ORIGINAL ARTICLE

HEART FAILURE PATIENTS ARE PRONE TO DEVELOP MAGNESIUM DEFICIENCY AS A RESULT OF DIURETIC/DIGOXIN THERAPY

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ABSTRACT

Objective: To evaluate serum magnesium level in chronic heart failure (CHF) patients receiving diuretic and digoxin therapy.

Study Design: A case-control study.

Patients and Methods: The study was conducted at the Basic Medical Sciences Institute (BMSI), Jinnah ostgraduate Medical Centre (JPMC), Karachi with collaboration of National Institute of Cardiovascular Diseases (NICVD), Karachi from April to December 2003. Serum magnesium levels were evaluated in 65 subjects including 45 patients of heart failure admitted in the NICVD, Karachi. Twenty subjects were healthy, age and gender matched controls (group-I). Patients were divided into two groups (groups-II and III) according to treatment with diuretics or combination of diuretic and digoxin. Other electrolytes including sodium, potassium, chloride and calcium were also evaluated. Student't' test at ranging p-values of (<0.05, <0.01, <0.001) were used to determine the statistical significance.

Results: The cardiac failure patients showed lower (1.72 ± 0.07 mg/dl) level of serum magnesium when compared with normal (0.53 ± 0.19 mg/dl) control subjects and even more significantly lowered (1.65 ± 0.09 mg/dl) in patients who were receiving diuretics and digoxin as compared to patients (1.80 ± 0.10 mg/dl) who were on diuretics only ($p<0.001$).

Conclusion: Patients with chronic heart failure were characteristically prone to develop magnesium deficiency along with other electrolytes (potassium, calcium, and chloride) due to administration of diuretics and digoxin.

Keywords: Chronic heart failure, Magnesium, Electrolytes, Diuretic, Digoxin

INTRODUCTION

Magnesium, a biologically essential cation, has recently received considerable attention in clinical medicine, especially with regard to the role of its depletion in cardiovascular patho-physiology.[1] After calcium, it is the second most abundant divalent cation present in serum.[2] Heart failure patients are prone to develop magnesium deficiency as a result of diuretic and digoxin administration.[3] Diuretic therapy increases urinary magnesium losses and may cause depletion of total body and regional magnesium stores when administered on a long term basis.[1] Two types of diuretics known as loop (such as furosemide) and thiazide (including hydrochlorothiazide) can deplete magnesium level. For this reason, doctors who prescribe diuretics may consider recommending magnesium supplements as well.[4] The diuretics in common use promote cation excretion almost exclusively in association with chloride.[5]

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It is important that normal levels of magnesium be maintained while taking digoxin (lanoxin) because low blood levels of magnesium can increase adverse effects from this drug. In addition, digoxin can lead to increased loss of magnesium in the urine.[4] Information on magnesium concentration in serum is important in treating cardiac arrhythmias, given the documented increases in incidence of supraventricular and ventricular arrhythmias in patients with hypomagnesemia.[6]

Because altered magnesium homeostasis, particularly a deficiency, can cause alterations in metabolic functions that result in clinically recognizable events require better understanding of the magnesium status. The aim of this study was to evaluate serum magnesium level in a representative cases of CHF patients receiving diuretic and digoxin as a treatment to compare magnesium level with normal control subjects.

PATIENTS AND METHODS

This case control study was conducted at department of Biochemistry, BMSI, JPMC, Karachi, with collaboration of NICVD Karachi from April to December 2003.

A total of 65 subjects, 45 cases of CHF selected from NICVD, Karachi and 20 healthy normal age and gender matched subjects were selected as controls. Diagnosed cases of chronic heart failure with ischemic heart disease, valvular heart disease, rhythm disturbances, cardiomyopathy and miscellaneous (pericarditis, pleural effusain, pulmonary oedema) group of cases were included in this study. Patients were excluded if they had liver diseases, thyroid diseases or history of alcohol consumption. Prior to collection of blood samples, the personal history, physical examination and clinical status were assessed and recorded on specially designed proforma. Blood samples of all subjects were collected under aseptic measures. To minimize the variability of the analytical method, all samples were processed at one time. Serum Magnesium was determined by colorimetric method using kit (Cat No 0137) supplied by Stanbio Laboratory with microlab-200 analyzer. Sodium, potassium, and chloride were measured by ion selective electrode (ISE) technology using Easylyte analyzer.

All results were expressed as means and ± standard errors of means (± s.e.m) with inter-group comparisons performed by 't'-tests. A p-value of <0.05, <0.01, and <0.001 was used to indicate statistical significance.

RESULTS

The demographic distribution of the study subjects, is shown in Table-1. Thirty nine (60%) were males and 26 (40%) were females. All selected subjects were distributed into three groups. Group-I comprised of 20 healthy normal control subjects including 15 (70%) males and 5 (30%) females. Group-II consisted of 24 patients of CHF receiving (diuretics and digoxin) 14 (58.3%) males and 10 (41.7%) females. In group-III receiving (diuretics) 21 patients, 10 (47.6%) were males and 11 (52.4%) females were studied. Age range in this study was 35-65 years. Mean age of total study subjects was 52.95±1.11 years.

Table 1: Demographic distribution of study
Values are expressed as mean±s.e.m.
The number of observations and units are given in parenthesis

Groups	No. of Subjects	Age (years)	Gender	
		Mean±s.e.m	Male	Female
			n (%)	n (%)
I Normal (Control)	20	51.10±1.60	15 (70)	5 (30)
II CHF (Diuretics + Digoxin)	24	52.62±2.09	14 (58.3)	10 (41.7)
III CHF (Diuretics)	21	55.09±1.93	10 (47.6)	11 (52.4)
Total	65	52.95±1.11	39 (60%)	26 (40%)

The mean values of serum magnesium of CHF patients was 1.72±0.07 mg/dl while in healthy controls, it was 2.53±0.19 mg/dl. The differences in serum magnesium between CHF patients and control was highly significant (p<0.001). The mean values of serum magnesium were also observed to be lower (1.60±0.09 and 1.80±0.10 mg/dl) respectively when total of groups-II and III of CHF patients respectively were compared with group-I normal (control) subjects the observations are shown in Figure-1, a and b.

The mean values of serum magnesium observed were significantly lower, in males of group-II (p<0.001)

and group-III ($p<0.01$) of CHF patients when compared with males of group-I normal control subjects. The mean values of serum magnesium were also observed to be similarly significantly lower

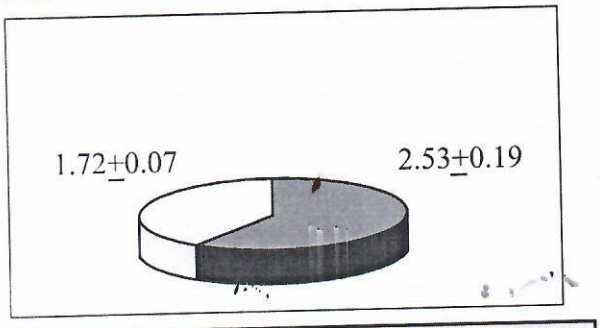


Figure 1(a): Comparison of Serum Magnesium Level of Normal (control) Subjects and total Chronic Heart Failure patients

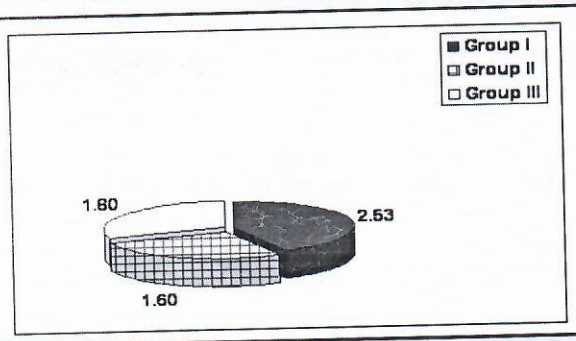
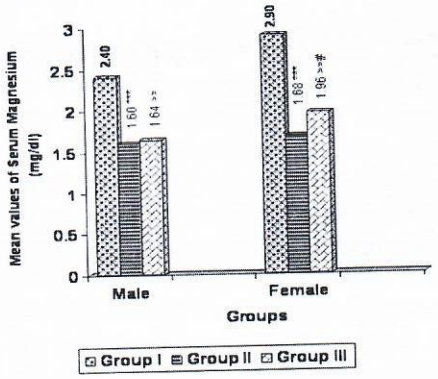


Figure 1(b): Comparison of Serum Magnesium Level of Normal Control (Group-I) Subjects and Chronic Heart Failure patients (Groups-II & III)

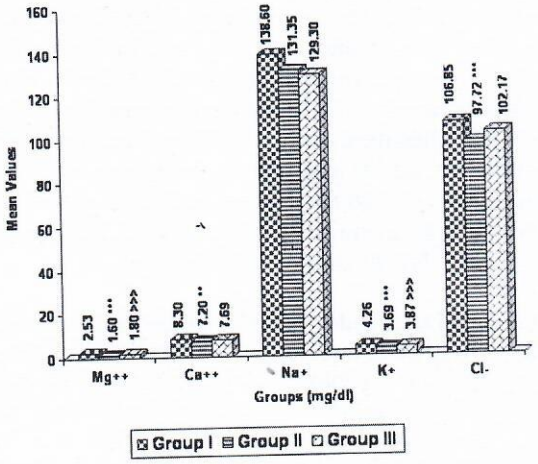
respectively in females of group-II and group-III of patients when compared with group-I normal (control) subjects. These findings are depicted in Figure-2.



*** P<0.001, Group-I vs Group-II
>> P<0.01, Group-I vs Group-III
# P<0.05, Group-II vs Group-III

Figure 2: Comparison of Serum Magnesium Level in Males and Females of Group-I normal (control), Group-II and Group-III of Chronic Heart Failure Patients

Figure-3 shows the comparison of mean values (±s.e.m) of serum electrolytes that include magnesium, sodium, potassium chloride and calcium. Magnesium, calcium, potassium and chloride were observed significantly lower ($p<0.001$, $p<0.01$, $p<0.001$, $p<0.001$) respectively in patients of group-II and



**P<0.01, ***P<0.001, Group-I vs Group-II, >>>P<0.001, Group-I vs Group-III

Mg++ = Magnesium Ca++ = Calcium Na+ = Sodium
K+ = Potassium Cl- = Chloride

Figure 3: Comparison of Mean Values of Serum Electrolytes (Magnesium, Calcium, Sodium, Potassium and Chloride) in Control (Group I) and (Group II & Group III) of CHF Patients (Groups-II & III) of CHE Patient

group-III of CHF when compared with group-I (control) subjects.

DISCUSSION

Magnesium deficit is one of the most frequent electrolyte abnormalities in current clinical practice.[7] There is growing evidence that magnesium status is important in pathogenesis and treatment of cardiovascular disease. Despite its importance, physicians frequently fail to consider magnesium status when managing a patient.[8] Gottlieb et al. indicated that abnormalities of the serum magnesium concentration are not merely laboratory curiosities but have important clinical implications.[9]

Recent advances in the analytic methods for serum magnesium determination have made the rapid and accurate measurement of this ion a useful clinical tool in a variety of disease states. This case control

study demonstrated hypomagnesemia in chronic heart failure patients receiving digitalis glycoside. Bloom stated digoxin, an inhibitor of Na, K-ATPase, increases both the abundance and size of myocardial lesions due to magnesium deficiency.[10] Magnesium depletion also was observed because of diuretic agents. Pronounced diuresis by diuretics and increased renal excretion of magnesium was the cause of magnesium deficiency in 55% of patients in a study carried out by Purvis and Movahed.[8] Patients on traditional non-potassium-magnesium sparing diuretics tend to have a potentially dangerous deficiency.[4]

In the present study the age range was 35 years to 65 years, the mean was 52.95±1.11. However, men comprised 60%, whereas women comprised 40%. When compared to this study, some other studies showed no significant difference in age and gender.[11,12] Shechter noted hypomagnesemia was common in hospitalized patients, especially in elderly patients with coronary artery disease and those with chronic heart failure.[13]

Co-existent magnesium and potassium deficiency was also observed in this study. Chakraborti et al showed that hypomagnesemia was commonly associated with an imbalance of electrolytes such as sodium, potassium and calcium.[14]

Ceremuzynski et al assessed the role of electrolyte imbalance in cardiac arrhythmias associated with congestive heart failure.[15] They concluded that hypomagnesemia was probably related to increased magnesium excretion is an essential feature of heart failure associated with complex ventricular arrhythmias. Strickberger et al found multifocal atrial tachycardia associated with hypokalemia and hypomagnesemia.[16]

It is also clear from the observation of Gettes that in certain groups of patients, particularly those with hypertension and congestive heart failure treated with thiazide and loop diuretics, the presence of ventricular arrhythmias is due to hypopotassemia and possibly also due to hypomagnesemia.[17]

A study done by Berkelhammer and Bear showed that hypocalcemia was prominent manifestation of magnesium deficiency.[18] Seelig found that diuretics and digitalis can intensify an underlying magnesium deficiency, leading to cardiac arrhythmias that are refractory unless magnesium is added to the regimen.[4] Magnesium has been found to be necessary for intracellular potassium repletion in these patients. Because patients with congestive heart failure and others receiving diuretic therapy are also prone to chloride loss leading to metabolic alkalosis that also interferes with potassium repletion, the addition of magnesium and chloride supplements in addition to the potassium seems prudent. In our study the chloride was also significantly low.

Chipperfield and Chipperfield proved that normal men have a significant lower concentration of magnesium in their heart muscle than women, this correlates well with the higher incidence of male ischemic heart disease. They also had good evidence that diuretics can cause magnesium deficiency which makes the heart susceptible to the development of arrhythmias, particularly during digitalis therapy.[19]

In accordance to this study, the diuretics and digitalis causing the electrolyte disturbances were also observed by Nicholls noting that loop and thiazide diuretics can induce deficits of sodium, potassium and magnesium in patients with heart failure.[20]

Cohen et al showed that various pathophysiological factors as well as pharmacological agents, mainly furosemide (frusemide) present in the setting of congestive heart failure may enhance magnesium loss and thus produce magnesium deficiency.[21]

Hypomagnesemia and depletion of intracellular magnesium stores have been held responsible for a variety of cardiovascular and other functional abnormalities including various arrhythmias, a few clinical studies have reported a significant association of serum magnesium levels with ventricular arrhythmias, impairment of cardiac contractility, and vasoconstriction.[22,23]

Magnesium should be employed as first line therapy in digitalis intoxication and drug related arrhythmias, and should also be considered an important adjuvant

therapy in diuretic treated patients. Study of Admopoulos showed that less serum magnesium level was associated with increased cardiovascular mortality.[24]

Hypomagnesemia increases potassium excretion, and hypokalemia is difficult to remedy with concurrent hypomagnesemia because the sodium-potassium-ATPase pump requires the presence of magnesium ions-potassium-sparing diuretics prevent urinary magnesium wasting.[25]

Magnesium deficiency may play a critical role in the pathogenesis of ischemic heart disease, cardiomyopathy and certain arrhythmias.

The present study is limited to the serum magnesium to demonstrate the clinically diagnostic importance of serum magnesium measurement in patients with CHF, taking diuretics and digoxin. Future investigations are needed to determine urinary excretion of magnesium along with serum magnesium measurement.

CONCLUSION

It is concluded that patients with chronic heart failure were characteristically prone to develop magnesium deficiency along with other electrolytes potassium, calcium, and chloride. In already diagnosed cardiac failure patients treated with loop diuretics and digoxin, the presence of further cardiac signs should trigger a search for underlying electrolyte abnormalities particularly hypomagnesemia.

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