Research Article

Effect of Insulin Resistance on Cardiac mass in Elderly Normotensive people: A Cross-Sectional Study

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Abstract

Aim: To study the independent effect of insulin resistance on LVM in the elderly normotensive population.

Methods: The study included 50 subjects excluding patients with myocardial infarction, heart failure, systemic hypertension and aortic stenosis. Group I included 30 patients with glucose intolerance, insulin resistance, or type 2 DM while Group II included 20 control subjects of matched age and sex. Participants involved in the study underwent clinical examination, laboratory investigation (including 75-g oral glucose tolerance test, HbA1c, Plasma insulin level, calculated HOMA-IR, Fasting Lipid profile, Serum albumin/creatinine ratio) and echocardiography.

Results: LV mass index was significantly different between the 2 group being higher (142.07±53.34) in the study group compared to (92.05±9.42) in the control group, (P=0.000). Waist circumference, HOMA-IR, FBS, HbA1c and systolic BP have significant positive correlations with LV mass index. However, only HOMA-IR has a significant independent positive correlation with LV mass index.

Conclusion: It is inferred from the present study that insulin resistance is associated with increased cardiac mass in normotensive elderly people.

Keywords: Type 2 diabetes mellitus; Insulin resistance; Echocardiography; Left ventricular

hypertrophy; Ventricular mass; Elderly normotensive subjects

List of Abbreviations

DM: Diabetes mellitus

CVD: Cardiovascular disease

MI: Myocardial Infarction

LVH: Left Ventricular Hypertrophy

IR: Insulin Resistance

TNF: Tumor Necrosis factor

LVWT: LV wall thickness

RWT: Relative wall thickness

HOMA: Homeostasis model assessment

BMI: Body Mass Index

AGE: Advanced glycation end products

Introduction

A significant rise in the incidence of metabolic syndrome, i.e. obesity, insulin resistance and dyslipidemia, has amounted to the presumption of epidemic proportions for type 2 or insulin resistant diabetes mellitus. Diabetes mellitus (DM), now emerges as one of the biggest threats in the 21st century affecting approximately 400 million people round the globe [1]. It is the world's most prevalent non-communicable disease and is placed to be the leading cause of death in developed countries [2]. DM is a fragmented cluster of disorder with elevated levels of blood glucose in the body [3]. Type 2 DM is represented by a differential degree of insulin resistance and β-cell dysfunction leading to hyperglycemia [4]. Single gene disorders affecting the capacity of the pancreatic β cell to secrete insulin or the capacity of muscle, fat and liver cells to respond to insulin action are identified as the underlying reason for the incidence of the disorder [5,6]. Insulin binding in the plasma membrane to its receptor sets in motion a sequence of intracellular signaling pathways leading to a multitude of insulin action on proteins, transporters and transcription [7]. DM is associated with both macrovascular and microvascular complications which includes coronary artery disease, myocardial infarction, hypertension, peripheral vascular disease, retinopathy, end-stage renal disease and neuropathy [8].

Cardiovascular disease (CVD) is the most prevailing factor of death and morbidity in people with diabetes, justifying an interconnection between diabetes and CVD [9]. In the United States, CVD mortality rates are reported to be approximately 1.7 times higher among adults with DM than those without DM, predominantly contributing to higher stroke risk and myocardial infarction (MI) [10].

The pathological pathways and co-morbidities identified with CVD starts to appear early in the childhood. Of particular note, obesity coupled with an abnormal lipid profile is strongly correlated with IR in younger subjects. Multiple factors, such as obesity, irregular lipid profiles and IR play prominent roles in CVD development, as illustrated in the publications [11,12].

Insulin promotes the usage of metabolic substrates in numerous tissues under physiological conditions. It facilitates glucose and fatty acid uptake in the cardiomyocytes, but prevents the use of fatty acids as a source of energy. Because of resistance to insulin, the pancreas overcompensates by secreting rising quantities of insulin leading to hyperinsulinemia [13].

Insulin resistance is characterized as a clinical state in which insulin imposes a lesser biological action as compared to the standard effect. This phenomenon is attributable to obvious irregularities in the insulin-

stimulated glucose uptake in glycogen synthesis and, to a lesser degree during glucose oxidation. The implications of insulin resistance in tissue types rely heavily on both the tissue's physiological and metabolic functions. Due to excessive metabolic demand insulin resistance has significant impacts on the skeletal muscle, adipocytes and liver tissue, which impose to be the key targets for intracellular glucose transport as well as glucose and lipid metabolism [14]. Insulin resistance induces compromised glycogen synthesis and protein catabolism in skeletal muscles. It also inhibits lipoprotein lipase activity in adipocytes leading to greater production of free fatty acids and inflammatory cytokines such as IL-6, TNFα and leptin. In addition, the liver contributes for 30% of insulin-stimulated glucose removal and insulin resistance corresponds to reduced glucose production and fatty acid metabolism resulting in higher triglyceride content and hepatic VLDL secretion [15]. Insulin resistance promotes endothelial cell dysfunction by reducing endothelial cell development of nitric oxide and boosting the release of pro-coagulant factors contributing to platelet aggregation. The PI3 K cascade is impaired in an insulin-resistant state while the MAP kinase pathway is preserved, triggering the mitogenic impact of insulin in the endothelial cells progressing to atherosclerosis [16]. The overload of lipids carted through non-oxidant networks in the cardiomyocyte contributes to the accretion of toxic lipid products leading to lipotoxicity, which modifies cellular signaling and cardiac architecture. Interruptions in numerous cellular signaling pathways have been identified with lipotoxicity, mitochondrial dysfunction and endoplasmic reticulum stress being the dominant examples.

Reports have suggested alterations in the left ventricular architecture to increase the risk of CVD furthering to death. With left ventricular hypertrophy (LVH), the risk of acute myocardial infarction, congestive heart failure, sudden death, ventricular ectopy, extreme arrhythmias and other cardiovascular events raises 6 to 8 fold [17].

LVH, which contributes to an improvement in the left ventricular mass (LVM), raises a substantial risk of an upsurge in cardiovascular diseases and deaths caused by them. Eight LVH can be minimized by removing the factors contributing to an increase in LVM, but the complexity of the factors causing an increase in LVM still appears to be fully explored among normotensive and even hypertensive people [18]. A previous study indicated that there was no improvement in LVM in 25–30 % of people with high blood pressure. These findings advocate the perspective that metabolic and genetic factors play a pivotal role in the increase in heart mass [19].

In vivo studies have showcased that insulin resistance (IR) and hyperinsulinemia have an impact on LVM [20]. However, other publications have established the fact that an independent relationship between insulin level and heart mass existed, it has not been fully demonstrated that IR is an independent predictor of the increase in LVM [21,22].

Patients with DM show changes in cardiac function and ultra structure of cardiomyocytes which can be plausibly linked to the precipitation of DM. Echocardiographic studies on the macroscopic level studies suggest the disorder to be associated with localized left ventricular hypertrophy and increased heart mass, with moderately reduced left ventricular systolic output [23].

That insulin resistance is a cause or effect of heart failure, or both, is not currently completely substantiated. Insulin resistance is a important contributing factor linked to heart disease development including hypertension, left ventricular dysfunction and heart failure. In comparison, cardiac failure promotes insulin resistance and is associated with a higher for type 2 DM development [24].

With the progression of CVD due to compromised insulin signaling, the emergence of insulin resistance is presumably multi-pronged in the patients with heart failure. Appropriate pathways by which insulin resistance induces heart failure typically involves sympathetic over activity, depletion of skeletal muscle mass, sedentary lifestyle followed by patients, endothelial dysfunction with decreased skeletal muscle blood flow, and a consequence of increased circulating cytokines, such as TNF, on peripheral insulin sensitivity [25]. There is however a shortfall of research findings supporting the relationship between insulin resistance and cardiac mass in the elderly normotensive community.

The present piece of research work focuses on the assessment of the effect of insulin resistance on cardiac mass in the elderly normotensive people.

Materials and Methods

The research was carried out in compliance with the principles of the Helsinki Declaration and approved by the University Ethics Committee. Before the study started, all participants who voluntarily agreed to participate in the study signed an informed written consent.

This is a cross-sectional study carried out to assess the effect of insulin resistance on cardiac mass in elderly normotensive people. It included 50 subjects consecutively recruited from outpatient clinic in Alexandria Main University Hospital. The study comprised of 2 study groups. Group I included 30 patients with glucose intolerance, insulin resistance, or type 2 DM. Group II included 20 control subjects of matched age and sex visiting the clinic for non cardiac, non metabolic consultations. Patients with previous myocardial infarction, heart failure, systemic hypertension, aortic stenosis or renal failure were excluded from the study.

Participants were subjected to full medical history which included blood pressure measurements, clinical examination of all palpable pulses, chest, heart and abdomen. Accurate measurements of the body weight, height, waist circumference and BMI were recorded. Clinical tests including 75-g oral glucose tolerance test, HbA1c, Plasma insulin level (fasting & 2-hrs post glucose challenge), fasting Lipid profile, serum albumin/ creatinine ratio and liver enzymes (ALT, AST) were performed. The degree of IR was calculated using the Homeostasis Assessment Model (HOMA) system at baseline.

Assessment of insulin resistance

Insulin levels were measured in plasma as total immunoreactive insulin (fasting and 2 hours after glucose challenge) and standardized to serum levels for reporting purposes. Insulin resistance (IR) was measured from the levels of fasting insulin and glucose and from the previously established homeostasis model; HOMA-IR was calculated by employing the following formula [26]:

HOMA-IR= [insulin (μU/ml) X glucose (mg/dl)/405] *(1)*

Echocardiography

Transthoracic echocardiography was performed for all participants with a single Hewlett Packard ultrasound machine and a standardized protocol. M-mode LV end-diastolic diameter (LVEDD), interventricular septum (IVST), posterior LV wall thickness (PWT) at the end of the diastole and LA size at the end systole were calculated using the leading edge technique in accordance with the guidelines of the American Echocardiography Society.

End-diastolic LV wall thickness (LVWT) was calculated as the sum of IVST and PWT, whereas relative wall thickness (RWT) was computed as (IVST_PWT)/LVEDD.

LV mass index formula of Devereux was calculated using the following equation:

LV mass index= 0.8[1.04(LVEDD+LVWT)3 - (LVEDD)3] + 0.6 (2)

Fractional shortening was used as an indicator of LV systolic function.

Statistical analysis

Data were analyzed using IBM SPSS software package version 20 (IBM Corp., Chicago, IL, USA). Qualitative data were ascribed in terms of number and percent. Quantitative data were described using Range (minimum and maximum), mean, and standard deviation and median. Comparison between the study and control groups regarding categorical variables was tested using Chi-square test. The distributions of quantitative variables were tested for normality. Parametric tests were applied when it reveals normal distribution of data. If the data is distributed abnormally, non-parametric tests were analyzed. Comparison between the two groups was performed using independent t-tests for normally distributed data, while abnormally distributed data was evaluated using Mann Whitney test. Using the Pearson coefficient the correlations between two quantitative variables were evaluated. The importance of the findings obtained was calculated at the level of 5%.

Results

The research study comprised of 50 subjects who were categorized in 2 treatment sections: Group I included 30 subjects with insulin resistance and Group II was a control group involving 20 subjects. Males represented 33.3% in the study group and 50% in the control group (p=0.188). There was no significant difference regarding age between the 2 groups; being (59.3±3.5 years) in the study group Vs (58.3±3.2) in the control group, (p=0.331). Similarly, no significant difference was observed regarding sex distribution. The Information of baseline characteristics of research subjects in the 2 the two groups are presented in table 1. The blood biochemistry findings of all the subjects involved in the study are presented in table 2.

Characteristics		Study Group	Control Group	Total	P Value
Weight(kg)	Min.	71	62	62	0.000*
	Max.	140	95	140	
	Mean	95.67	78.10	88.64	
	S.D.	17.281	9.968	17.054	
Height(meter)	Min.	1.5	1.5	1.5	0.020*
	Max.	1.8	1.9	1.9	
	Mean	1.607	1.665	1.630	
	S.D.	0.085	0.084	0.088	
BMI	Min.	30.0	25.3	25.3	0.000*
	Max.	62.2	30.0	62.2	
	Mean	37.165	28.135	33.553	
	S.D.	6.8350	1.6278	6.9746	
Waist circumference(cm)	Min.	88	78	78	0.000*
	Max.	145	95	145	
	Mean	108.23	87.30	99.86	
	S.D.	14.574	5.420	15.634	

*: Statistically significant at $p \leq 0.05$

Table 1: Comparison of the baseline characteristics of the subjects between the two groups (as regard to weight, height, BMI and Waist circumference)

Variable	**Study Group**	**Control Group**	**p value**
BMI (kg/m^2)	37.16±6.83	28.13±1.62	0.000*
Waist circumference (WC) (cm)	108.23±14.57	87.3±5.42	0.000*
FBS (mg/dl)	225.4±88.483	95.45±9.389	0.000*
PPPG(mg/dl)	278.33±70.153	130.15±17.593	0.000*
HbA1c%	8.847±1.8059	5.075±0.6423	0.000*
Cholesterol(mg/dl)	202.3±29.503	202.15±35.82	0.656
HDL(mg/dl)	52.13±9.232	49.85±8.851	0.388
LDL(mg/dl)	128.97±22.369	129.85±25.113	0.937
TG(mg/dl)	133.27±43.049	116.75±34.623	0.242
Albumin/Creatinine ratio(mg/gm)	11.727±4.5692	10.265±4.8298	0.284
Fasting Insulin (mu/L)	12.837±3.9664	7.730±2.5186	0.000*

*: Statistically significant at $p \leq 0.05$

Table 2: Clinical and biochemical characteristics of both study and control groups

The LV mass index was significantly different between the 2 group being higher (142.07±53.34) in the study group compared to (92.05±9.42) in the control group, (P=0.000). Regarding HOMA-IR, it was higher in the study group (6.48±1.96) compared to (1.74±0.51) in the control group (Table 3).

		Study Group	Control Group	Total	P Value
LV mass index	Min.	4.082	75.000	4.082	0.000*
	Max.	263.127	106.000	263.127	
	Mean	142.077	92.050	122.066	
	S.D.	53.342	9.417	48.283	
HOMA (IR)	Min.	4.6	0.4	0.4	0.000*
	Max.	12.3	2.4	12.3	
	Mean	6.489	1.745	4.591	
	S.D.	1.9638	0.5125	2.8100	

*: Statistically significant at $p \leq 0.05$

Table 3: Comparison between the two groups as regard to LV mass index and HOMA

Table 4 shows the correlation of different clinical and metabolic parameters with the LV mass index. Among these different parameters in the study group, waist circumference, HOMA-IR, FBS, HbA1c and systolic BP had significant positive correlations with LV mass index. However, on applying linear regression analysis, only HOMA-IR retained its significant independent positive correlation with LV mass index as shown in Table 4.

	LV mass index			
	Study Group		**Control Group**	
	r	p	r	p
Waist Circumference	0.653*	0.002	0.371	0.107
BMI	0.368	0.055	0.029	0.903
HOMA-IR	0.726*	<0.001	0.127	0.593
FBS	0.515*	0.004	0.009	0.969
PPBS	0.508	0.054	0.265	0.259
HbA1c	0.480*	0.007	-0.053	0.825
Albumin/Creatinine Ratio (mg/gm)	0.290	0.120	0.208	0.380
Total Cholesterol	0.250	0.184	-0.104	0.663

HDL-C	0.151	0.425	0.186	0.433
LDL-C	0.030	0.874	0.106	0.658
Triglycerides	-0.418	0.221	0.172	0.469
Systolic BP	0.549*	0.012	0.154	0.517
Diastolic BP	-0.021	0.912	0.017	0.942

r: Pearson coefficient

*: Statistically significant at $p \leq 0.05$

Table 4: Correlations of different parameters with LV mass index

As regard to the linear regression for LV mass index with HOMA-IR, WC, FBS, HbA1c and systolic blood pressure, a strong relation was noted between Homa-IR and LV mass index (Table 5).

	B	S	p	95% CI	
				LL	UL
Constant	-10.139	104.404	0.923	-225.618	205.339
HOMA-IR	17.144	3.955	<0.001*	8.981	25.307
WC	0.406	0.546	0.464	-0.721	1.532
FBS	0.085	0.116	0.469	-0.154	0.324
HbA1c	3.614	5.469	0.515	-7.673	14.900
Systolic blood pressure	-0.447	0.790	0.577	-2.077	1.183

*: Statistically significant at $p \leq 0.05$

Table 5: Linear regression for LV mass index, HOMA-IR, WC, FBS, HbA1c and systolic blood pressure

Discussion

It is ubiquitously embraced that DM is a potential trigger factor for heart failure and this association is partially mediated by its impact on the structure of LV [27]. Researchers have therefore explored the relationships of lower rates of glucose sensitivity and insulin resistance to the structure of LV [28]. Left ventricular hypertrophy (LVH) and hyperinsulinemia/insulin resistance are documented independent risk factors for cardiovascular diseases. Investigational analysis has also displayed that pathophysiological outcomes equate LV hypertrophy and insulin resistance. Scientific proof suggests the fact that the LV remodeling reflects on the hemodynamic parameters of preload, afterload, contractility stage of LV as well as duration and intensity of disease condition. At the other hand, genetic, environmental, and metabolic factors are considered the non-hemodynamic factors that influence LV mass and geometry. The prevalence of insulin resistance (IR) has been noted to be correlated with growth in LV among the metabolic factors [29]. Most IR calculation procedures are not practicable for use in huge populations as they are expensive and time-consuming. Homeostasis model assessment (HOMA) is a modern approach that allows IR to be tested quickly and cost-effectively [30].

This research expands preceding work by exploring the relationship between insulin resistance (assessed by HOMA-IR) and echocardiographic measurements. Our findings demonstrated a significant independent relationship between insulin resistance and LV mass index. This is in accordance with the reports of Ilercil et al., who documented a positive relationship between insulin resistance and insulin levels and LV mass [31]. This finding contrasts with Top et al, who analyzed 70 diabetic patients and found that there was no statistically significant link between LVH and IR derived from HOMA [32].

The study figured that the intensity of hyperglycemia is more closely related to LVH, and hyperglycemia in either sex affected fractional shortening, which is incongruent with some earlier studies [33]. The explicit framework on LV geometry for compromised glucose metabolism persists to be ascertained. Raised LV rigidity, caused by a buildup of collagen with advanced glycation end products and ensuing fibrosis in diabetic cardiomyopathy, was predicted to correspond to LV remodeling [34]. A declining reserve of myocardial perfusion has also been highlighted to be equated with LV torsion and strain in individuals with DM caused by an impeded myocardial blood flow [35]. Current studies indicate that intensive LV remodeling is synonymous with myocardial steatosis, excess accumulation of cardiac triglycerides and compromised myocardial energetic [36].

By analyzing the effect of obesity (BMI and WC) on LV mass, we found that a significant relationship existed between central obesity (WC) and LVM, compliant with previous studies which showed measurements of abdominal obesity representing increased visceral fat, such as waist circumference or waist-to-hip ratio, increase the risk of CV death regardless of body mass index (BMI) [37]. The results are in corroboration with the findings reported by Messerli et al. who correlated higher LVH in obese people [38].

It is firmly recognized that peripheral hyperinsulinemia is a sign of insulin resistance in subjects with critical hypertension [39]. This is in accordance with our result that analyses the relationship between LVM and systolic blood pressure in our study group.

Multiple frameworks for engagement of IR in the development of LVH have been advocated. Some of the mechanisms include up-regulation of the activity and numbers of Angiotensin II type 1 receptors by the inclusion of IR, maladaptive and elevated sodium re-absorption in the kidneys, heightened regulation of the sympathetic nervous system and insulin growth factor-1 release [40-43].

Direct action of elevated insulin levels on the heart's myocytes culminating in cardiac hypertrophy and remodeling, facilitating the development of smooth vascular muscle cells, and lipotoxicity may be some additional factors contributing to the involvement of IR in incidence of LVH.

However, there are alternate mechanisms by which DM may be associated with LV configuration and hypertrophy. DM can lead to ventricular functional modifications by raising the pro-inflammatory immune mediators emerging from hyperglycemia-induced oxidative stress. The involvement may also be regulated by the development of advanced glycation end products (AGE), which can impede ventricular compliance by responding to diminished collagen depletion [44].

Our study has certain limitations. Firstly, we could not determine causal relationships due to the cross-sectional nature of the study. Secondly, the study included a limited number of subjects which may provide bias in the observed results leading to a lack of concrete supporting data.

Conclusion

Left ventricular hypertrophy (LVH) and resistance to hyperinsulinemia / insulin are independent risk factors reported for cardiovascular diseases. Scientific research has also shown that LV hypertrophy and insulin resistance are equated with pathophysiologic outcomes. Among the metabolic factors, the prevalence of insulin resistance (IR) was noted to be associated with growth in LV. Most IR calculation procedures are not feasible for use in large populations because they are expensive and time-consuming. Homeostasis model assessment (HOMA) is a modern methodology that allows for a rapid and cost-effective testing of IR. The present study explored the independent effect of insulin resistance on LVM in the elderly normotensive population. Our study result represented that LV mass index is significantly higher in the treatment group comprising of elderly normotensive subjects with insulin resistance than those in the control group. Waist circumference, HOMA-IR, FBS, HbA1c and systolic BP was found to have significant positive correlations with LV mass index. However, only HOMA- IR has a significant independent positive correlation with LV mass index. Follow-up studies are mandated to provide solid proof to the observed results. It is envisioned that multi-centric trial with the involvement of more number of study population could add more value to the pre-existing data in relation to the stated disorder. Potential research work is urgently needed to comprehend the detailed mechanism between insulin resistance and cardiac disorders, with an emphasis on the generation of novel therapeutic regimens.

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