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Original Article

Biochemistry Section

Study of Serum Magnesium, Potassium and their Correlation with Lipid Profile in Ischaemic Heart Disease

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ABSTRACT

Introduction: Ischaemic Heart Disease (IHD) is a common health burden. Dyslipidemia is an established risk factor for the disease. Studies have been conducted to evaluate any possible relation of the disease with alterations of magnesium and potassium. But, among patients of Eastern India, studies to associate the condition with these analytes as well as their possible relationship with serum lipid profile have been rare.

Aim: To evaluate the non diabetic, normotensive IHD patients attending a tertiary care hospital to find out whether there was any association of the disease with altered serum Magnesium (Mg) and Potassium (K) and to detect possible correlation of these electrolytes with serum lipid levels.

Materials and Methods: This case-control study was conducted in the Departments of Biochemistry and Medicine of the Institute of Postgraduate Medical Education and Research, Kolkata, West Bengal, India, from January 2019 to June 2020. This study included 106 non diabetic, normotensive IHD cases {encompassing 52 Chronic Coronary Syndrome (CCS) and 54 Acute Myocardial Infarction (AMI) patients} along with 103 age and sex matched healthy controls. Serum magnesium, potassium and lipid profiles were assessed. Student's unpaired t-test and Pearson correlation tests were performed using Statistical Package for the Social Sciences (SPSS) version 23 software.

Results: Mean age of the control and case groups were 63.95±7.94 and 63.60±7.56 years, respectively. The case and control groups were comparable for age and gender distribution as no statistically significant difference was found. The cases had a significantly lower serum Mg and K ($p<0.001$ in each case) than the controls. There were significant positive correlations between serum Mg and K ($r=0.498$, $p<0.001$) while significant negative correlations ($r=-0.204$, $p=0.036$) were established between magnesium and low density lipoprotein cholesterol of the cases.

Conclusion: Low levels of serum magnesium and potassium are associated with coronary heart disease. Patients with deranged lipid profile should be regularly screened for deficiencies in serum magnesium. Further longitudinal studies are warranted to establish potential therapeutic role of supplementation of magnesium and potassium in IHD.

Keywords: Acute myocardial infarction, Cholesterol, Chronic coronary syndrome, Dyslipidemia, Serum electrolytes

INTRODUCTION

The Ischaemic Heart Disease (IHD) is presently a leading cause of death worldwide [1]. In 2017, IHD contributed to the demise of 8.93 million people, accounting for approximately 15.9% of the yearly deaths; rendering it the most common cause of death worldwide. It also became the leading cause of global Years of Life Lost (YLL) [2]. India has experienced more than doubled rate of deaths as well as disability from IHD in the last 30 years [3]. In 2016, the prevalence of IHD in India was 23.8 million and it was responsible for 17.8% of total yearly death as well as 8·7% of total loss of Disability-Adjusted Life Years (DALYs), making it the leading individual cause of disease burden in India in 2016 [4,5].

The IHD usually arises out of reduced regional blood supply to a section of myocardium, commonly resulting from an atherosclerosis of the coronary arteries, ultimately presenting as a variety of clinical symptoms [6]. Dyslipidemia is a well-established, modifiable, independent risk factor of IHD and often a prerequisite for development of the disease [7]. Deficiency of magnesium may be associated with an atherogenic lipid profile [8]. The relationship of magnesium to the human heart has been a subject of interest. Magnesium performs important functions in metabolic processes, endothelial cell functioning and normal myocardial functions, including myocyte regulation [9].

Possible association of magnesium deficiency with free-radical induced myocardial tissue damage and ischaemia has been hinted [10]. Magnesium is also an essential co-factor for NA^+-K^+-ATPase Sodium (Na) pump. It maintains the ionic gradients between extracellular and intracellular fluid compartments and is responsible for maintaining potassium homeostasis [11]. Deficiency in serum magnesium may lead to altered potassium concentration. In animal model studies, potassium has demonstrated a tendency to reduce the calcification of Vascular Smooth Muscle Cells (VSMCs) and inhibit neointimal proliferation [12,13]. Existence of serum potassium deficiency as independent risk factors of IHD in human has also been under study [14-16]. Yet, studies to elicit associations of serum magnesium and potassium with IHD as well any correlation of these analytes with the serum lipid levels in IHD patients have been rare, especially in Indian population. In such a background, the present study was conducted to look out for possible association of serum magnesium and potassium with the disease as well as any correlation between serum lipid parameters with magnesium and potassium in non diabetic, normotensive IHD patients attending a tertiary care hospital of Eastern India.

MATERIALS AND METHODS

This case control study was conducted in accordance with Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [17] from January 2019 to June 2020 in the Department of Biochemistry in collaboration with the Department of Medicine at Institute of Postgraduate Medical Education and Research, Kolkata, West Bengal, India. The study protocol was approved by the Institutional Ethics Committee (IEC) via Memo No. IPGME&R/IEC/2019/061. A voluntary informed consent was signed by every participant. Apart from minimal phlebotomy associated risks, the process was entirely harmless. To minimise these risks, phlebotomy was done using disposable syringe and needle under strict aseptic conditions and direct supervision.

Subjects were observed for phlebotomy related complications for approximately an hour after the procedure.

Inclusion criteria: A total of 106 IHD cases and 103 age and sex matched healthy controls were selected to be a part of the study. Entire study population was non diabetic and normotensive.

Exclusion criteria: Pregnant women, cases of trauma, thyroid disorders, diabetes mellitus, hypertension, hepatic or renal pathology, acute vomiting and/or diarrhoea, alcoholics, and those with prolonged ingestion of certain drugs such as proton pump inhibitors, fibrates, diuretics, potassium or magnesium supplementations in recent period were excluded from the study by detailed history, clinical evaluation and biochemical examinations.

Sample size calculation: The sample size was calculated after assuming the power of the study as 80% and average prevalence of coronary heart diseases in India as 6% [18]. To correlate the difference of Low Density Lipoprotein Cholesterol (LDLC) concentration between case and control group, sample size required was:

$\{(1.96+0.84)^2 \times 2 \times 0.94 \times 0.94\} / (0.39 \times 0.39) = 91$.

Here, 1.96 was the Z-value for 80% power of study, 0.94 was the standard deviation of LDLC from previous study [19] and 0.39 used in the denominator was the difference to be detected, here it was 10% of the mean (3.91 mMol/L) from the previous study [19]. Similar calculations were done for serum magnesium and potassium and the minimum sample size necessary was less than 91. Hence, sample size for cases was 106, which was greater than the required minimum sample size.

Study Procedure

The IHD cases were further classified into two groups: 52 cases were CCS and the remaining 54 were diagnosed cases of AMI. The CCS cases were diagnosed on the basis of clinical features, non invasive functional imaging for myocardial ischaemia, coronary computed tomography angiography or invasive coronary angiography combined with functional evaluation as per the European Society of Cardiology guidelines [20]. The AMI cases were selected on basis of a combination of clinical features, 12-lead electrocardiogram and cardiac-specific troponin-t assays according to the Fourth Universal Definition of Myocardial Infarction [21].

Selection of patients: Cases were selected from patients attending the Outpatient Department (OPD) or admitted to the in-patient department and intensive coronary care unit of the hospital. Controls were selected from the peers and relatives of patients as well as persons attending the OPD for routine health check-ups, on agreeing to sign the informed consent form.

Methods of collection of biochemical data: Various socio-demographic data such as name, age, sex, address of the subjects along with data regarding their physical examination and clinical history was taken by a predesigned, pretested, semi-structured questionnaire [22]. Ten milliliters of venous blood samples were collected from the subjects following 12 hours of overnight fasting in clotted vials. Serum completely free from haemolysis was used for biochemical assay. In case of delay, serum was preserved in -20°C for a maximum period of 2 weeks.

Serum magnesium was estimated by calmagite method in an Erba Manheim semi-autoanalyser. Magnesium, in alkaline medium, reacts with calmagite to synthesise a red colored complex [23].

Direct Ion-Selective Electrodes (ISEs) were used for estimation of serum potassium in Easylyte Plus Na^+-K^+-Cl^- analyser [24]. In an RX-Imola autoanalyser, serum total cholesterol was estimated by Cholesterol Oxidase Phenol 4-aminoantipyrine Peroxidase (CHOD-PAP) method, High Density Lipoproteins (HDL) cholesterol by immunoturbidimetric method (Randox RX series) and triglyceride via the Glycerine Phosphate Oxidase Peroxidase (GPO-PAP) method [25-29]. Serum LDL and Very Low Density Lipoprotein (VLDL) cholesterol were calculated using Friedewald Equation [30].

STATISTICAL ANALYSIS

Following derivation of the results, the data was collected in Microsoft excel spreadsheets. The data was checked for any errors, double-entered and checked for entry errors. Suitable statistical analysis was performed by IBM SPSS version 23 software. Student's unpaired t-tests were used to compare means across various groups and Pearson's correlation (r) tests were employed to find out any correlations of aforesaid parameters. Analysis was two-tailed and p-value less than 0.05 was considered as statistically significant.

RESULTS

The study population was between 40 to 85 years of age. Mean age of the control and case groups were 63.95±7.94 and 63.60±7.56 years, respectively. With a p-value of 0.746, there was no statistically significant difference of age distribution between the cases and control group.

The control group (n=103) consisted of 68 males and 35 females while the IHD case group (n=106) had 72 males and 34 females. Under Chi-square observation, no statistically significant difference was found with respect to gender (p-value=0.770).

The IHD cases demonstrated a statistically significant lower serum concentration of magnesium and potassium concentration as compared to the control group [Table/Fig-1].

Parameter (Mean±SD)	Control (n=103)	Case (n=106)	p-value
Total cholesterol (mg/dL)	155.85±14.20	177.24±23.10	<0.001*
LDL cholesterol (mg/dL)	87.00±15.73	110.53±23.55	<0.001*
VLDL cholesterol (mg/dL)	25.77±4.33	26.364±5.98	0.428
HDL cholesterol (mg/dL)	43.08±5.11	40.37±7.25	0.002*
Triglycerides (mg/dl)	128.95±21.50	131.57±29.90	0.468
Magnesium (mEq/L)	1.855±0.263	1.462±0.228	<0.001*
Potassium (mEq/L)	4.432±0.477	3.899±0.596	<0.001*

[Table/Fig-1]: Serum lipid profile, magnesium, potassium level in control and cases.
* Student's unpaired t-tests used
p-value <0.05 considered significant

Neither cases nor controls demonstrated any statistically significant difference in the serum magnesium or potassium level between the male and female population [Table/Fig-2].

Analyte	Cases			Controls		
	Male (n=72)	Female (n=34)	p-value	Male (n=68)	Female (n=35)	p-value
Mean serum Mg^{++} (mEq/L)	1.474	1.435	0.405	1.840	1.883	0.436
Mean serum K^+ (mEq/L)	3.913	3.871	0.737	4.468	4.363	0.307

[Table/Fig-2]: Gender distribution of mean serum magnesium and potassium level.
*Student's unpaired t-tests used

Lowest serum magnesium (1.346±0.181 mEq/L) and potassium (3.669±0.644 mEq/L) concentration was seen in the AMI group, followed by the CCS group (magnesium 1.582±0.211 mEq/L), potassium 4.138±0.432 mEq/L) and controls (magnesium 1.855±0.263 mEq/L and potassium 4.432±0.477 mEq/L) had highest mean serum concentration of both electrolytes [Table/Fig-3]. The differences in means for both magnesium and potassium were statistically significant between the control and CCS group [Table/Fig-3a], control and AMI group [Table/Fig-3b] as well as between the CCS and AMI group [Table/Fig-3c] (p-value is <0.001 in each case).

Correlations between magnesium, potassium and lipid parameters were analysed. A statistically significant negative correlation was found between magnesium and LDL cholesterol in IHD cases [Table/Fig-4].

There was a statistically significant positive correlation between serum magnesium and potassium levels in IHD cases [Table/Fig-5].

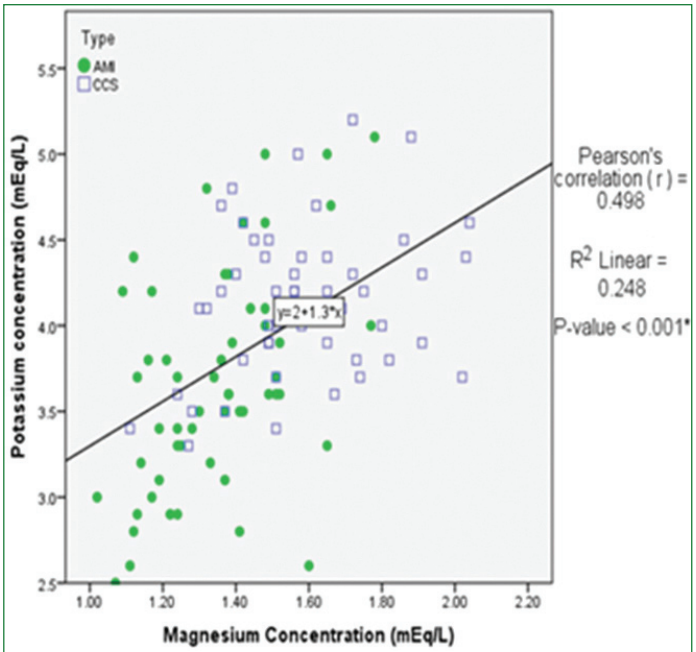
The CCS group also demonstrated a similar statistically significant positive correlation between magnesium and potassium (r=0.298, p=0.049). Similar statistically significant positive correlation between magnesium and potassium was also observed in the AMI group (r=0.472, p<0.001).

3A: Comparison of serum magnesium and potassium in control and CCS group.			
Parameter (Mean±SD)	**Control (n=103)**	**CCS group (n=52)**	**p-value**
Magnesium (mEq/L)	1.855±0.263	1.582±0.211	<0.001*
Potassium (mEq/L)	4.432±0.477	4.138±0.432	<0.001*
3B: Comparison of serum magnesium and potassium in control and AMI group			
Parameter (Mean±SD)	**Control (n=103)**	**AMI group (n=54)**	**p-value**
Magnesium (mEq/L)	1.855±0.263	1.346±0.181	<0.001*
Potassium (mEq/L)	4.432±0.477	3.669±0.644	<0.001*
3C: Comparison of serum magnesium and potassium in CCS and AMI group			
Parameter (Mean±SD)	**CCS group (n=52)**	**AMI group (n=54)**	**p-value**
Magnesium (mEq/L)	1.582±0.211	1.346±0.181	<0.001*
Potassium (mEq/L)	4.138±0.432	3.669±0.644	<0.001*

[Table/Fig-3]: Serum Magnesium and Potassium level in control, CCS and AMI groups.
*Student's unpaired t-tests used.
p-value <0.05 considered significant

Variables		Total choles-terol	Triglyc-eride	HDL choles-terol	LDL choles-terol	VLDL choles-terol
Magnesium	Pearson's correlation	-0.160	0.045	0.127	-0.204	0.037
	Significance (2-tailed)	0.101	0.648	0.196	0.036*	0.703
Potassium	Pearson's correlation	-0.154	-0.068	0.075	-0.153	-0.081
	Significance (2-tailed)	0.114	0.486	0.445	0.118	0.410

[Table/Fig-4]: Correlation of magnesium and potassium with lipid profile in IHD cases (n=106).
*Pearson's correlation tests were done; p-value <0.05 considered significant.



[Table/Fig-5]: Correlation of magnesium and potassium in IHD.
*Pearson's correlation tests done

However, serum potassium levels of IHD patients did not exhibit statistically significant correlation with any of the lipid parameters.

DISCUSSION

This study found that healthy controls had a 1.27 fold higher serum magnesium concentrations than IHD cases (1.462±0.228 mEq/L in cases as compared to 1.855±0.263 mEq/L in controls). It was further revealed that magnesium concentration was lowest in the AMI group, followed by the CCS group and highest in the controls. A previous study by Kughapriya P et al., in Southern India had found similarly low levels of magnesium in IHD patients [14]. Magnesium helps in modulating lipid metabolism, takes part in protection of myocardium from the oxygen derived free radicals, improves endothelial function and inhibits platelet aggregation and adhesion [31]. A study by Stevanovic S et al., on Serbian population revealed an inverse association between dietary magnesium intake and risk of IHD [32]. Several mechanisms that have been proposed for the role of magnesium deficiency in the pathogenesis of IHD include intracellular calcium accumulation, oxidative stress, cytokine synthesis, release of inflammatory mediators and adhesion molecules by the endothelial cells, thereby increasing the risks of atherogenesis and precipitation or progression of myocardial ischaemia. Hypomagnesemia also causes hyper-reactivity of the coronary arteries to vasoconstrictive stimuli [33]. Hypomagnesaemia in the setting of AMI has also been attributed to an elevated catecholamine level which in turn increases synthesis of cyclic AMP by activating adenyl cyclase. The cyclic Adenosine Monophosphate (AMP) may increase lipolysis to induce free fatty acid level that can cause chelation of magnesium [34].

In this study, serum potassium concentrations were also found to be significantly low in IHD cases as compared to the controls. Moreover, a statistically significant positive correlation was established between magnesium and potassium level among the IHD patients by the current study. These findings corroborated well with prior studies by Choudhury M et al., in Bangladesh who established a strong positive correlation of magnesium and potassium across cases of AMI, chronic IHD and normal healthy control subjects [15].

Potassium may have a potential role in atherosclerosis via reduction of oxidative stress and smooth muscle cell proliferation. Hence, antiatherothrombotic role has been attributed to potassium. Sun Y et al., demonstrated that low-normal serum potassium caused an elevation in intracellular calcium concentration, thus activating a Cyclic AMP Response Element-Binding protein (CREB) signal that subsequently enhanced autophagy and promoted VSMC calcification, ultimately resulting in arterial stiffness and atherosclerotic changes [35]. A population based meta-analysis by D'Elia L et al., hinted toward an inverse association between potassium intake and risks of CHD [36]. Further fall in serum potassium concentration during the early phases of AMI can be associated with sympathetic over activity. Elevated serum levels of catecholamines and the modulation of the β-adrenergic receptor signaling pathways can lead to potassium influx within cells thereby further decreasing serum potassium concentration [37].

A positive correlation between magnesium and potassium could be due to the close relation in the metabolism of these minerals. Magnesium is an essential co-factor of Na^+-K^+-ATPase Sodium (Na) pump. Fall in serum magnesium can cause reduced cellular uptake of potassium. Magnesium is also linked to renal potassium excretion. In the kidney, potassium is taken up by the cells across the basolateral membrane of the distal convoluted tubules and the cortical collecting ducts of nephron, via the NA^+-K^+-ATPase Na pumps and then secreted into the lumen by the apical Renal Outer Medullary Potassium (ROMK) as well as maxi-K channels. This basal potassium secretion through the luminal membrane of distal nephrons is the principle regulator of renal excretion of potassium. Magnesium blocks the ROMK channels to reduce the potassium secretion into the tubular lumen. A fall in serum magnesium concentration and subsequent lowering of intracellular magnesium content may lead to increased urinary excretion of potassium, thereby leading to a secondary fall in serum potassium concentration [38,39].

The present study found that IHD cases demonstrated a significantly higher serum concentration of total and LDL cholesterol and a much

lower serum High Density Lipoprotein (HDL) cholesterol level than the controls. The causal relationship of LDL cholesterol with coronary atherosclerosis is well-known. Similarly, HDL cholesterol has been attributed with antiatherosclerotic properties and cardioprotective role due to its antioxidant, anti-inflammatory, anticoagulant, profibrinolytic and antiaggregating nature as well as its role in cholesterol efflux [40,41]. Magnesium deficiency has been associated with an atherogenic lipid profile. Low extracellular magnesium concentration has also been stated to enhance endothelial permeability and facilitate the transport of low density lipoproteins through the endothelial layer [42]. Multiple studies found a negative correlation of magnesium and LDL cholesterol [43-45]. The present study also established a significant inverse correlation between magnesium and LDL cholesterol levels in patients of IHD. However, some previous studies yielded contradictory results on interrelationship between magnesium and total cholesterol and HDL cholesterol. While Sajjan N and Shamsuddin M demonstrated a positive correlation between magnesium and HDLC, no such statistically significant relationship could be demonstrated in another study by Guerrero-Romero F and Rodríguez-Morán M [43,46]. The current study did not establish any statistically significant correlation of these lipid parameters except LDL cholesterol with magnesium.

In the present study, no statistically significant relationship was established between serum potassium and lipid profile. Previous studies in this regard yielded somewhat inconclusive results. A study by Lai Y-H et al., that associated low normal levels of potassium with elevated risk of cardiovascular mortality, found no statistically significant correlation of the electrolyte with lipid parameters [47]. Another systematic review found significant correlation of potassium with blood pressure but not with serum lipids [48]. Present study excluded hypertensive patients, which may be responsible for non significant relationship of these parameters.

Limitation(s)

There were certain limitations of this study. It had a small sample size and was a hospital based study. So, it might not have properly reflected the trends in general population of the community. The study did not include patients having cardiovascular disease other than IHD. It was only case control study which could establish an association of magnesium to IHD and its inverse correlation with LDL cholesterol. Further longitudinal studies are required for establishing any definitive causal relationship between the parameters and the disease as well as any potential therapeutic benefits of magnesium supplementation on lipid parameters in IHD patients and reduction of disease severity in these cases.

CONCLUSION(S)

It can be concluded that low serum magnesium and potassium concentrations are associated with IHD in non diabetic, normotensive patients of Eastern India. Furthermore, serum magnesium is positively correlated with potassium and inversely correlated to LDL cholesterol level in the IHD patients of this region. Routine measurement of serum magnesium and potassium in patients of IHD is recommended. Periodic magnesium assessment in patients of Eastern Indian region suffering from dyslipidemia and CCSs with efforts to maintain optimal serum levels may be beneficial in reduction of disease severity or possible prevention of precipitation of AMI.

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