
	No	%	No	%
Hypertension	22	48.89	20	44.44
Diabetes mellitus	19	42.22	11	24.44
Ischaemic heart disease	7	15.56	9	20.00
Cerebrovascular disease	5	11.11	0	0.00

In the present study, among the patients with magnesium levels < 1.8 mg/dL, 48.89% of patients had previous history of hypertension and 42.22% reported to have diabetes mellitus. In patients with magnesium levels ≥ 1.8 mg/dL 44.44% of patients had hypertension and 24.44% had diabetes mellitus.

Table 5. Glasgow coma score

Score	Serum magnesium levels (mg/dL)			
	< 1.8		> 1.8	
	No	%	No	%
11 to 15	26	57.78	35	77.78
5 to 10	18	40.00	8	17.78
< 5	1	2.22	2	4.44
Total	**45**	**100.00**	**45**	**100.00**

p = 0.064



In the present study at time of admission, Glasgow coma score was between 11 to 15 in 57.78% of the patients with magnesium levels < 1.8 mg/dL compared to 77.78% of patients with magnesium levels > 1.8 mg/dL. However this difference was statistically not significant (p=0.064).

Table 6. Diagnosis - Respiratory system

Diagnosis	Serum magnesium levels			
	< 1.8		> 1.8	
	No	%	No	%
Acute exacerbation of COPD	2	4.44	1	2.22
Pneumonia with septicemia	6	13.33	4	8.89
Pneumothorax	0	0.00	1	2.22
Pulmonary tuberculosis with septicemia	2	4.44	1	2.22
Lung abscess with septicemia	3	6.67	2	4.44
Asthma with allergic bronchopulmonary aspergillosis	0	0.00	1	2.22
Total	**13**	**28.89**	**10**	**22.22**

In this study 13.33% of the patients with magnesium levels < 1.8 mg/dL were diagnosed to have pneumonia with septicemia , 6.67% of the patients had lung abscess with septicemia . In patients with magnesium levels ≥ 1.8 mg/dL, pneumonia with septicemia was present in 8.89%, lung abscess with septicemia in 4.44% and asthma with allergic bronchipulmonary aspergillosis, acute exacerbation of COPD, pneumothorax and Pulmonary tuberculosis with septicemia in 2.22% patients each.

Table 7. Diagnosis - Cardiovascular system

Diagnosis	Serum magnesium levels			
	< 1.8		> 1.8	
	No	%	No	%
Acute pulmonary oedema	3	6.67	1	2.22
Infective endocarditis with septicemia	0	0.00	1	2.22
Right ventricular failure	1	2.22	0	0.00
Pulmonary thromboembolism	0	0.00	1	2.22
Acute myocardial infarction	3	6.67	2	4.44
Total	**7**	**15.56**	**5**	**11.11**

In the present study, 6.67% of the patients with magnesium levels < 1.8 mg/dL were diagnosed to have acute pulmonary oedema and acute myocardial infarction. In patients with magnesium levels ≥ 1.8 mg/dL, Acute myocardial infarction was present in 4.44%, right ventricular failure, infective endocarditis with septicemia and acute pulmonary oedema in 2.22% each.

Table 8. Diagnosis - Central nervous system

Diagnosis	Serum magnesium levels			
	< 1.8		> 1.8	
	No	%	No	%
Cerebrovascular accident	9	20.00	3	6.67
Meningitis	3	6.67	4	8.89
Cortical venous thrombosis	0	0.00	5	11.11
Metabolic encephalopathy	1	2.22	0	0.00
Intracranial haemorrhage	0	0.00	1	2.22
Total	**13**	**28.89**	**13**	**28.89**

In this study, cerebrovascular accident, meningitis and metabolic encephalopathy was diagnosed in 20%, 6.67% and 2.22% of patients with magnesium levels < 1.8 mg/dL while in patients with magnesium levels ≥ 1.8 mg/dL, cortical venous thrombosis, meningitis, cerebrovascular accident and intracranial haemorrhage was noted in 11.11%, 8.89%, 6.67% and 2.22% respectively.

Table 9. Diagnosis - Gastrointestinal system

Diagnosis	Serum magnesium levels			
	< 1.8		> 1.8	
	No	%	No	%
Liver abscess with septicemia	2	4.44	2	4.44
Mesenteric venous thrombosis with septicemia	1	2.22	2	4.44
Fulminant viral hepatitis	0	0.00	1	2.22
GI bleed	1	2.22	0	0.00
Total	**4**	**8.89**	**5**	**11.11**

In the present study, diagnosis of liver abscess with septicemia was noted in 4.44% and of the patients and mesenteric venous thrombosis with septicemia in 2.22% in patients with patients with magnesium levels < 1.8 mg/dL while in patients with magnesium levels ≥ 1.8 mg/dL, liver abscess, mesenteric venous thrombosis were noted in 4.44% and fulminant viral hepatitis in 2.22% of the patients.

Table 10. Diagnosis - Miscellaneous

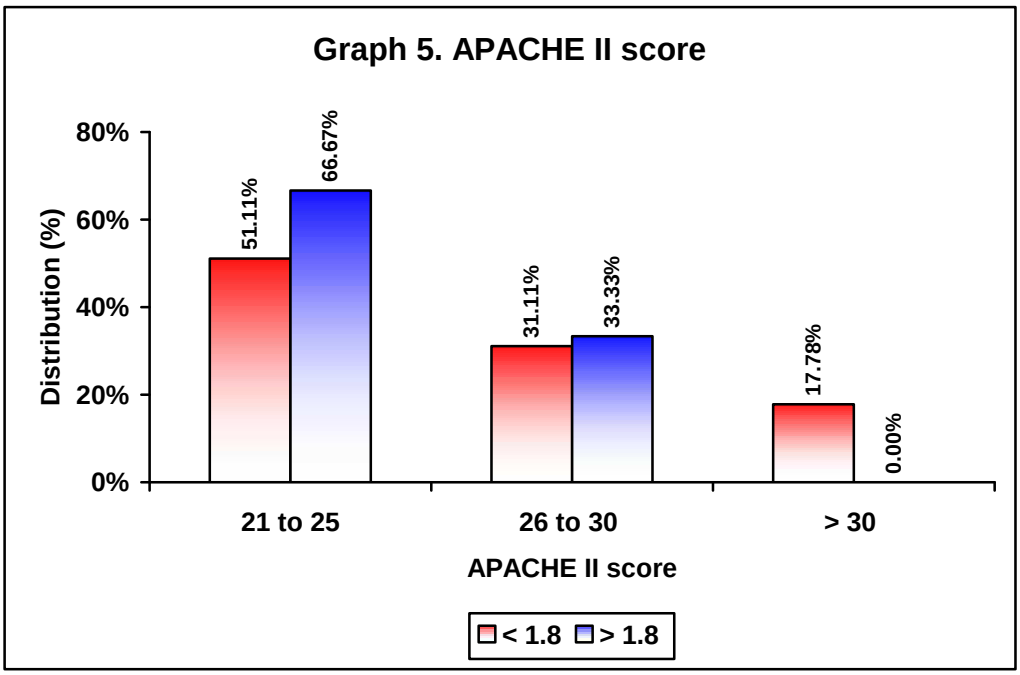
Diagnosis	Serum magnesium levels			
	< 1.8		> 1.8	
	No	%	No	%
UTI with septicemia	4	8.88	2	4.44
Malaria	1	2.22	1	2.22
Dengue haemorrhagic fever	2	4.44	1	2.22
Leptospirosis	0	0.00	2	2.22
OP Poisoning	1	2.22	4	8.88
Total	**8**	**17.78**	**11**	**24.44**

In this study, dengue haemorrhagic fever (4.44%), malaria (2.22%), urinary tract infection with septicemia (8.88%) and OP poisoning (2.22%) were the diagnosis in patients with patients with magnesium levels < 1.8 mg/dL and in patients with magnesium levels ≥ 1.8 mg/dL, the same diagnosis were noted in 2.22%, 2.22%, 4.44% and 8.88% of patients respectively and OP poisoning was noted in 2.22% of patients.

Table 11. APACHE II Score

APACHE II score	Serum magnesium levels (mg/dL)			
	< 1.8		> 1.8	
	No	**%**	**No**	**%**
21-25	23	51.11	30	66.67
26-30	14	31.11	15	33.33
> 30	8	17.78	0	0.00
Total	**45**	**100.00**	**45**	**100.00**

p = 0.011

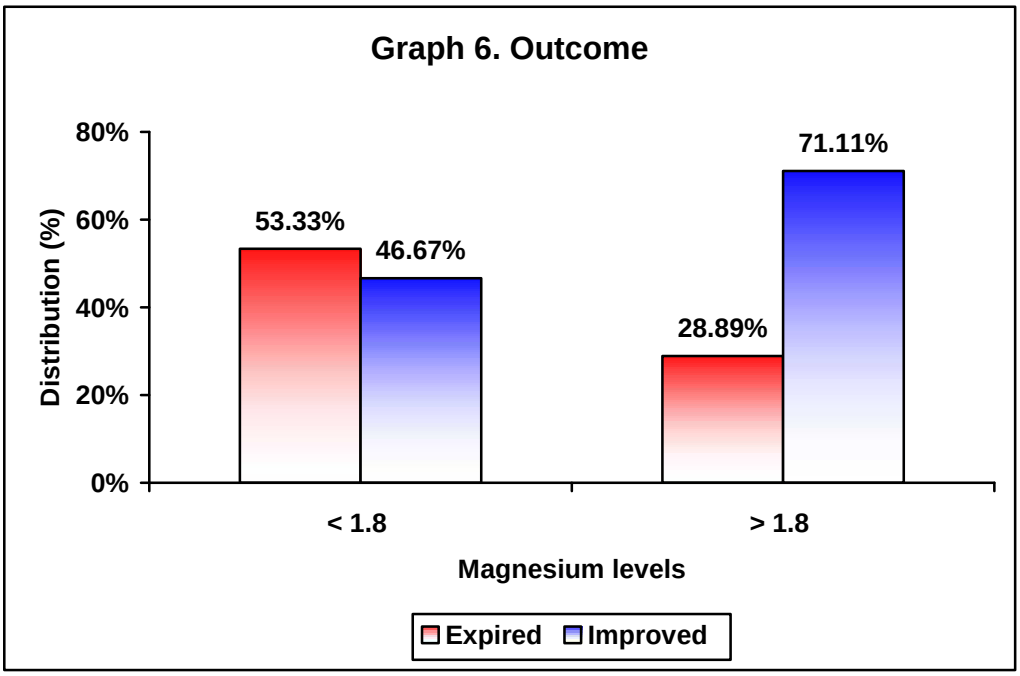


In this study 17.78% of patients with magnesium levels < 1.8 mg/dL had APACHE II score of > 30 compared none of the patient in with magnesium levels ≥ 1.8 mg/dL had APACHE II score > 30. This difference was statistically significant (p=0.011).

Table 12. Outcome

Outcome	Serum magnesium levels (mg/dL)			
	< 1.8		> 1.8	
	No	%	No	%
Improved	21	46.67	32	71.11
Expired	24	53.33	13	28.89
Total	**45**	**100.00**	**45**	**100.00**

p = 0.018

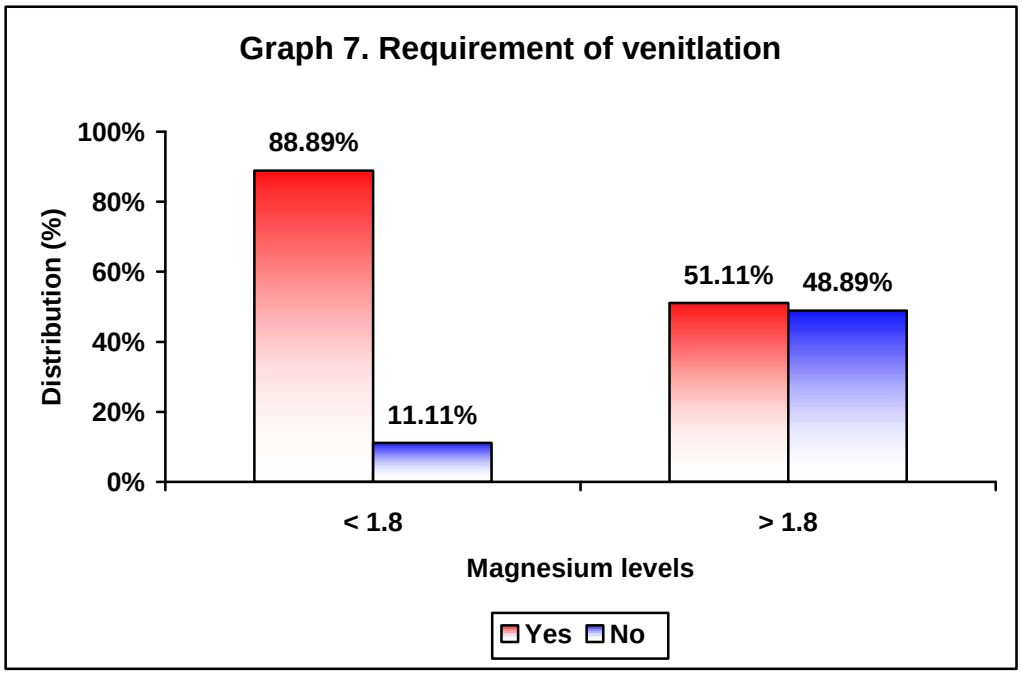


In this study 53.33% of patients with magnesium levels < 1.8 mg/dL expired as compared to 28.89% of patients with magnesium levels ≥ 1.8 mg/dL. This difference was statistically significant (p=0.018).

Table 13. Requirement of ventilation

Ventilation	Serum magnesium levels (mg/dL)			
	< 1.8		> 1.8	
	No	%	No	%
Yes	40	88.89	23	51.11
No	5	11.11	22	48.89
Total	**45**	**100.00**	**45**	**100.00**

p < 0.001



In the present study significantly higher number of patients with magnesium levels < 1.8 mg/dL required ventilation (88.89%) compared to patient with magnesium levels ≥ 1.8 mg/dL (51.11%) (p<0.001).

Table 14. Comparison of qualitative data in patients with hypomagnesemia and normomagnesemia

Components	Serum magnesium levels				p value
	< 1.8		> 1.8		
	Mean	**SD**	**Mean**	**SD**	
Age (Years)	57.44	17.29	49.16	18.40	**0.030**
Temperature (0C)	102.01	2.19	102.85	2.53	0.096
Pulse rate (/min)	120.87	31.04	116.58	32.96	0.527
Respiratory rate (/min)	41.33	13.95	37.16	12.88	0.144
SBP (mm Hg)	87.45	35.05	93.41	44.82	0.490
DBP (mm Hg)	58.65	20.84	62.82	31.87	0.500
GCS	11.16	3.23	12.22	3.25	0.122
APACHE II score	25.91	4.44	24.07	3.00	**0.011**
Ventilatory support (Days)	7.93	5.46	5.53	4.11	**0.038**
Hospital Stay (Days)	12.11	10.28	8.13	4.18	**0.019**

Table 14 shows comparison of qualitative data in patients with hypomagnesemia and normomagnesemia. It was observed that, mean age, APACHE II score, duration of ventilation and hospital stay differed significantly ($p<0.050$).

Chapter 6

Discussion

DISCUSSION

ICUs are the units with the highest mortality frequencies within hospital departments. Mortality rates in ICUs ranges between 16% and 67% depending on the patient groups followed-up and their characteristics. Critically ill patients have a high prevalence of electrolyte disorders because of the presence of multiple causative factors. Early diagnosis and treatment is necessary. Clinicians should be cautious about electrolyte homeostasis and the underlying pathophysiology of electrolyte disorders to provide optimal therapy for patients.[29]

Magnesium is one of the most common plasma cation. It regulates ion channels and plays very important role in neuromuscular transmission and enzymatic activity. Hypomagnesemia is an emerging electrolyte disturbance in hospitalized patients; especially in the critically ill ones and it has been shown to predict mortality in the ICU. Its prevalence has a wide range (11% to 61%).[15] It is an unnoticed problem, although it should be searched because of its importance for the prognosis of patients.[77]

However, there is a paucity of data on serum magnesium at admission as a predictor of morbidity or mortality. The present study was conducted with an aim to determine the impact of admission serum magnesium levels with regard to patient outcome considering, mortality, need and duration of ventilatory support, length of stay in ICU and APACHE 2 SCORE.

The present one year prospective study was conducted under the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum on critically ill patients. A total of 90 patients from

January 2012 to December 2012, divided into two groups based on magnesium levels that is, magnesium levels < 1.8 (hypomagesemics; n=45) and > 1.8 (normomagnesemics; n=45) mg/dL.

In the present study among the patients with hypomagnesemia 64.44% were males and 35.56% were females and male to female ratio 1.8:1 while in those with normal magnesium levels 75.56% were males and 24.44% females with male to female ratio of 3.09:1. Though the prevalence of hypomagnesemia was high in the male patients but it was not true statically (p=0.250). In contrast, Safavi M et al[74] reported 51% of the patients with hypomagnesemia were males and 49% were females with male to female ratio of almost 1:1

In this study, in patients with hypomagnesemia 48.89% of patients were aged more than 60 years whereas patients with normal magnesium levels, 28.89% of patients each were aged between 31 to 45 and 46 to 60 years. This difference was statistically significant (p=0.008). The mean age in in patients with hypomagnesemia was 57.44 ± 17.29 years compared to 49.16 ± 18.40 years (p<0.030). These findings suggest statistically significant association of hypomagnesemia with age. These findings were in agreement with Safavi M et al,[74] who reported mean age of 60.27 ± 0.82 in patients with hypomagnesemia and 58.84 ± 0.86 years in patients with normal magnesium levels.

In the present study, among the patients with hypomagnesemia, 48.89% of patients reported history of hypertension and 42.22% reported diabetes mellitus and the same history was present in 44.44% and 24.44% of the patients with normal magnesium levels. Hypomagnesemia has been known to be

associated with diabetes mellitus, insulin resistance and hypertension. Magnesium supplementation is associated with decreased insulin requirements and better control of blood sugar.[79,80]

Hypomagnesemic patients have more severe organ dysfunction and higher APACHE II score than the other patients. This may be explained by a strong association of hypomagnesemia with sepsis and septic shock, a common cause of death in the ICU patient. In the present study more than one third (35.55%) of the patients with hypomagnesemia were diagnosed with septicemia. 17.78% of patients with magnesium levels < 1.8 mg/dL had APACHE II score of > 30 compared to none of the patient in with magnesium levels ≥ 1.8 mg/dL had APACHE II score > 30 (p=0.011). Also, the mean APACHE II scores in hypomagnesemics were significantly high compared to normomagnesemics (25.91±4.44 vs 24.07±3.00; p=0.011). These findings suggest that, patients with hypomagnesemia may have significantly higher mortality risk based on APACHE II score at admission (p=0.016).

Soliman et al[81] found that those patients who develop hypomagnesemia during their ICU stay had higher APACHE II score on admission while, Demircan F et al[78] could not find significant difference between the groups about the APACHE II scores.

In this study 53.33% of patients with hypomagnesemia expired compared to 28.89% of patients with normal magnesium levels. This difference was statistically significant (p=0.018) posing strong association between

hypomagnesemia and mortality. Some studies had been published about the relationship between hypomagnesemia and mortality.

Similar to the findings of this study, Rubeiz et al.[72] reported nearly double mortality rates (46% vs 25%) in hypomagnesemic patients compared with those with normomagnesemia.

Another study by Demircan F et al[78] showed significant difference between patients with hypomagnesemia or normomagnesemia at admission in ICU mortality. In contrast, Guerin et al.[15] found no significant difference between hypomagnesemic and normomagnesemic patients in ICU mortality (18% vs 17%).

Chernow et al.[14] similarly reported no difference between hypomagnesemic and normomagnesemic patients in mortality (13% vs 11%).

Safavi et al.[74] had found no significant difference between hypomagnesemic and normomagnesemic groups in ICU mortality; but noted a higher mortality rate among hyper magnesemic patients.

Broner et al,[82] who studied critically ill pediatric patients, found a mortality rate of 8% in both the hypomagnesemic and normomagnesemic groups, but the mortality rate in the hypermagnesemic patients was significantly higher.

The disparity in rates of mortality among the hypomagnesemics could be attributed to the various other factors such as age, history and clinical presentation at admission. For example, sepsis is one of the independent risk factors for developing hypomagnesemia during the ICU stay and magnesium may

play an important role in sepsis, as magnesium ions are essential for several important immunologic functions and serve as a natural calcium antagonist, an important step in propagating cellular injury.[83]

Hypomagnesemia is known to cause muscle weakness and respiratory failure. It is one of the factors causing difficulty in weaning the patient from the ventilator.[84] In the present study higher number of patients with hypomagnesemia required ventilation (88.89%) compared to patient with normal magnesium levels ($p<0.001$). The mean days of ventilation among patients with hypomagnesemia was significantly high (7.93 ± 5.46 days) compared to normomagnesemic patients (5.53 ± 4.11; $p=0.038$). It was observed that, the mean duration of hospital stay patients with hypomagnesemia was significantly high (12.11 ± 10.28 days) compared to normomagnesemic patients (8.13 ± 4.18; $p=0.019$) indicating strong association of ventilation and prolonged hospital stay with hypomagnesemia.

Demircan F et al[78] showed that patients with hypomagnesemia needed ventilatory support more frequently and for a longer duration.

Magnesium is an important element in the regulation of various processes in the cell and cell membrane. It also has a role in protein and DNA synthesis, DNA and RNA transcription, translation of messenger RNA, and the regulation of mitochondrial function. So early diagnosis and treatment of hypomagnesemia in patients requiring ICU may be important and has been discussed several times.[13,14,85,86] Moreover, it is comprehensible that hypomagnesemia is associated with severity of illness or increased mortality.

Overall, hypomagnesemia is a common electrolyte imbalance in the critically ill patients and is associated with higher mortality rate, more frequent and more prolonged ventilatory support. Therefore, early diagnosis and treatment of hypomagnesaemia is necessary. Monitoring of serum magnesium levels may have prognostic, and perhaps therapeutic, implications and physicians should be alert to the high incidence of magnesium deficiency in critically ill patients.

Chapter 7

Conclusion

CONCLUSION

Based on the present study findings it may be concluded that, patients with hypomagnesemia on admission are significantly at high risk of mortality, requirement of ventilation, prolonged ventilatory support and longer duration of hospital stay. Further, patients with lower levels of serum magnesium levels at admission predict higher APACHE II scores.

Chapter 8

Summary

SUMMARY

Magnesium is one of the most common plasma cation. Hypomagnesemia is an emerging electrolyte disturbance in hospitalized patients; especially in the critically ill ones and it has been shown to predict mortality in the ICU. The present study was aimed to determine the impact of admission serum magnesium levels and patient outcome considering,mortality, need and duration of ventilatory support, length of stay in ICU and APACHE II Score.

The present one year prospective study was conducted under the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum on critically ill patients. A total of 90 patients from January 2012 to December 2012 were studied. Patients were divided as hypomagnesemics and normomagnesemics.

In the present study in 64.44% in hypomagnesemics and 75.56% in normomagnesemics were males. In hypomagnesemics 48.89% of patients each were aged more than 60 years whereas normomagnesemics, 28.89% were aged between 31 t 45 and 46 to 60 years ($p=0.008$). 17.78% of patients with magnesium levels < 1.8 mg/dL had APACHE II score of > 30 compared none of the patient in with magnesium levels ≥ 1.8 mg/dL had APACHE II score > 30 ($p=0.011$). 53.33% patients hypomagnesemia expired compared to 28.89% with normomagnesemia ($p=0.018$). Significantly higher number of patients with hypomagnesemia required ventilation (88.89%) compared to patient with normomagnesemia (51.11%) ($p<0.001$).

Overall, the present study showed that, patients with hypomagnesemia at admission are significantly at high risk of mortality, requirement of ventilation, prolonged ventilatory support and longer duration of hospital stay and also predict higher APACHE II scores.

Chapter 9

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Annexures

Annexure I

ANNEXURE I – CONSENT FORM

"Impact of serum magnesium levels in the clinical outcome of critically ill patients- A one year prospective study"

Objective and purpose of the study

This research is intended to estimate the Impact of serum magnesium levels in the clinical outcome of the critically ill patients. The principal investigator of the study is Dr. **** ***** under the guidance of Dr. ********.

Procedure

If you agree to be part of the research study you will be asked the relevant history and will be subjected to relevant clinical examination and investigations. You will also have to give blood sample for the study.

Risk and Benefits

The only risk and possible discomfort you might get is while taking blood from your arm for the investigations. It may cause swelling, pain, redness, bruising or infection (rarely happens) at the site from where the blood is drawn.

Alternatives

Taking part in this study is voluntary. You may choose not to take part in this study, or if you decide to take part you can later change my mind and withdraw from the study. Your decision will not change the present or future health care or other services that you receive. The study doctor or sponsorer may stop your participation in this study any time. If you choose not to take part in the study you will receive the standard treatment for patients with your condition.

Voluntary participation/ withdrawal

Your participation in this study is entirely voluntary and you may withdraw from the study at any time.

Privacy and Confidentiality

All information collected about you during the course of this study will be kept confidential to the extent permitted by law. The code numbers will identify you in this research record. Information from this study may be published but your identity will be confidential in any publication.

Institution / Sponsor's policy

Does not apply to this research

Financial incentives for participation

You will not be paid / offered any gifts /incentives for participating in the study.

Authorization to publish the results

The results of the study would be forwarded to the KLE University, Belgaum as part of requirement towards the completion of MD degree, review and publishing. If you have any questions about my rights as a participant you may call Dr. ***** ******, Principal and Chairman, J.N.M.C Ethical Committee for Human Research phone number ***** ******.

CONSENT FORM

I voluntarily agree to take part in this study by signing on the line below. I may withdraw at any time. I am not giving up any of my legal rights by signing this form. My signature below indicated that I have read this entire consent form or it has been read to me, and has been explained to me in my vernacular language and had all my questions answered. I will be given a copy of this consent form.

Signature /Left Thumb print of the Participant or legally authorized representative.

Participant's Name/ : …….

Signature/ Left Thumb Impression of the participant's : …….

Name of the legally authorised representative/ Guardian : …….

Signature/ Left Thumb Impression. : …….

Witness's Name : …….

Signature/ Left Thumb Impression. :…….

Investigators name and Signature : …….

Date and Place : …….

Dr.*********
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Ph.No. ***** ******
Ext. ****

Dr. **** ***** *****
Post-Graduate,
Department of Medicine,
J.N. Medical College,
Belgaum
Ph.No. **** *****
Ext. ****

Annexures

Annexure II

ANNEXURE II – PROFORMA

Patient Name: I.P number:

Age: Sex:

Address: Occupation:

Date of admission: Date of discharge:

Symptoms:

1. Fever Yes/No
2. Cough with expectoration Yes/No
3. Breathlessness Yes/No
4. Burning micturition Yes/No
5. Headcahe Yes/No
6. Vomiting Yes/No
7. Altered consciousness Yes/No
8. Abdominal Pain Yes/No
9. Decreased urine output Yes/No

Past history

1. Blood transfusion Yes/No

Treatment history

Received magnesium preparation in past -- Yes/No

PERSONAL HISTORY:

Habits: h/o smoking Yes/No

H/o Alcohol consumption Yes/No

PHYSICAL EXAMINATION:

GENERAL CONDITION:

Pallor: Yes/No

Icterus: Yes/No

Lymphadenopathy: Yes/No

Cyanosis: Yes/No

Clubbing: Yes/No

Edema: Yes/No

VITALS:

Temperature:

Pulse:

Respiratory rate:

Blood pressure:

Mean Arterial Pressure

Glasgow COMA Scale

SYSTEMIC EXAMINATION:

R. S.:

C.V.S.:

P.A.:

C.N. S:

LABORATORY INVESTIGATIONS:

- CBC
- Serum bilirubin
- Serum calcium

- Serum albumin
- Serum potassium and sodium
- Serum magnesium
- Arterial Blood Gases

DIAGNOSIS:

FOLLOW UP

OUTCOME –

Mortality

Length of stay in ICU

Need for Ventilatory support

Duration of Ventilatory support

Improvement in APACHE Score

Annexures

Annexure III

ANNEXURE III – KEY TO MASTER CHART

AECOPD	-	Acute exacerbation chronic obstructive pulmonary disease
APACHE	-	Acute physiology and chronic health evaluation
APH	-	Aphasia
AS	-	Altered sensorium
bpm	-	Beats per minutes
BR	-	Bronchial breathing
C	-	Crepitations
CNP	-	Cranial nerve palsy
dL	-	Decilitre
DST	-	Distension
DT	-	Diffuse tenderness
E	-	Expired
F	-	Female
gm	-	Gram
HPT	-	Hepatomegaly
I	-	Improved
KS	-	Kernig sign
L	-	Litre
LH	-	Left hemiplegia
M	-	Male
meq	-	Milli equivalent
mg	-	Milligram
mm	-	Millimeter

N	-	No
NR	-	Neck rigidity
OP	-	Organo phosphorous compound
PaO2	-	Partial pressure of oxygen
R	-	Rhonchi
RH	-	Right hemiplegia
SPL	-	Splenomegaly
T HPT	-	Tender hepatomegaly
TACH	-	Tachycardia
TD	-	Tenderness
UNC	-	Unconscious
WBC	-	White blood cell
Y	-	Yes