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A Study of Relation of Insulin Level on Left Ventricular Mass in Hypertensives

Ashwini N.G[1], Anil Kumar T[2], Ashwin Kulkarni[3], Bhavana Magaji[4], Gayathri Sujive[4]

[1]Assistant Professor, Department of Medicine, ESIC Medical College, Bangalore, India
[2]Professor and Head, Department of Medicine, Sapthagiri Institute of Medical Sciences, Bangalore, India
[3]Associate Professor, Department of Medicine, Ramaiah Medical College, Bangalore, India
[4]Intern, Ramaiah College of Pharmacy, Bangalore, India

Abstract

Background: Hypertension has been established as the leading cause of left ventricular hypertrophy (LVH) as a consequence of the pressure load imposed on the ventricles. Insulin plays a key role in the regulation of various aspects of cardiovascular metabolism and function including glucose and long chain fatty acid (LCFA) metabolism, protein translation, and vascular tone. Our study aims to demonstrate the relation between serum insulin levels and left ventricular mass in hypertensive and normotensives. **Material and Methods:** An institution-based case control study conducted for over a period of 12 months from October 2017 to September 2018 in the inpatient as well as the outpatient departments of the Internal medicine. A detailed clinical history, physical examination including the measurement of blood pressure readings was recorded. With the help of the echocardiogram, left ventricular end diastolic dimension (LVEDd), interventricular septum (IVSd), posterior wall thickness (LVPWd) and left ventricular mass index (LVMI) were determined. Left ventricular mass (LVM) was obtained with the application of Devereux formula. Serum post prandial insulin (PPI) levels were estimated and correlated. **Results:** The mean blood pressure (BP) was 143.76/83.2 mm Hg among cases and 117.66/75.16 mm Hg among controls**.** The echocardiogram parameters LVEDd, IVSd, LVM and LVMI were found to be statistically significant among the case group when compared to the control group (p value $\leq$ 0.01). Serum post prandial insulin levels were significantly higher among hypertensives (p=0.01). There was positive correlation between insulin levels and left ventricular mass index among normotensives and hypertensives. **Conclusion:** The study exhibited that insulin levels have a positive correlation with hypertension and left ventricular mass. It can be indirectly concluded that adequate blood pressure control will help in preventing left ventricular remodeling.

Keywords: Serum insulin left ventricular mass, 2D Echo, and hypertension.

Corresponding Author: Dr Ashwin Kulkarni, Associate Professor, Ramaiah Medical College, Bangalore, India Email: kulkarniashwin86@gmail.com

Introduction

Hypertension has been established as the leading cause of left ventricular hypertrophy (LVH) as a consequence of the pressure load imposed on the ventricles. Other factor such as obesity, hyperinsulinemia and conventional risk factors may impact LVM. Despite these many risk factors, a typical link between them has not been identified yet.[1] The Framingham Heart Study has developed sex-specific criteria for LVH, based on the distribution of left ventricular mass in a healthy reference population, the application of which to a large, free-living population studied with echocardiography has documented a prevalence of LVH of 15 to 20% higher in adults, than the prevalence of LVH determined by ECG.[2] The regression or

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prevention of LVH during antihypertensive therapy is associated with a reduced rate of major CV events.[3] Insulin plays a key role in the regulation of various aspects of cardiovascular metabolism and function including glucose and long chain fatty acid (LCFA) metabolism, protein translation, and vascular tone. In the recent years much of the attention has been focused on both LVH and insulin resistance to be the strong adverse factors for cardiovascular diseases as a predictor of morbidity and mortality. The role of insulin resistance in the pathogenesis of LVH has been inconclusive from various previous studies.[4] Our study aims to demonstrate the relation between serum insulin levels and left ventricular mass in hypertensive individuals and normotensives.

Material and Methods

An institution-based case control study was conducted for over a period of 22 months from October 2017 to September 2018 in the inpatient as well as the outpatient departments of the general medicine unit. Ethical clearance of the study was obtained from ethics committee so as to allow data collection. Patients of either sex aged 18 years and above who is hypertensive and on treatment with anti – hypertensive medications. Pregnant women with hypertension, patients who were prediabetic and diabetic with hypertension, secondary hypertension and those patients associated with cardiac conditions with influence on left ventricular mass (valvular heart disease, cardiac failure, and cardiomyopathy) were excluded from the present study. A detailed clinical history, physical examination including the measurement of systolic blood pressure and diastolic blood pressure. The blood pressure readings were estimated after 5 minutes of rest in sitting position using a sphygmomanometer having a standard cuff size. Three blood pressure readings were obtained with five minutes intervals between each reading. Measurements of study participants body mass index, waist circumference and waist – hip ratio were also noted. The levels of two hours post oral glucose load (75g) serum insulin levels were estimated using the ARCHITECT insulin assay for the quantitative determination of human insulin from sera. Fasting and post prandial blood sugars and fasting lipid profile were also assessed of each study subjects. With the help of the echocardiogram, LV end diastolic dimension (LVEDd), interventricular septum (IVSd), posterior wall thickness (LVPWd) and left ventricular mass index (LVMI) were determined. Left ventricular mass (LVM) was obtained with the application of Devereux formula. Whereby, LVM = 0.8 {1.04 (IVSd + LVEDd + LVPWd)^3 – (LVEDd)^3} + 0.6 .The LVM index (LVMI) was calculated using the formula: LVMI = LVM/BSA. The relative wall thickness (RWT) was also calculated using the formula: RWT = (2 x LVPWd) / LVEDd.

Statistical Analysis

Quantitative variables like BMI, SBP, DBP, WHR, LVM, LVMI, post oral glucose serum insulin, fasting blood sugars were determined using descriptive statistics such as mean and standard deviation. All qualitative statistics were evaluated using frequency and percentage. Spearman correlation coefficient was used to estimate the correlation between post oral glucose load serum insulin levels and other parameters such as LVM, BMI, SBP, DBP, etc. Multiple linear regressions were employed to detect the predictors of left ventricular mass. Statistical analysis using the software, SPSS version 24 was used.

Results

In the study, the case and control population, each consisting of 30 individuals, were matched for age and gender. The mean age of the case was 55.83 years (± 17.44 years) and of the control population was 55.30 years (± 17.58 years). The basic demographic details have been explained in the [Table 1].

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On comparison of the blood pressure recording of the two groups, systolic and diastolic blood pressure readings was found to be significantly higher among the cases than the controls. The average blood pressure recording of cases was found to 143.77/83.3 mmHg. The average blood pressure recording among the controls was noted to be 117.67/75.17 mmHg. [Table 2]
The ECHO parameters and the post prandial insulin levels were compared between the cases and controls. The post prandial serum insulin levels were found to be statistically significant among the cases (43.94 ± 29.54) than the control group (25.31 ± 24.01). Significant (p=0.01). It was observed that the average left ventricular mass was 192.07 in cases and 139.8 among the controls. This difference was statistically significant (p<0.001). LVEDd, IVSd, LVPWd and LVMI were more in cases were statistically significant. [Table-3]
Average left ventricular mass and left ventricular mass index recordings were higher in the cases when compared to that of the control group. There was no significant difference noted in the fasting and post prandial blood sugars among the two study groups. The measured post prandial serum insulin level among the obese population (65.26 ± 39.08) was significantly greater as compared to non – obese population (36.18 ± 21.44; p value = 0.014) [Table 4]. Obese population had higher post – prandial serum insulin levels when compared to that of the controls/ Left ventricular mass is also higher in those with BMI > 30 kg/m^2 but LV mass index is almost the same among the two – study population. In Pearson correlation analysis, a positive correlation was noted between the post prandial serum insulin levels and left ventricular mass among the cases (r = 0.065, p value = 0.737) and controls (r=0.025, p value=0.825). A statistically significant correlation was noted between post prandial serum insulin levels and diastolic blood pressure in the control group (r = 0.307, p value = 0.099), indicating a raise in diastolic blood pressure with raising serum insulin. A positive correlation was noted among the case group between serum insulin and weight (r = 0.356, p value – 0.053) as well as body surface area, (r = 0.349, p value = 0.059), indicating higher serum insulin levels are found with increasing weight and body surface area and body mass index [Table 5]. The regression analysis of the predictors has been explained in the [Table 6] which summarizes the results of regression analysis. Since all the covariates have p>0.05, except WHR, the effects of covariate WHR on LVM is significant (p<0.05). The adjusted R^2 was found to be 0.17 (i.e. 17%), which means that only 17% variability in LVM could be explained by the covariates, which is very less. This implies that the LVM does not vary significantly with other covariates except WHR.

Table 1: Intergroup comparison of the frequency distribution of the various parameters

Parameter		**Case [N (%)]**	**Control [N (%)]**	**Statistics**
Age group (years)	20-30	5 (16.66)	5 (16.66)	F=0.177, df=5, p=0.99
	31-40	1 (3.33)	1 (3.33)	
	41-50	6 (20)	6 (20)	
	51-60	4 (13.33)	5 (16.66)	
	61-70	8 (26.66)	7 (23.33)	
	71-80	6 (20)	6 (20)	
Gender	Female	15 (50)	15 (50)	χ^2=0, df=1, p=0.99
	Male	15 (50)	15 (50)	
Hypertension	Yes	30 (100)	0 (0)	F=56.06, df=1, p=7.005*10^-14*
	No	0 (0)	30 (100)	
	No	16 (53.33	26 (86.66)	
Dyslipidemia	Yes	21 (70)	4 (13.33)	F=17.55, df=1, p=2.79*10^-5*
	No	9 (30)	26 (86.66)	

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Smoker	Yes	11 (36.66)	6 (20)	χ^2=1.31, df=1, p=0.25
	No	19 (63.33)	24 (80)	
Alcohol	Yes	4 (13.33)	4 (13.33)	F=0, df=1, p=0.99
	No	26 (86.66)	26 (86.66)	
Body mass index (kg/m^2)	<20	2(6.66)	9(30)	F=12.47, df=2, p=0.001*
	20-30	20(66.66)	21(70)	
	>30	8(26.66)	0(0)	
Body mass index (kg/m^2)	<30	22 (73.33)	30 (100)	F=7.06, p=0.007*
	>30	8 (26.66)	0	

Abbreviations: * Significant at 5% level of significance; χ^2 = Chi square; F = Fisher's value,

Table 2: Average blood pressure readings

Average	Cases	Controls	Total	P value
SBP (mmHg)	143.77 ± 12.72	117.67 ± 8.66	130.72 ± 17.02	<0.001**
DBP (mmHg)	83.20 ± 6.34	75.17 ± 4.89	79.18 ± 6.92	<0.001**

Table 3: Comparison of ECHO parameters and post prandial insulin levels

	Cases	Controls	Total	P value
Post prandial insulin	43.94 ± 29.54	25.31 ± 24.01	34.62 ± 28.29	0.010 **
LVEDd	4.22 ± 0.37	3.87 ± 0.52	4.05 ± 0.48	0.004**
IVSd	1.31 ± 0.44	1.08 ± 0.10	1.20 ± 0.34	0.006**
LVPWd	1.16 ± 0.09	1.12 ± 0.11	1.14 ± 0.10	0.142
LVM	192.07 ± 67.08	139.80 ± 33.38	165.93 ± 58.77	<0.001**
LVMI	113.77 ± 41.81	87.50 ± 22.19	100.63 ± 35.73	0.004**
RWT	0.55 ± 0.06	0.59 ± 0.11	0.57 ± 0.09	0.090+

Table 4: Comparison of study variables in relation to BMI levels in cases studied

Variables	BMI (kg/m^2)		Total	P value
	< 30	> 30		
Post prandial insulin	36.18 ± 21.44	65.62 ± 39.08	43.94 ± 29.54	0.014*
LVEDd	4.20 ± 0.38	4.26 ± 0.35	4.22 ± 0.37	0.699
IVSd	1.30 ± 0.49	1.35 ± 0.32	1.31 ± 0.44	0.784
LVPWd	1.15 ± 0.09	1.19 ± 0.09	1.16 ± 0.09	0.291
LVM	188.68 ± 71.86	201.38 ± 54.92	192.07 ± 67.08	0.655
LVMI	112.59 ± 44.40	117.00 ± 36.21	113.77 ± 41.81	0.803
RWT	0.55 ± 0.06	0.55 ± 0.04	0.55 ± 0.06	0.871

Table 5: Pearson correlation of post prandial insulin (PPI) with study variables

Pair of Variables	Cases		Control	
	r value	P value	r value	P value
PPI vs LVM	-0.065	0.737	0.025	0.894
PPI vs LVPWd	0.361	0.050+	0.362	0.049*
PPI vs SBPAV	-0.016	0.931	0.048	0.803
PPI vs DBPAV	0.118	0.533	0.307	0.099+

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PPI vs age	-0.073	0.700	0.109	0.566
PPI vs height	-0.076	0.091+	-0.350	0.058+
PPI vs weight	0.356	0.053+	0.088	0.643
PPI vs BSA	0.349	0.059+	-0.022	0.906

Table 6: Regression analysis of predictors

Model	**Unstandardized coefficients**		**Standardized coefficients**	**T**	**Sig.**	**95% confidence interval for B**	
	B	Std. Error	Beta			Lower Bound	Upper Bound
1 (constant)	-1638.154	839.188		-1.952	0.57	-3326.383	50.075
HTN	46.333	17.062	0.398	2.716	0.009	12.010	80.657
HT	6.782	4.795	1.264	1.415	0.164	-2.864	16.429
WT	-6.907	5.820	-1.376	-1.187	0.241	-18.615	4.802
BSA	-91.636	230.123	-0.301	-0.398	0.692	-554.584	371.312
BMI	16.937	13.598	1.471	1.246	0.219	-10.418	44.293
WHR	621.123	477.718	0.898	1.300	0.200	-339.923	1582.168
WC	-7.004	5.217	-1.551	-1.343	0.186	-17.498	3.490
HC	7.675	4.923	1.312	1.559	0.126	-2.230	17.580
FBS	1.652	0.820	0.272	2.015	0.050	0.002	3.302
TG	-0.088	0.123	-0.095	-0.719	0.476	-0.336	0.159
HDL	0.554	0.663	0.122	0.835	0.408	-0.779	1.887
PPI	0.063	0.286	0.30	0.218	0.828	-0.514	0.639

Discussion

The current study attempted to assess the correlation between post prandial serum insulin levels and left ventricular mass in hypertensive individuals. Our study reveals that post prandial serum insulin levels were higher among hypertensives. This shows that hypertensive patients have higher insulin resistance. It also showed that post prandial insulin levels had a positive correlation with Left ventricular mass among normotensives and hypertensives. This reflects that with increasing post prandial insulin levels there was increase in left ventricular mass which was seen in both cases and controls.Though the degree of left ventricular hypertrophy can be explained secondary to hypertension, a statistically significant correlation could not be established, and this can be explained due to effect of drugs, adequate blood pressure control and other factors. Hence, it can also be noted that as the patients were on antihypertensives, the left ventricular hypertrophy and remodeling was limited. The study conducted by Kothari et al., obtained a statistically significant correlation between serum insulin levels and left ventricular mass in hypertensive patients. The mean left ventricular mass and mean left ventricular mass index was 196.60 ± 65.13 g and 118.71± 37.75g/m^2 respectively and also stated that greater the degree of hyperinsulinemia, greater the Left Ventricular Mass in hypertensive.[5]

Also, greater the degree of hyper insulinemia (insulin resistance), the greater was the left ventricular mass in hypertensives in the study by Khurana et al. However, this association was reproduced in normotensive population in our study. In the study by Khurana et al., it was also hypothesized that in an insulin resistant state certain anti-hypertensive agent might

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worsen the insulin resistant state. Left ventricular hypertrophy is an established cardiovascular risk factor, adequate blood pressure control may lower this risk.[6]

In a study by Z Sasson, Y Rasooly, T Bhesania, I Rasooly. , LV mass was strongly correlated with BMI (r=.59, P=.0001), insulin-90 (r=.61, P=.0001), and k value (r=.55, P=.003) and less strongly with basal insulin and insulin integration over 90 minutes of IVGTT(r= .44, P=.005 and r=.46, P=.003, respectively).[7] Age and blood pressure showed a weak and nonsignificant correlation with LV mass. Similar results for univariate correlates of LV mass were obtained when analyzing the men and women separately (for BMI, r=.66 and .54, respectively; for insulin-90, r=.56 and .66;and fork value, r=.67 and .44; P<.05 for all these analyses) and, insulin-90 and k value were found to be the only significant independent predictors of LV mass (P=.03 and P=.04, respectively).Although BMI and insulin resistance were both found to be strong uni-variate predictors of LV mass, insulin resistance remained the only independent predictor of LV mass in multivariate analysis, accounting for 50% of the variance in LV mass.[8]

A report from the Framingham Heart Study demonstrated in 3922 healthy normotensive participants that obesity of even mild to moderate degree was strongly correlated with increased LV mass independently of age and blood pressure.[9]

However, Bulut et al and Nkum et al found no association between IR and LVH in HTN cases.[10,11]

Regression analysis also revealed that the effect of WHR on LVM was significant ($p<0.05$). A study done by Salvetti et al reported a similar independent direct correlation between WHR and LVM, accounting for upto 39.6% of the overall LVM variability.[12] Avignon et al also observed a positive correlation between LVM and WHR ($r=0.45$; $p=0.03$).[13] The association of increased LV mass with insulin resistance and hyper insulinemia has been described previously in several rare genetic disorders such as leprechaunism and total lipodystrophy as well as in other metabolic diseases such as acromegaly and hypothyroidism. It also has been demonstrated in infants of diabetic mothers and in infants with nesidioblastosis, both conditions characterized by intrauterine hyper insulinemia.

Insulin resistance can be modified by pharmacological and nonpharmacological means these results should stimulate further research to assess the effect of such interventions on LV mass and the morbidity and mortality associated with it in the obese.

Conclusion

The present study shows that post prandial insulin levels are elevated among hypertensive patients. There is a positive correlation between post prandial insulin levels and left ventricular mass. The study demonstrates that there are pathogenetic mechanisms related to insulin resistance and left ventricular mass. The results of the study pave the way for further research where drugs reducing insulin resistance can help to reduce left ventricular hypertrophy and cardiac remodeling.

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