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A STUDY OF ELECTROCARDIOGRAPHIC AND ECHOCARDIOGRAPHIC CHANGES IN NON-DIABETIC INSULIN RESISTANCE STATE.

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ABSTRACT

Background- cardiovascular diseases account for approximately 17.9 million deaths annually and is the most common cause of deaths in the world and Type 2 Diabetes Mellitus is one of them because it is highly prevalent and doubles heart disease risk. Since all Type 2 Diabetes Mellitus patients are insulin resistant, it is difficult to assess its role in the development of cardiovascular disease of diabetics. Therefore, to assess its individual role in various cardiac pathologies, we must study non-diabetic patients who developed insulin resistance.

Methods- All the patients visiting Medicine OPD, LLRM Medical College were screened for eligibility. Informed consent was taken from the eligible patients and enrolled in the present study. The patients were interviewed and underwent thorough physical examination. Their Data comprising of name, age, sex, personal, occupational and history proper was recorded on the proforma.

Results- In our study, we found that there was no significant variation in heart rate and PR interval in both groups. The QRS duration ($p=0.043$) and QTc interval ($p<0.001$) was prolonged significantly in group B as compared to group A.

We also found that in group A, 92.10% of individuals had normal ECG whereas in group B, only 32.40% had normal ECG. In group A (HOMA-IR<6), 3.2% had Q-waves, 1.6% had LVH with LBBB, 3.2% had ST-T changes. In group B (HOMA-IR≥6), 13.5% had Q-waves, 5.4% had LVH, 5.4% had LBBB, 5.4% had LVH with LBBB, 37.8% had ST-T changes.

Conclusions- This study consisted of 100 non-diabetic individuals with insulin resistance as calculated by HOMA-IR and they were evaluated for cardiac diseases by electrocardiography and 2D echocardiography.

Diabetics, obese, hypertensive, patients with metabolic syndrome, renal or thyroid disease were excluded from the study.

The study group consisted of 59 males and 41 females with the mean age of 36.29. The HOMA-IR levels did not vary with age and sex.

Serum insulin and HOMA-IR was found to be significantly higher in patients with ECG abnormalities.

Among ECG abnormalities, there were prolonged QTc intervals, q waves, LBBB, LVH and ST-T changes.

Patients found to have Left ventricular diastolic dysfunction had higher HOMA-IR levels.

In our study, no correlation was found between Left Ventricular Ejection Fraction and HOMA-IR levels.

Keywords- Type 2 Diabetes Mellitus, Insulin resistance, Echocardiography, Cardiovascular diseases.

1. INTRODUCTION

Cardiovascular diseases account for approximately 17.9 million deaths annually and is the most common causes of death in the world and Type 2 Diabetes Mellitus is one of them because it is highly prevalent and doubles heart disease risk. Since all type 2 diabetic patients are insulin resistant, it is difficult to assess its role in the development of cardiovascular disease of diabetics. Therefore, to assess its individual role in various cardiac pathologies, we must study non-diabetic patients who have developed Insulin Resistance.

Insulin is a key hormone that functions as a regulator of cellular metabolism in many tissues in the human body. Insulin resistance is defined as a decrease in tissue response to insulin stimulation thus insulin resistance is characterized by defects in uptake and oxidation of glucose, a decrease in glycogen synthesis, and, to a lesser extent, the ability to suppress lipid oxidation. Literature widely suggests that free fatty acids are the predominant substrate used in the adult myocardium for ATP production, however, the cardiac metabolic network is highly flexible and can use other substrates, such as glucose, lactate or amino acids. During insulin resistance, several metabolic alterations induce the development of cardiovascular disease.

Cardiovascular diseases may be a consequence of insulin resistance rather than being caused by toxic effects of high insulin or glucose concentrations. Homeostasis model assessment insulin resistance (HOMA-IR) is a validated and commonly used marker of insulin resistance which incorporates both glucose and insulin concentrations and represents insulin resistance. The relationship between them is interesting because insulin resistance is increasing nowadays and if the studies prove this, medication and lifestyle changes will decrease insulin resistance, then cardiovascular disease can be prevented.

The aim of this study was to evaluate correlation between insulin resistance and cardiovascular diseases in non-diabetic patients. In our study, electrocardiographic variables including intervals, rhythm, axis, presence of block, left ventricular hypertrophy and ST-T changes were recorded. In echocardiographic parameters, systolic function is assessed by left ventricular ejection fraction and diastolic dysfunction by left ventricular diastolic dysfunction.

2. METHODS

The study was conducted in Department of medicine, S.V.B. P. Hospital associated with L.L.R.M Medical College, Meerut.

2.1 STUDY DESIGN

The present study is a Cross Sectional Study on non-diabetic patients with insulin resistance.

ISSN:0975 -3583,0976-2833 VOL 15, ISSUE 07, 2024

SAMPLE SIZE

By taking the prevalence of non-diabetic non hypertensive insulin resistant individuals to be 6.4% with 5% absolute precision and 95% confidence interval, the following formula is used to calculate minimum sample size.

$$n = (1.96)^2 \frac{pq}{d^2}$$

2.2 ELIGIBLITY CRITERIA

Inclusion Criteria:

- Age more than 18 years and less than 60 years.
- Insulin resistant state (Assessed by HOMA-IR, 1985)

Exclusion criteria:

- All individuals with Diabetes mellitus, kidney disease and Thyroid disorders.
- All individuals with acute infection.
- All individuals with increased BMI.
- All individuals with metabolic syndrome (NCEP ATP-III guidelines).
- All individuals on antihypertensive treatment.

2.3 COLLECTION OF DATA

All the patients attending to Medicine OPD, LLRM Medical College were screened for eligibility. Informed consent was taken from the eligible patients and enrolled in the present study. The patients were interviewed and underwent thorough physical examination. Their Data comprising of name, age, sex, personal, occupational and proper history was recorded on the proforma.

2.4 INSULIN RESISTANCE

HOMA-IR index (insulin µu/mL x glycemia mg/dL/405) is used to quantify insulin resistance.

The Homeostasis Model Assessment (HOMA) – HOMA, developed in 1985, is a model of interactions between glucose and insulin dynamics that is then used to predict fasting steady-state glucose and insulin concentrations for a wide range of possible combinations of insulin resistance and beta cell function. The model assumes a feedback loop between the liver and β-cell; glucose concentrations are regulated by insulin-dependent HGP while insulin levels depend on the pancreatic β-cell response to glucose concentrations. Thus, deficient β-cell function reflects a diminished response to glucose-stimulated insulin secretion. Likewise, insulin resistance is reflected by diminished suppressive effect of insulin on HGP. HOMA model describes this glucose-insulin homeostasis by a set of empirically derived non-linear equations. The model predicts fasting steady-state levels of plasma glucose and insulin for any given combination of pancreatic β-cell function and insulin sensitivity. Computer simulations, have been used to generate a grid from which, mathematical transformations of fasting glucose and insulin data from individual subjects determine unique combinations of insulin sensitivity (HOMA %S) and beta cell function (HOMA %B) from steady-state conditions. An important caveat for HOMA is that it imputes a dynamic beta cell function (i.e., glucose-stimulated insulin secretion) from fasting steady-state data. In the absence of dynamic data, it is difficult, if not impossible, to determine the true dynamic function of beta cell insulin secretion.

2.5 HISTORY AND EXAMINATION

A detailed history was elicited from all patients and necessary examination was done.

Body mass index (BMI) was calculated and subjects were included accordingly:

Cut-offs of BMI in Indians:

- Normal BMI: 18.0-22.9 kg/m2
- Overweight: 23.0-24.9 kg/m2
- Obesity: >25 kg/m2

2.6 INVESTIGATIONS

All patients were subjected to the following investigation at the time of inclusion into the study.

- Hemogram.
- Glycosylated haemoglobin.
- Fasting blood sugar.
- Serum fasting insulin.
- Thyroid profile.
- Blood urea and serum creatinine.
- Resting Electrocardiogram.
- 2D Echocardiography

2.7 STATISTICS

Data was collected and entered in MS Excel and analysed in IBM SPSS (Statistical Package for Social Sciences) software. Categorical data is summarized in terms of frequency and their percentage whereas quantitative data is summarized thorough mean + SD. Normality of the data is also checked by **Kolmogorov-Smirnov test** and then analysed by using appropriate statistical test, $p<0.05$ is considered as significant.

ISSN:0975 -3583,0976-2833 VOL 15, ISSUE 07, 2024

3. OBSERVATION AND RESULTS

We studied a total number of 100 cases of insulin resistance without diabetes in LLRM Medical College, Meerut and following observations were noted.

Clinical characteristics of the study subject and baseline laboratory results are given in Table 1.

Table 1: Descriptive Statistics

Variable	Minimum	Maximum	Mean		Std. Deviation
	Statistic	Statistic	Statistic	Std. Error	Statistic
AGE	19.00	59.00	36.29	1.15	11.53
FBS	89.00	120.00	101.50	0.61	6.06
S. INSULIN	13.80	40.10	22.46	0.64	6.42
HOMAIR	3.17	10.63	5.63	0.16	1.62
HBA1C	4.90	6.30	5.73	0.04	0.37
BMI	18.60	24.50	21.80	0.16	1.61
Heart rate	62.00	92.00	73.32	0.83	8.28
PR interval	138.00	228.00	161.26	1.56	15.59
QRS interval	84.00	176.00	93.77	1.62	16.24
QTc interval	389.00	484.00	417.12	2.55	25.54
LVEF	48.00	65.00	58.84	0.30	3.00
Valid N (listwise)	100.00				

We divided the Cases into two groups, Group A (individuals with HOMA-IR < 6) and Group B (individuals with HOMA-IR >= 6).

3.1 AGE

Distribution of age of the cases are presented in Table 2. The mean age of the study subjects was 36.29 years; standard deviation (SD) of 11.53 years with a range of 19-59 years.

TABLE 2. Distribution of observed variables in Group A (HOMA-IR < 6; N=63) and Group B (HOMA-IR>=6; N=37)

GROUPS		Mean	Std. Deviation	Std. Error Mean	p-value
AGE	A	35.38	10.28	1.30	0.306
	B	37.84	13.41	2.20	

3.2 SEX

Out of 100 cases, 59 were males and 41 were females.

The proportion of males and females were evenly distributed in both groups. Based on Pearson Chi-Square test, p-Value of 1.000 indicates the difference in gender across both groups is statistically not significant.

TABLE 3. Distribution of sex in Group A (HOMA-IR < 6; N=63) and Group B (HOMA-IR>=6; N=37)

SEX	GROUP		Total
	A	B	
Male	37	22	59
	58.70%	59.50%	59.00%
Female	26	15	41
	41.30%	40.50%	41.00%
Total	63	37	100
	100.00%	100.00%	100.00%

Distribution of observed variables of the cases are presented in Table 4. Independent t-test was used to calculate the statistical significance between the two groups.

TABLE 4. Distribution of observed variables in Group A (HOMA-IR < 6; N=63) and Group B (HOMA-IR>=6; N=37)

GROUPS		Mean	Std. Deviation	Std. Error Mean	p-value
FBS	A	100.83	5.30	0.67	0.147
	B	102.65	7.10	1.17	
S. INSULIN	A	18.48	3.14	0.40	0.000
	B	29.25	4.61	0.76	
HBA1C	A	5.78	0.35	0.04	0.110
	B	5.65	0.40	0.07	
BMI	A	21.68	1.60	0.20	0.330
	B	22.01	1.61	0.27	

ISSN:0975 -3583,0976-2833 VOL 15, ISSUE 07, 2024

Result showed that there was insignificantly higher mean Fasting Blood sugar level (mg/dL) in group B as compared to group A (100.83±5.30 vs 102.65± 7.10, p=0.147). There was significantly higher mean Serum insulin value in group B as compared to group A (18.48±3.14 vs 29.25±4.61, p<0.001). The differences in HBA1C values in the two groups was not statistically significant (5.78±0.35 vs 5.65±0.40, p=0.110). Similarly, the mean BMI level showed no significant difference between group A and B (21.68±1.60 vs 22.01±1.61, p=0.330).

3.3 ELECTROCARDIOGRAPHIC EVALUATION

Distribution of electrocardiographic parameters of the cases are presented in Table 5. Independent t-test was used to calculate the statistical significance between the two groups.

TABLE 5. Distribution of electrocardiographic parameters in Group A (HOMA-IR < 6; N=63) and Group B (HOMA-IR>=6; N=37)

	GROUPS	Mean	Std. Deviation	Std. Error Mean	p-value
Heart rate	A	73.24	8.46	1.07	0.898
	B	73.46	8.08	1.33	
PR interval	A	160.38	14.27	1.80	0.465
	B	162.76	17.72	2.91	
QRS interval	A	91.25	7.25	0.91	0.043
	B	98.05	24.59	4.04	
QTc interval	A	408.83	16.96	2.14	0.000
	B	431.24	31.20	5.13	

Result showed that there was no significant difference in heart rate in both groups (73.24±8.46 vs 73.46± 8.08, p=0.898).
Similarly, PR interval was insignificantly higher in group B as compared to group A (160.38±14.27 vs 162.76± 17.72, p=0.465).
QRS interval was prolonged significantly in group B as compared to group A (91.25±7.25 vs 98.05± 24.59, p=0.043).
The QTc interval was also prolonged significantly in group B as compared to group A (408.83±16.96 vs 431.24± 31.20, p<0.001).
Further, additional abnormalities on electrocardiogram were graded according to the Minnesota Code. Distribution of electrocardiographic findings of the cases are presented in Table 6.
Fisher's Exact Test was used to calculate the statistical significance between the two groups.
P value <0.001 was found and this shows that there were significant findings in electrocardiogram in group B as compared to group A.
In group A, 92.10% of individuals had normal ECG whereas in group B, only 32.40% had normal ECG.
In group A, 3.2% had Q-waves, 1.6% had LVH with LBBB, 3.2% had ST-T changes.
In group B, 13.5% had Q-waves, 5.4% had LVH, 5.4% had LBBB, 5.4% had LVH with LBBB, 37.8% had ST-T changes.

TABLE 6. Distribution of Electrocardiographic findings in Group A (HOMA-IR< 6; N=63) and Group B (HOMA-IR>=6; N=37)

	GROUP		Total
	A	B	
Normal	58	12	70
	92.10%	32.40%	70.00%
Q-wave	2	5	7
	3.20%	13.50%	7.00%
LVH	0	2	2
	0.00%	5.40%	2.00%
LBBB	0	2	2
	0.00%	5.40%	2.00%
LVH with LBBB	1	2	3
	1.60%	5.40%	3.00%
ST-T changes	2	14	16
	3.20%	37.80%	16.00%
Total	63	37	100

[LVH= Left Ventricular Hypertrophy, LBBB= Left bundle branch block]

3.4 ECHOCARDIOGRAPHIC EVALUATION

In group A, 55 cases were normal while 8 cases had grade 1 LVDD. In group B, 16 cases were normal, 15 had grade 1 LVDD, 6 cases had grade 2 LVDD while there were no cases with grade 3 LVDD. Fisher's Exact Test was used to calculate the statistical significance between the two

ISSN:0975 -3583,0976-2833 VOL 15, ISSUE 07, 2024

groups. P-value <0.001 was found and this shows that there were significant findings in Left ventricular diastolic dysfunction (LVDD) in group B as compared to group A.

TABLE 7. Distribution of Grades of Left ventricular diastolic dysfunction (LVDD) in Group A (HOMA-IR < 6; N=63) and Group B (HOMA-IR>=6; N=37)

LVDD	GROUP		Total
	A	B	
No LVDD	55	16	71
Grade 1	8	15	23
Grade 2	0	6	6
Grade 3	0	0	0
Total	63	37	100

Distribution of Left Ventricular Ejection fraction in cases are presented in Table 8. Independent t-test was used to calculate the statistical significance between the two groups.

TABLE 8. Distribution of Left Ventricular Ejection fraction in Group A (HOMA-IR < 6; N=63) and Group B (HOMA-IR>=6; N=37)

	GROUPS	Mean	Std. Deviation	Std. Error Mean	p-value
LVEF	A	59.11	2.84	0.36	0.240
	B	58.38	3.24	0.53	

Result showed that there was no significant difference in LVEF in both groups (59.11±2.84 vs 58.38± 3.24, p=0.240).

4. DISCUSSION

1. Diabetes is a common metabolic disorder associated to elevated cardiovascular morbidity and mortality that is not explained by hyperglycaemia or traditional cardiovascular risk factors such as smoking or hypercholesterolemia.
2. Intensive glycaemic control with insulin that achieves near-normal glycemia does not reduce significantly macrovascular complications compared with conventional glycaemic control.
3. Cardiovascular disease continues to develop in patients with diabetes despite adequate glycaemic control.
4. In contrast, intensive control with metformin (leading to insulin resistance improvement) reduces diabetes complications, including cardiovascular events, suggesting that enhancement of insulin sensitivity rather than plasma glucose level has a major role improving diabetes outcomes.
5. Accordingly, insulin resistance estimated by glucose tolerance tests is better predictor of future cardiovascular events than fasting glucose level in nondiabetic individuals.
6. Insulin resistance precedes for decades the clinical onset of type 2 diabetes and deteriorates metabolic control of type 1 diabetes.
7. Numerous investigations including cross-sectional and prospective studies, meta-analyses, and systematic reviews provide compelling evidence that insulin resistance by itself is a cardiovascular risk factor in a variety of population groups, including the general population and patients with diabetes.
8. Several estimations of insulin resistance have been consistently associated with elevated rate of cardiovascular events independently of other cardiovascular risk factors and diabetes status.
9. In the present study, we assessed 100 individuals with insulin resistance who were non-diabetics. Insulin resistance was defined using the homeostatic model assessment for insulin resistance.
10. Diabetics, obese, hypertensive, patients with metabolic syndrome, renal or thyroid disease were excluded from the study.
11. Cardiovascular abnormalities were assessed by various electrocardiographic and echocardiographic parameters.
12. We also compared the various indices obtained among the cases by dividing them into two groups based on HOMA-IR levels, group A (<6) and group B (>6).

4.1 ELECTROCARDIOGRAPHIC ASSESSMENT

1. In our study, we found that there was no significant variation in heart rate and PR interval in both groups.
2. The QRS duration (p=0.043) and QTc interval (p<0.001) was prolonged significantly in group B as compared to group A.
3. We also found that in group A, 92.10% of individuals had normal ECG whereas in group B, only 32.40% had normal ECG.
4. In group A (HOMA-IR<6), 3.2% had Q-waves, 1.6% had LVH with LBBB, 3.2% had ST-T changes. In group B (HOMA-IR≥6), 13.5% had Q-waves, 5.4% had LVH, 5.4% had LBBB, 5.4% had LVH with LBBB, 37.8% had ST-T changes.
5. In a previous study, M Graner et al [102] found some different findings in which the heart rate was increased (p < 0.001), the PR interval was longer (p < 0.044), the frontal plane QRS axis shifted to the left (p < 0.001), and the QRS voltage (p < 0.001) was lower in subjects with Metabolic syndrome.

ISSN:0975 -3583,0976-2833 VOL 15, ISSUE 07, 2024

4.2 ECHOCARDIOGRAPHIC ASSESSMENT

1. In our study, we found that in group A (HOMA-IR<6), 55 cases were normal while 8 cases had grade 1 LVDD. In group B (HOMAIR≥6), 16 cases were normal, 15 had grade 1 LVDD, 6 cases had grade 2 LVDD while there were no cases with grade 3 LVDD. P-value <0.001 was found and this shows that there were significant findings in Left ventricular diastolic dysfunction (LVDD) in group B as compared to group A.
2. We also found that there was no significant difference in LVEF in both groups (59.11±2.84 vs 58.38± 3.24, p=0.240).
3. According to Demmer et al, in ECHO-SOL they found that prediabetes, controlled diabetes mellitus, uncontrolled diabetes mellitus, and insulin resistance to be associated with modest differences in several measures of cardiac structure and function.
4. Prevalence of increased LV hypertrophy was 26%, abnormal LV geometry 45%, systolic dysfunction
5. 3.6%, and DD (grades I–III) was 61%.
6. According to Sirkeci et al, statistically significant relationship was found between presence of insulin resistance (HOMA-IR ≥ 2.6) and diastolic dysfunction (p = 0.001).
7. However impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) revealed no statistically significant correlation with the presence of diastolic dysfunction.
8. In another study, according to Wilfried Dinh et al, the prevalence of LVDD was 92% in subjects with insulin resistance vs. 72% in patients without insulin resistance, respectively (p = 0.013).
9. From all these studies, we can say that glucose intolerance and insulin resistance are associated with unfavourable cardiac structure and function, particularly worsened measures of diastolic function, even before the development of diabetes mellitus.

5. CONCLUSION

This study consisted of 100 non-diabetic individuals with insulin resistance as calculated by HOMA-IR and they were evaluated for cardiac diseases by electrocardiography and 2D echocardiography.

1. Diabetics, obese, hypertensive, patients with metabolic syndrome, renal or thyroid disease were excluded from the study.
2. The study group consisted of 59 males and 41 females with the mean age of 36.29.
3. The HOMA-IR levels did not vary with age and sex.
4. Serum insulin and HOMA-IR was found to be significantly higher in patients with ECG abnormalities.
5. Among ECG abnormalities, there were prolonged QTc intervals, q waves, LBBB, LVH and ST-T changes.
6. Patients found to have Left ventricular diastolic dysfunction had higher HOMA-IR levels.
7. In our study, no correlation was found between Left Ventricular Ejection Fraction and HOMA-IR levels.
8. The limitation of the present study is that it examined only a small number of patients.
9. To date only few studies have been conducted to examine whether insulin resistance is correlated with cardiovascular disease.
10. Thus, it can be taken as a preliminary study for further largescale studies. The present study failed to testify the reproducibility since it did not measure the value of HOMA–IR in a repetitive manner.
11. The concentration of serum glucose and insulin can be altered at each different measuring time, although the present study measured them only once.

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ISSN:0975 -3583,0976-2833 VOL 15, ISSUE 07, 2024

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