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RESEARCH ARTICLE

RELATIONSHIP OF SERUM CALCIUM AND LACTATE DEHYDROGENASE IN DIAGNOSING CORONARY ARTERY DISEASE PATIENTS OF MYOCARDIAL INFARCTION WITH AND WITHOUT ST ELEVATION

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ABSTRACT

There exist varied opinions regarding the role of Calcium in Coronary Artery Disease. Some studies have suggested that increase in serum Calcium is responsible for Coronary Artery Disease events while others have observed hypocalcemia to be a risk factor for Coronary Artery Disease mortality and Calcium supplementation in these patients could re-establish the normal cardiac function. Aim of our study was to evaluate the role of Calcium in Coronary Artery Disease patients with and without Myocardial Infarction and its relationship with serum Lactate Dehydrogenase. 200 subjects included in the study were categorized into 50 normal healthy individuals as Group I, 50 Coronary Artery Disease patients without Myocardial Infarction as Group II, 50 Coronary Artery Disease patients with Myocardial Infarction and having no ST segment elevation as Group III (a) and 50 Coronary Artery Disease patients with Myocardial Infarction and having ST segment elevation as Group III (b). These subjects were investigated for serum Calcium and Lactate Dehydrogenase. Lactate Dehydrogenase was significantly raised in the Coronary Artery Disease patients when compared to normal healthy individuals. A negative correlation was observed between serum Calcium and Lactate Dehydrogenase.

INTRODUCTION

Coronary Artery Disease (CAD) is a condition in which there is an inadequate supply of blood and oxygen to a portion of the myocardium. It typically occurs when there is an imbalance between myocardial oxygen supply and demand. The most common cause of myocardial ischemia is atherosclerotic disease of an epicardial coronary artery (or arteries) sufficient to cause a regional reduction in myocardial blood flow and inadequate perfusion of the myocardium supplied by the involved coronary artery (Libby 2002).

The prevalence of CAD is approximately 1 in 20 or 13.2 million people and incidence is approximately 1 in 226 or 1.2 million people in USA. Risk of CAD in Indians is 3-4 times higher than white Americans and 6 times more than Chinese (Enas 1998).

Serum Calcium and inorganic Phosphorous levels are tightly regulated in our body and are required for various physiological processes, including bone formation, vascular function, several metabolic pathways, and intracellular signaling. Abnormalities in Calcium and Phosphorus levels can lead to various skeletal, endocrine, and cardiovascular disorders (Palmer *et al* 1987; Hangstrom *et al* 2007; Hangstrom *et al* 2006). Recent studies have shown that Calcium and Phosphorus plays a role in the pathogenesis of atherosclerosis, especially in the coronary arteries (Tomlyama *et al* 2006; Goodman 2000).

Large-scale epidemiological studies have shown that in middle-aged men, serum Ca levels are an independent, prospective risk factor for CVD (Lind *et al* 1988; Jorde et 1999), and high-normal serum Ca levels are associated with increased cardiovascular mortality (Leifsson *et al* 1996).

However studies are available that say hypocalcemia plays a significant role in cardiovascular events and that the low Calcium levels are associated with higher mortality in ST Elevation Myocardial Infarction (STEMI) patients (Lu *et al* 2014). Moreover, it has been suggested that Calcium supplementation may reduce the risk of hospitalization and mortality in patients with pre-existing CAD (Lewis *et al* 2011). Some studies (Stoner *et al* 1971; Kudoh *et al* 1992) have documented an inverse relationship between serum Calcium and serum Lactate Dehydrogenase (LDH) activity. Moreover serum LDH levels are associated with the severity of CAD (Peppes *et al* 2008)

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In spite of many efforts the role of serum Calcium in Coronary Artery Disease and it's relationship with serum LDH is not very clear. In order to fill these lacunae and to establish the utility of serum Calcium estimation in Coronary Artery Disease patients, the present study was conducted.

MATERIAL AND METHODS

A total of 200 subjects were included in the present study. These 200 subjects were divided into four groups:

Group I: 50 age and sex matched healthy individuals from the general population, who volunteered to be included in the present study.

Group II: 50 newly diagnosed Coronary Artery Disease (CAD) patients.

Group III (a): 50 Non-ST Segment Elevation Myocardial Infarction (NSTEMI) patients.

Group III (b): 50 ST Segment Elevation Myocardial Infarction (STEMI) patients.

The CAD patients in the present study were recruited from the O.P.D. and wards of Department of Medicine of Guru Nanak Dev Hospital in Government Medical College, Amritsar. Categorization of patients into CAD without MI (Myocardial Infarction), ST Elevation MI (STEMI) and Non ST Elevation MI (NSTEMI) was done on the basis of E.C.G. and cardiac markers (Troponin T and CK-MB).

Subjects were excluded from the study if they had renal complication, liver disease, Tuberculosis, Pancreatitis, alcohol abuse, Hemolytic anemia, Thyroid problems, Rickets, Osteomalacia and any cancer.

The subjects included in the study were assessed for serum Calcium, serum Phosphorus and serum LDH. A comparison of serum Calcium, Phosphorus and LDH was done in patients of CAD and normal healthy individuals.

Statistical analyses

Analysis of variance (ANOVA) test was applied to calculate the significance of difference in means of various parameters between the four groups. The groups were individually compared applying Student's t test. Bivariate correlation analysis was conducted to find the relationship between serum Calcium and serum Lactate Dehydrogenase. M.S. office 2010 was used to perform the analysis.

RESULTS

Variation in serum LDH levels

Table 1 Comparison of serum LDH levels in Normal Healthy Individuals (NHI) and CAD patients with and without MI

S. No.	Group	Serum LDH 240 – 480 IU/L	
		Range	**Mean ± S.D.**
1.	Group I	228 – 444	311 ± 56
2.	Group II	250 – 675	422 ± 123
3.	Group III(a)	340 – 1134	525 ± 178
4.	Group III(b)	433 – 2156	845 ± 365
	ANOVA	F= 57.9897	P<0.001
	TTEST	t value	p value
	Group I vs Group II	6.4229	<0.001
	Group II vs Group III (a)	3.3877	<0.001
	Group III (a) vs Group III (b)	5.5728	<0.001

The rise in serum LDH levels in the CAD patients with and without MI was statistically significant ($p<0.001$) when compared to NHI. While comparing the groups individually the rise in mean serum LDH level was significantly higher in STEMI patients when compared to NSTEMI patients, $p<0.001$, in NSTEMI patients when compared to CAD patients without MI, $p<0.001$ and in CAD patients without MI when compared to NHI, $p<0.001$.

Variation in serum Calcium levels

Table 2 Comparison of serum Calcium levels in Normal Healthy Individuals and CAD patients with and without MI

S. No.	Group	Serum Calcium 8.4 – 10.4 mg %	
		Range	**Mean ± S.D.**
1.	Group I	7.32 – 12.17	8.59 ± 0.84
2.	Group II	7.52 - 11.21	8.71 ± 0.91
3.	Group III(a)	7.67 – 10.48	8.65 ± 0.55
4.	Group III(b)	7.69 – 10.45	8.59 ± 0.52
	ANOVA	F=0.2958	p=0.8284
	TTEST	t value	p value
	Group I vs Group II	0.6850	0.4950
	Group II vs Group III (a)	0.4124	0.6810
	Group III (a) vs Group III (b)	0.4866	0.6277

The mean serum Calcium levels did not show any statistically significant variation in the CAD patients with and without MI when compared to NHI. Even when the groups were compared individually there was not any significant difference in the mean serum Calcium levels.

Variation in serum Phosphorus levels

Table 3 Comparison of serum Phosphorus levels in Normal Healthy Individuals (NHI) and CAD patients with and without MI

S. No.	Group	Serum Phosphorus 2.5 – 5 mg %	
		Range	**Mean ± S.D.**
1.	Group I	2.12 – 4.5	3.17 ± 0.66
2.	Group II	2.38 – 4.88	3.63 ± 0.6
3.	Group III (a)	2.25 – 5.18	3.61 ± 0.69
4.	Group III (b)	2.15 – 7.72	3.30 ± 1.01
	ANOVA	F= 4.5317	p<0.01
	TTEST	t value	p value
	Group I vs Group II	3.6177	0.00047
	Group II vs Group III (a)	0.1230	0.90237
	Group III (a) vs Group III (b)	2.2367	0.02755

The rise in serum Phosphorus levels in the CAD patients with and without MI was statistically significant ($p<0.01$) when compared to the NHI. While comparing the groups individually the rise in mean serum Phosphorus level was significantly higher in STEMI patients when compared to NSTEMI patients, $p<0.05$ and in CAD patients without MI when compared to normal healthy individuals, $p<0.001$. However, serum Phosphorus levels in NSTEMI patients did not differ significantly when compared to CAD patients without MI.

Relationship between serum Calcium and LDH

Table 4 - Correlation between serum Calcium and LDH levels in Normal Healthy Individuals (NHI) and CAD patients with and without MI

S. No.	Groups	r*	p value
1.	Group I	-0.30932	<0.05
2.	Group II	-0.44550	<0.01
3.	Group III (a)	-0.44474	<0.01
4.	Group III (b)	-0.34481	<0.05

r* = Correlation Coefficient

A statistically significant negative relationship was observed between serum Calcium and LDH levels in CAD patients with and without MI and NHI in all the groups.

Distribution of subjects on the basis of serum Calcium levels

Table 5 Classification of CAD patients and Normal Healthy Individuals on the basis of serum Calcium concentration as Hypocalcemic, Normocalcemic and Hypercalcemic individuals

S. No.	Group	Subgroup	No. of subjects	Percentage	Mean Calcium (mg %)	Mean LDH (IU/L)	Mean LDH comparison Hypocalcemic v/s normocalcemic p value
1.	Group I	Hypocalcemic	23	46	7.32	335	p<0.01
		Normocalcemic	26	52	9.03	288	
		Hypercalcemic	1	2	12.17	314	
2.	Group II	Hypocalcemic	24	48	7.95	480	p<0.01
		Normocalcemic	23	46	9.21	369	
		Hypercalcemic	3	6	10.94	365	
3.	Group III(a)	Hypocalcemic	16	32	8.07	621	p<0.01
		Normocalcemic	33	66	8.88	484	
		Hypercalcemic	1	2	10.48	345	
4.	Group III(b)	Hypocalcemic	19	38	8.14	1045	p<0.01
		Normocalcemic	30	60	8.82	717	
		Hypercalcemic	1	2	10.45	870	

Mean serum LDH levels were statistically significantly higher in hypocalcemic subjects in all the groups when compared to normocalcemic subjects. Since there was only 1 hypercalcemic patient in Group I, III (a) and III (b) and 3 hypercalcemic patients in Group II, comparison of mean serum LDH of normocalcemic and hypocalcemic subjects with hypercalcemic subjects was not possible.

Relationship between serum Calcium and LDH in hypocalcemic and normocalcemic subjects

Table 6 Correlation between serum Calcium and Lactate Dehydrogenase in hypocalcemic and normocalcemic Normal Healthy Individuals (NHI) and CAD patients with and without MI

S. No.	Groups	Sub-groups	r*	p value
1.	Group I	Hypocalcemic	-0.32921	0.1251
		Normocalcemic	**0.06371**	0.7572
2.	Group II	Hypocalcemic	-0.26631	0.2085
		Normocalcemic	-0.25883	0.2331
3.	Group III (a)	Hypocalcemic	-0.31776	0.2305
		Normocalcemic	-0.25223	0.2457
4.	Group III (b)	Hypocalcemic	-0.10592	0.6661
		Normocalcemic	-0.22107	0.2406

r* = Correlation coefficient

Although insignificant but a negative relationship was observed between serum Calcium and LDH in hypocalcemic as well as normocalcemic subjects in all the groups except the normocalcemic subjects of NHI.

DISCUSSION

In the present study a statistically significant increase in the mean serum Lactate Dehydrogenase (LDH) levels was observed in the CAD patients with and without MI when compared to the controls p<0.001. There was also a statistically significant increase, p<0.001 in the mean serum Lactate Dehydrogenase level of STEMI patients when compared to NSTEMI patients. Similarly there was a statistically significant increase, p<0.001 in the mean serum Lactate Dehydrogenase levels in the NSTEMI patients when compared to CAD patients without MI. Also the mean serum Lactate Dehydrogenase level of CAD patients without MI was significantly higher when compared to controls, p<0.001 (Table 1).

The statistically significant increase in LDH levels of CAD patients with and without MI when compared to controls could be attributed to cardiac muscle damage in these patients leading to liberation of this enzyme in the serum and hence the rise in its level. A statistically significant increase in LDH levels of STEMI patients as compared to NSTEMI patients could be due to complete occlusion of a large coronary artery causing ischemia and extreme cardiac muscle damage as compared to NSTEMI where there is a complete occlusion of a small coronary artery or a partial occlusion of a large coronary artery with only mild damage to the cardiac muscle.

Calcium has been reported to respond in specific ways in different types of human cells. It plays a significant role in calcification, signal transduction and muscle contraction etc.

In muscle cells Calcium plays a significant role in promoting muscle contraction via Calmodulin protein and protein kinase C activation. Calcium has been reported to regulate several signaling pathways such as stimulation of endothelial Nitric Oxide Synthase (NOS) to produce Nitric Oxide (NO) and also cause hyperpolarization of the cell membrane by causing efflux of K^+ ion from Potassium-Calcium ($K_{ca)}$ channels that cause the smooth muscle to relax. Any dysfunction in Calcium activating pathways can therefore lead to increase in tone because of unregulated smooth muscle contraction called as endothelial dysfunction.

It has been reported that increased serum Calcium levels are a risk factor for CAD. Rasouli *et al* 2005 found that the concentrations of serum total calcium, albumin-corrected calcium, phosphorus and the ion product of calcium and phosphorus were significantly higher in the CAD patients with one or more coronary arteries stenosed compared to the CAD patients with no stenosis in any artery. Shin *et al* 2012 reported that raised Calcium and Phosphate and high Calcium Phosphate Product (CPP) are associated with increased cardiovascular morbidity.

Lu *et al* 2014 however observed that hypocalcemia rather than hypercalcemia played a significant role in cardiovascular events and that the low Calcium levels are reported to be the risk factor associated with higher mortality in STEMI patients. In the present study serum Calcium levels of the CAD patients with and without MI were estimated and compared to that of normal healthy individuals. It was observed that serum Calcium levels in CAD patients without MI did not show any significant variation when compared to that of controls ($p=0.4590$). These findings are suggestive of the fact that the plaque formation in CAD patients is independent of serum Calcium concentrations.

Similar trend was observed in serum Phosphorus levels (Table 3) as in serum Calcium levels but there was a statistically significant increase, $p<0.01$ in serum Phosphorus levels in the CAD patients with and without MI in comparison to the controls. There was also a statistically significant increase, $p<0.05$ in the mean serum Phosphorus level of STEMI patients when compared to NSTEMI patients. However mean serum Phosphorus level of CAD patients without MI did not show any significant variation when compared to CAD patients with MI and having no ST elevation. Also the mean serum Phosphorus level of CAD patients without MI was significantly higher when compared to controls, $p<0.001$ (Table 3). Although there was a statistically significant increase in serum Phosphorus levels in the CAD patients with and without MI in comparison to the controls, yet the mean serum Phosphorus levels of all the groups were within the normal range (2.5 – 5 mg %). These findings are consistent with Rasouli *et al* 2005, Dhingra *et al* 2007 and Aronson et 2013 who stated that serum Phosphorus levels within the normal range are elevated in CAD patients. Recent studies suggest that high serum Phosphate is associated with abnormal vascular phenotypes such as increased carotid intima-media thickness (Onufrak *et al* 2008), arterial stiffness (Ix *et al* 2009) and cardiovascular mortality (Dhingra *et al* 2007).

Kudoh *et al* 1992 observed hypocalcemia in a patient with hypothyroidism-induced cardiomyopathy and when hypocalcemia was corrected there was a dramatic improvement of cardiac function suggesting the role of extracellular Calcium concentration on the strength of the Myocardial contraction through excitation – contraction coupling. These workers also observed elevated LDH levels of the patient that returned back to the normal level, when Calcium deficiency was corrected. Ines *et al* 2012 observed that cardiac performance is demonstrably reduced by hypocalcemia, with decreased myocardial contractility and hence decreased left ventricular stroke work index, ejection fraction and cardiac index.

In the present study a statistically significant negative correlation was observed between serum Calcium and LDH in all the groups (Table 4). The normal healthy individuals and CAD patients were further classified on the basis of serum Calcium levels as hypocalcemic (serum Calcium <8.4 mg %), normocalcemic (serum Calcium = 8.4 – 10.4 mg %) and hypercalcemic (serum Calcium >10.4 mg %) individuals (Table 5) to observe the changes in LDH levels with change in Calcium concentration. Serum LDH levels were significantly higher, $p<0.01$, in hypocalcemic patients as compared to normocalcemic individuals. A negative correlation was observed between serum Calcium and LDH in hypocalcemic and normocalcemic CAD patients with and without MI and also in patients with and without ST elevation MI and in hypocalcemic normal healthy individuals (Table 6) but not in normocalcemic normal healthy individuals suggesting thereby that serum Calcium plays a significant role in excitation and contraction of heart muscle fibers by inflow of Calcium from extracellular fluid and stimulated sarcoplasmic reticulum stores raising the levels of cytosolic Calcium available to bind to troponin C. This in turn interacts with the troponin–tropomyosin complex to form crossbridges between actin and myosin, resulting in muscle contraction and if the Calcium levels are low the damage to myocardial cells is observed as depicted by the raised LDH levels. Any hypocalcemia due to hypovitaminosis or hypothyroidism could be a risk factor for cardiac function. Thus it is suggested that all the patients diagnosed as a case of CAD should be investigated for serum calcium levels and hypocalcemia if observed should be corrected to achieve the normal functioning of the heart.

CONCLUSIONS

The present study suggests that hypocalcemia may be playing a critical role in the severity of CAD as depicted by raised serum LDH levels with declining serum Calcium in CAD patients with and without MI and even in normal healthy individuals. Moreover the rise in serum LDH in hypocalcemic CAD patients with MI and having ST elevation was much more (1045 IU/L, Table 5) than what it was observed in hypocalcemic CAD patients with MI and having no ST elevation (621 IU/L, Table 5). Hence Calcium estimation along with serum LDH measurement can be of greater significance in diagnosing CAD patients of MI with ST elevation and CAD patients of MI without ST elevation. Hypocalcemia if observed should be corrected to achieve the normal functioning of the heart.

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