Original Research Article

A study of high serum calcium level in diabetes mellitus and its association with left ventricular remodeling

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Abstract

Background: Hypocalcemia is one of the important complications of diabetes mellitus. It occurs when the patient develops renal insufficiency but hypercalcemia occurs in diabetes due to many mechanisms including insulin resistance. Meanwhile, hypercalcemia itself produces insulin resistance and the calcium is the important one for the production of insulin and glucose uptake in the cells.

Aim of the study: To assess left ventricular dimension and wall thickness mass in diabetic patients having high serum calcium level.

Materials and methods: This study was conducted in Government Royapettah Hospital, Chennai for duration of 6 months from April 2018 to September 2018. 2016 patients were enrolled in the study. After obtaining an informed written consent, demographic details, past medical history and clinical examination was done. Following investigation was done in all patients. Serum calcium, serum creatinine, total cholesterol, triglycerides, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), fasting blood glucose was done. 2D ECHO – echocardiography was done in all patients. In left lateral position ECHO was performed in parasternal long axis, 4 chamber view. M mode was used to assess the septal wall, posterior wall thickness and left ventricular diastolic dimension. By using wall thickness left ventricular mass is calculated.

Results: According to our serum calcium was main Determinator of left ventricular remodeling by many mechanisms. Serum calcium was > 10.2 in LVH group people but in non-LVH group people serum calcium level was within the normal limit that was given as < 10.2 mg/dl. 1 patient in non-LVH group was having high serum calcium but does not make statistical changes in that group. The mean serum calcium of LVH group was 10.6mg/dl.

Conclusion: Normal calcium mandatory for excitation-contraction coupling but high calcium adversely affect the ECC and produces ventricular dysfunction and through neurohormonal mechanism it produces cardiac muscle hypertrophy. According to this study increased serum calcium in diabetes has strong correlation with occurrence of cardiac remodeling.

Key words

Calcium Ions, Diabetes mellitus, Left Ventricular Hypertrophy, Ejection fraction.

Introduction

Apart from the organs, diabetes alters the metabolic components of the body. It produces the metabolic abnormality in both extremes like hypocalcemia as well as hypercalcemia, hyponatremia, and hypernatremia. Because of this metabolic abnormalities many internal structures which depends the metabolic products are also affected. Internal organelle dysfunction finally leads the organ dysfunction and death [1]. Hypocalcemia is one of the important complications of diabetes mellitus. It occurs when the patient develops renal insufficiency [2]. But hypercalcemia occurs in diabetes due to many mechanisms including insulin resistance. Meanwhile, hypercalcemia itself produces insulin resistance. And the calcium is the important one for the production of insulin and glucose uptake in the cells. Ionized serum calcium is the active form of calcium [3]. Around 40% of calcium is protein bounded. Before commenting about the calcium level, serum albumin should be considered because low serum albumin level has an effect on serum calcium. To avoid this thing this study is conducted to evaluate the cardiac complication of calcium by excluding the conditions which produce hypoalbuminemia. By using the serum calcium (spot) we can able to identify the cardiac complications [4]. Heart is the vital organ of our body. Any changes in the function of myocardium will affect the function of the whole-body system. The heart is damaged by many conditions like hypertension, diabetes, dyslipidemia and also hypercalcemia. Even though the hypercalcemia is not defined as risk factor for cardiac complication.in older days, many trials and studies are proved that hypercalcemia will produce severe cardiac abnormality including systolic and diastolic dysfunction [5]. In 1982, Hockman and Buckey have coined the term “remodeling”. Remodeling is based on morphological changes of the heart. The morphological changes include ventricular cavity diameter, wall thickness, and scarred area. So the remodeling is defined as it is the morphological changes of the heart after injury [6]. Myocardial ischemia is the important disease which produces ventricular remodeling and cardiac dysfunction. Apart from MI many cardiac conditions are benign and some are significant. But some benign condition will progress into significant myocardial abnormality [7]. Cardiac muscle hypertrophy will occur in many subjects like athletes, pregnant women. But that does not produce any significant damage. But a middle-aged man or women develop the same hypertrophy because of hypertension or diabetes or hypercalcemia which in turn leads to hypertrophic changes finally leading to cardiac failure, arrhythmias, and death [8].

Materials and methods

This study was conducted in Government Royapettah Hospital, Chennai for the duration of 6 months from April 2018 to September 2018. 2016 patients were enrolled in the study. After obtaining an informed written consent, demographic details, past medical history and clinical examination was done.

Inclusion criteria

- Patients with type 2 diabetes.
- Diabetes in this study will be defined by the American diabetes association as either.
- Fasting plasma glucose (FBS) of >125 mg/dl postprandial blood sugars at 2

hour (PPBS) >200 mg/dl.

Exclusion criteria

- Patients with hypertension
- On treatment with sulfonylureas.
- A history of myocardial infarction, coronary artery bypass or angioplasty, atrial fibrillation, moderate to severe valvular heart disease, stroke or occlusive peripheral vascular disease, heart failure.
- Serum creatinine> 110 micromoles/ L. (>1.2 mg/ dL).
- A history of parathyroid disease or vitamin D related disorder.6.Medication history including vitamin D, bisphosphonate, estrogen replacement therapy and diuretics.
- Uncontrolled thyroid diseases.
- Patient with chronic liver diseases.

Following investigation was done in all patients. Serum calcium, serum creatinine, total cholesterol, triglycerides, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), fasting blood glucose was done. 2D ECHO – echocardiography was done in all patients. In left lateral position ECHO was performed in parasternal long axis, 4 chamber view. M mode was used to assess the septal wall, posterior wall thickness and left ventricular diastolic dimension. By using wall thickness left ventricular mass is calculated.

Statically analysis

The collected data were analyzed with IBM.SPSS statistics software 23.0 Version. To describe the data descriptive statistics frequency analysis, percentage analysis was used for categorical variables and the mean and S.D were used for continuous variables. To find the significant difference between the bivariate samples in Paired groups the Paired sample t-test was used & for Independent groups the Unpaired sample t-test was used.

Results

Table - 1 shows totally 206 patients were included in this study after exclusion. All patients were diabetic patients. Most of the study subjects were within the age limit of 50-59 years.

Table – 1: Overall age distribution in the study.

Age (Years)	Frequency	Percent
40 - 49	51	24.8
50 - 59	108	52.4
60 - 69	42	20.4
> = 70	5	2.4
Total	206	100.0

According to our study serum calcium was the main determinator of left ventricular remodeling by many mechanisms. Serum calcium was > 10.2 in LVH group people. But in non-LVH group people serum calcium level was within normal limit that was given as < 10.2 mg/dl. 1 patient in non-LVH group was having high serum calcium but does not make statistical changes in that group. The mean serum calcium of LVH group was 10.6mg/dl (**Table – 2**).

The mean age group in non-LVH group people was 52.62 but it was 56.16 years in LVH group people. Gender does not make any significance in LVH prevalence. Serum calcium level was normal in the non-LVH group and the mean value was 9.04 mg/dl. This calcium was high in LVH group people. The mean serum calcium level in LVH group people 10.63. The value above 10.2 was considered abnormal. The mean of left ventricular end-diastolic dimension, inter ventricular septal wall thickness, posterior wall thickness, and relative wall thickness in LVH group was 52.01, 13.09, 10.99, 0.4233 respectively. The mean left ventricular mass in LVH group was 229.51 but this low in non-LVH group. After adjusting LV mass with body surface area the mean LV mass index in LVH group was 177.38. In this study t-test was used to assess the significance of variables towards the development of left ventricular remodeling. The p-value was significant if it was <0.01. The serum calcium level p-value was significant (p<0.005) in LVH group. It indicates the strong

association of serum calcium for the development of left ventricular remodeling. Age also had significant p-value in LVH group. Serum calcium levels were increasing in age advances. Serum cholesterol, LDL cholesterol, triglycerides also had a significant p-value in LVH group population. But gender makes any significance. The left ventricular end-diastolic dimension, septal wall thickness, posterior wall thickness also have significant p-value. This was the obvious one because the determinant of ventricular dimension is by above three parameters. The relative wall thickness was also significant in LVH group. But it does not make any change in left ventricular mass. It tells about the type of ventricular hypertrophy whether is it concentric or eccentric (**Table – 3**).

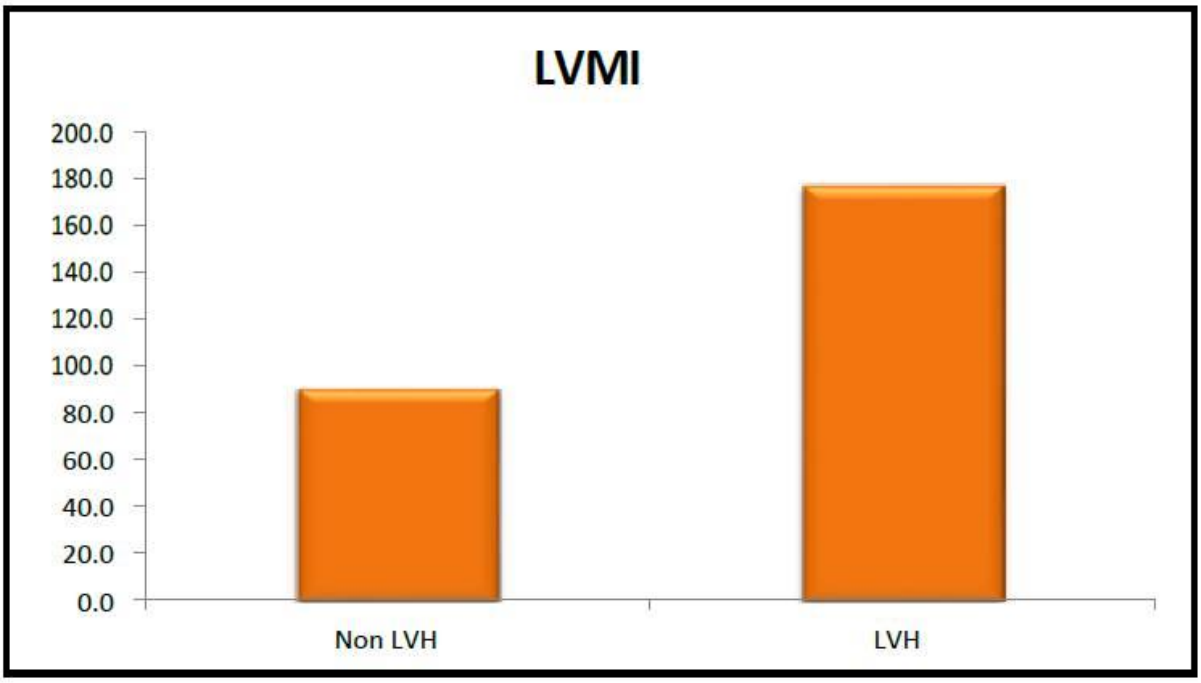
Table – 2: Serum calcium level association with LVH.

Serum calcium			**Groups**		**Total**
			Non-LVH	**LVH**	
	> 10.2	Count	0	103	103
		% within Groups	0.0%	99.0%	50.0%
	< = 10.2	Count	102	1	103
		% within Groups	100.0%	1.0%	50.0%
Total		Count	102	104	206
		% within Groups	100.0%	100.0%	100.0%

Table – 3: Mean, standard deviation of variables in both LVH and non-LVH group.

Groups		**N**	**Mean**	**Std. Deviation**	**Std. Error Mean**
AGE	Non LVH	102	52.62	5.794	.574
	LVH	104	56.16	6.889	.676
Sr. Calcium	Non LVH	102	9.0435	.08905	.00882
	LVH	104	10.6365	.27591	.02706
LV EDD	Non LVH	102	45.51	2.362	.234
	LVH	104	52.01	3.823	.375
IVS d	Non LVH	102	10.40	.761	.075
	LVH	104	13.09	1.359	.133
PWd	Non LVH	102	8.85	.604	.060
	LVH	104	10.99	1.186	.116
RWT	Non LVH	102	.3899	.02616	.00259
	LVH	104	.4233	.04514	.00443
LVMASS	Non LVH	102	148.23	20.414	2.021
	LVH	104	229.51	61.256	6.007
LVMI	Non LVH	102	90.60	12.638	1.251
	LVH	104	177.38	61.697	6.050
Cholesterol	Non LVH	102	182.31	30.854	3.055
	LVH	104	212.70	36.546	3.584
TGL	Non LVH	102	131.96	31.825	3.151
	LVH	104	159.47	28.298	2.775
LDL	Non LVH	102	97.85	21.520	2.131
	LVH	104	112.46	18.140	1.779

Graph – 1: Incidence of LVMI.



LVH is diagnosed as if LVMI > 115 in men and LVMI > 95 in women. If relative wall thickness and left ventricular mass index was normal that LV geometry was called as normal. Increased relative wall thickness and normal left ventricular mass index called concentric remodeling. Eccentric hypertrophy was defined as increased relative wall thickness and increased left ventricular mass index (**Graph – 1**).

Discussion

It is now clear that impaired calcium hemostasis is the key factor for cardiac hypertrophy, arrhythmias, and heart failure. Other than direct calcium, dysfunction of calcium channels, proteins are also playing a role in development of cardiac failure [9]. Hypercalcemia causes hypertrophy in many ways. The most important mechanism is calcium calmodulin-dependent calcineurin activation that leads to translocation of NFAT protein into the nucleus. In myocardial cells mitochondria also regulates the calcium levels in dyadic space. The calcium overload condition leads to increased myocardial calcium uptake that leads to increased oxidative followed by mitochondrial dysfunction and death. Myocardial calcifications because of hypercalcemia impair the ventricular relaxation and cause diastolic dysfunction [10]. In our study calcium has high positive predictive value for the development of cardiac muscle hypertrophy. Increased serum calcium >10.2 is the margin for the development of cardiac hypertrophy [11]. Calcium exerts its hypertrophic response through dyslipidemic effect by inhibiting cholesterol catabolism. But statistical analysis shows there is no direct correlation between LVH occurrence and dyslipidemia. So it is cleared that LVH in diabetic patient is due to increased calcium levels [12]. Increased calcium level has a positive correlation with LVH occurrence. In our study we checked the albumin adjusted serum calcium levels but we have excluded the conditions which cause hypoalbuminemia [13]. This study only considered only 1 simple tests for LVH prediction. That is serum calcium which is highly cost-effective. By our study results the main influencing factors for left ventricular hypertrophy is left ventricular end-diastolic dimension, posterior wall thickness, and interventricular septal thickness [14]. But the increased calcium leads to thickness of all the walls. Hence produces left ventricular hypertrophy. Relative wall thickness classifies the type of hypertrophy whether it is concentric or eccentric. Along with this age is also

influencing the left ventricular hypertrophy. Initial detection is serum calcium can help to identify the risk of arrhythmias [15].

Conclusion

Serum calcium also increases diabetic prevalence by interacting with GLUT 4 receptors. Normal calcium mandatory for excitation-contraction coupling but high calcium adversely affects the ECC and produces ventricular dysfunction and through neurohormonal mechanism it produces cardiac muscle hypertrophy. According to this study increased serum calcium in diabetes has strong correlation with occurrence of cardiac remodeling. Hence always check the serum calcium level in diabetic patient which will predict the development of LVH. Unnecessary calcium supplementation in diabetic patients WILL produces many adverse effects including left ventricle remodeling.

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