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Original Research Article

Electrocardiographic Alterations in Non-Obese Asian Indian Patients with Hypertension and Insulin Resistance

Sudhanshu Shekhar Jha[1], Rakesh Kumar[2]

[1]Senior Resident, Department of Medicine, Government Medical College and Hospital, Purnia, Bihar, India

[2]Senior Resident, Department of Medicine, Government Medical College and Hospital, Purnia, Bihar, India

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Corresponding author: Rakesh Kumar

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Abstract

Objective: The objective was to study the connection between insulin resistance and electrocardiographic alterations in hypertension without the interference of confounding factors, plasma glucose, and insulin responses to oral glucose.

Methods: A prospective study consisting of 35 hypertension participants and 25 normotensive subject altogether was carried out from September 2021 to August 2022 at Government Medical College and Hospital, Purnia, a resting ECG was performed and categorized as normal or abnormal.

Results: 17 of the 35 participants showed abnormal ECGs. The glucose tolerance of every hypertensive individual was normal. In comparison to normotensive and hypertension participants without ECG abnormalities, the serum insulin response of hypertensive subjects with ECG alterations was 42% greater. In participants with aberrant ECGs, the ratio of AUC glucose/AUC insulin, which measures insulin sensitivity, was considerably lower. The greatest levels of serum LDL cholesterol were found in hypertensive participants with irregular ECGs. Total cholesterol to HDL cholesterol was at an increased level. 17 hypertension participants (6 with and 11 without aberrant ECGs) showed a 51% decrease in the number of insulin receptors as compared to normotensive subjects. In 83% of cases, the correct classification was determined by multiple logistic regression analysis using mean blood pressure, serum total cholesterol, LDL cholesterol/HDL cholesterol, insulin level at 50 minutes in the OGTT, treatment, serum triglyceride, and the presence of a family history of diabetes, CHD, hypertension, or tobacco as independent variables causing ECG changes. The insulin level in the OGTT was the factor that had the greatest impact on the aberrant ECG readings.

Conclusions: The information points to a potential link between electrocardiographic anomalies and hyperinsulinemia or insulin resistance in Asian Indian hypertension people who are not fat or diabetic.

Keywords: Hypertension, Insulin resistance, ECG, LDL, HDL.

Introduction

An important and modifiable risk factor for cardiovascular disease is hypertension [1]. As blood pressure rises, the risk of cardiovascular death increases proportionately. Hence, sustained blood pressure elevation of 5 to 10 mm Hg causes a 34%–56% increase in stroke and a 21%–37% increase in coronary heart disease [2]. According to epidemiological research, insulin resistance or resistance to insulin-stimulated glucose absorption is linked to hypertension [3,4] (Figure 1). The incidence of obesity decreased glucose tolerance, diabetes, and bad effects from several antihypertensive medications all contribute to this association's explanation.

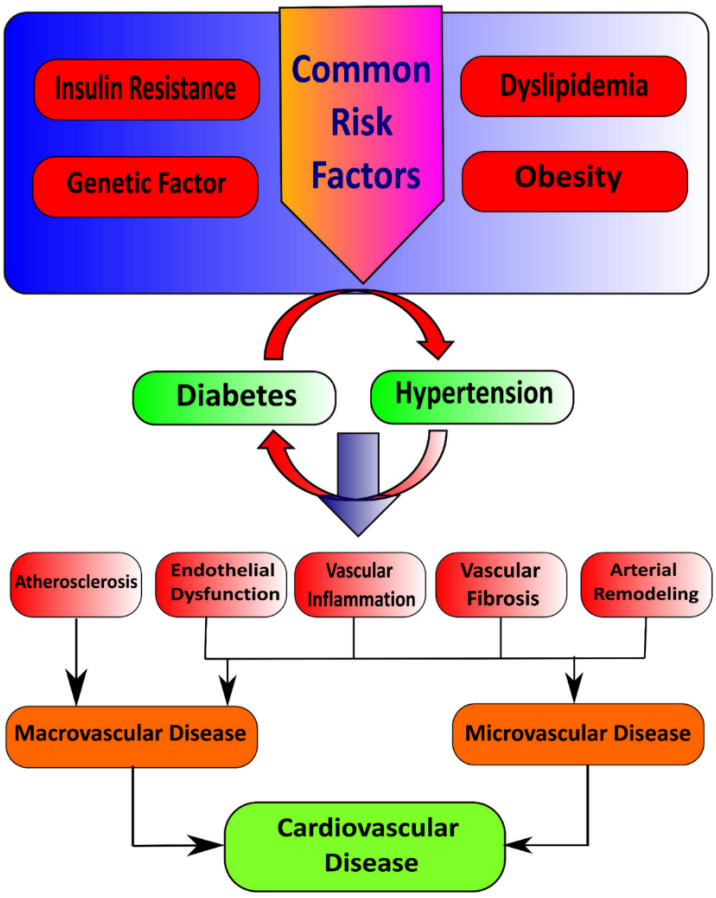

Figure 1: Association of Insulin resistance with Hypertension

Hence, in the absence of additional confounding factors, it is unclear if insulin resistance occurs as a pathogenetic factor in hypertensive individuals. In this regard, we previously demonstrated [5] that Asian Indian people with hypertension who are not obese, not diabetic, and who are not receiving beta blockers or thiazide medication therapy also have insulin resistance.

In the current investigation, the association between insulin resistance and electrocardiographic alterations in a subset of hypertensive people was assessed without the presence of any known confounding factors, such as obesity, diabetes, or unfavorable antihypertensive medication. 41% of the participants have indications of insulin resistance, and only these 41% have

electrocardiographic abnormalities when compared to other subjects.

Methods

Among the population previously surveyed, a total of 60 subjects (35 hypertensive and 25 normotensive subjects) were selected [6]. A few hypertension patients were chosen from the Government Medical College and Hospital, Purnia. Prior descriptions of the selection criteria for non-diabetic, non-obese, normotensive, and hypertensive participants were made [5]. Upon consenting to participate, each individual made two back-to-back trips to the lab. All individuals underwent a thorough physical examination, resting electrocardiograms with 11 leads, and resting blood pressure measurements during the initial visit. Blood tests were conducted during the second appointment. The Institutional Ethics and Scientific Advisory Council of ABC Hospital gave the project their blessing.

After a 10-15 hour overnight fast, the individuals underwent a routine 75g oral glucose tolerance test. A sample of fasting (heparinized) blood was utilised to measure the insulin binding using I'25. Radioimmunoassay was used to measure serum insulin. Enzymatic techniques were used to measure the levels of fasting serum triglycerides, cholesterol, and plasma glucose [5]. Precipitation of lipoproteins containing ApoB was used to evaluate high density lipoprotein (HDL) cholesterol. Friedwald's formula was employed to determine LDL cholesterol.

According to the Minnesota code criteria (items 1.0–1.2), abnormal Q or QS patterns, abnormal T waves, and the presence of LVH, a resting ECG was classified as normal or abnormal using these criteria. Two cardiologists independently interpreted electrocardiograms. lin I-125-Insulin binding to erythrocytes was assessed using the Gambhir djd technique in a subset of 6 normotensive and 16 hypertensive individuals [8]. After Ficoll separation, erythrocytes were extracted. An aliquot of 300 p1 of 4.1–4.3 11 RBC/ml was then incubated for 80 minutes at 15°C with 0.2–0.3 ng of I–125– Insulin and 1-104 ng/ml unlabelled human insulin in a total volume of 400 p1 of Buffer G.

After incubation, 100 pl of the cell solution were centrifuged in a microfuge using a dibutylphthalate oil gradient. In a Gamma counter, the radioactivity that is bound to cells was measured. Nonspecific binding was defined as binding while 104 ng/ml of unlabelled insulin was present.

The data are displayed as mean plus SEM. Using an unpaired "t" test, mean values between groups were compared. AUC was computed by adding the areas of subsequent triangles and rectangles beneath the graph to determine the area under the curve. Using the computer application "LIGAND," Scatchard analysis of insulin binding data was carried out [9]. The SPSS, Version 4.0 computer programme was used to do a logistic regression analysis of the ECG results. Chi-square analysis was used to assess the goodness of fit.

Results

The subjects were divided into three groups based on the results of the ECG: 25 normotensive people with normal ECGs, 20 hypertension people with normal ECGs, and 15 hypertensive people (42%) with aberrant ECG alterations (Table I).

Table 1: Baseline Physical characteristics of patients

Parameter	Normotensive	Hypertensive Normal ECG	Hypertensive
Number	25	20	15
Age (years)	57.4±1.8	58.3±2.2	60.2±2.8

Gender			
Male	14	12	13
Female	11	8	2
BMI (Kg/m^2)			
Male	21.5±0.5	21.6±0.4	21.4±0.5
Female	19.2±0.5	19.3±0.4	21.2±0.2
Blood Pressure (mm/Hg)			
Systolic	120.1±2.5	148.1±12.8	156.1±5.5
Diastolic	79.0±1.5	95.1±1.6	94.2±3.1
Mean	92.7±1.7	112.2±2.1	113.6±3.7
Electrolytes(mmol/l)			
Na^+	142.3±1.3	142.5±0.8	113.2±1.3
K^+	4.5±0.2	4.5±0.2	4.3±0.2
Family History			
DM	18%	21%	5%
CHD	37%	21%	11%
HBP	45%	30%	24%
Smoking or Chewing Tobacco	30%	62%	37%

For age, gender, and body mass index, the three groups were comparable. There was no overlap and both groups of hypertensive participants had blood pressure that was significantly higher than that of the normotensive group. Nine patients remained untreated among the 20 hypertensive participants without ECG abnormalities (7 were newly identified and 3 had hypertension for three months), while 12 patients were receiving antihypertensive medication.

9 participants were on calcium channel blockers, while 3 subjects had been taking ACE inhibitors for 1-2 years. Treatment with the latter lasted 5 months for 1 subject, 6 months for 8 patients, and 1 year for 2 patients. Seven people in the group with abnormal ECGs had undiagnosed hypertension while seven were receiving treatment. Three individuals utilized ACE inhibitors for a total of one year, compared to six patients who received calcium channel blockers for five months, two patients for six months, and two patients for one year. Na.±/K.± concentrations and serum creatinine levels were within acceptable ranges (Table I).

The hypertensive group with abnormal ECGs had a slightly reduced family history of diabetes mellitus. The three groups had comparable family histories of CHD and high blood pressure, with a somewhat lower frequency among the participants who had an irregular ECG. In all subject groups, tobacco use in the form of cigarettes or chewing tobacco was equally noted. Six of the 17 participants with abnormal ECGs had hypertrophic changes, four had conduction problems, and four had solely ischemic changes. Three other subjects had both ischemia and hypertrophic changes.

Both groups of hypertensive participants had a slightly (but not significantly) greater plasma glucose response to a 70g oral GTT. Although the fasting plasma glucose levels of hypertensive patients were comparable to those of normotensive subjects, greater levels were observed at 2 and 3 hours after a glucose load, which led to a slight rise in AUC glucose in hypertension (Table 2).

Table 2: Metabolic characteristics of Patients

Parameter	Normotensive	Hypertensive Normal ECG	Hypertensive
Number	25	20	15
AUC Glucose (mg/dl 1 h)	246.4±9.2	260.2±8.2	266.1±10.1
Fasting serum insulin (U/ml)	18.8±4.0	29.8±11.7	18.2±3.1
Fasting Hyperinsulinemia	-	26%	43%
Hyperinsulinemia AUC Insulin (U/ml 1h)	197.5±16.0	198.4±18.1	265.1±22.2
AUC Insulin/ AUC Glucose	0.764±0.061	0.734±0.064	1.01±0.10
AUC Glucose / AUC Insulin	1.45±0.10	1.51±0.13	1.11±0.12
Fasting serum triglycerides	137.8±12.5	135.5±11.6	135.8±18.4
Total Cholesterol/HDL Cholestrol	4.97±0.30	5.1±0.28	5.7±0.46

Serum insulin response was substantially higher (42%) ($p<0.04$) in hypertensive participants with irregular ECG than in normotensive subjects.

Hypertensive people with normal ECGs have serum insulin responses that are identical to normotensive subjects. Although hypertensive participants with irregular ECG had slightly lower basal insulin levels than those with normal ECG, post-glucose insulin levels were raised by 42% at 2 hours and by 54% at 2 hours in these subjects. In comparison to normotensive and hypertensive participants with normal ECG, the AUC insulin of hypertension subjects with aberrant ECG was substantially higher ($p<0.01$) and ($p<0.04$), respectively (Table 2).

In the hypertensive group with irregular ECG, the ratio of AUC insulid AUC glucose, a measurement of insulin secretion (glucose induced), is greater (Table 11). The participants with ECG abnormalities have a considerably lower ratio of AUC glucose/ACU insulin (1.11.± 0.12 vs. 1.51.± 0.13), which measures the amount of glucose that is used to raise insulin levels.

Hypertensive subjects with aberrant ECGs have considerably higher LDL cholesterol values in their fasting serum lipid profiles. In hypertension participants with irregular ECG, HDL cholesterol was lowest (40.8.± 2.0 mg/dl vs. 43.1.± 1.7 mg/dl in normotensive subjects), although this difference was not statistically significant. The hypertension group with irregular ECG had the greatest total cholesterol/HDL cholesterol ratio. All three groups' serum triglyceride levels were comparable (Table 2).

I-125-labeled insulin binding to erythrocytes was investigated in 17 hypertensive participants from the 60 total subjects, including a subset of 5 normotensive subjects (6 with irregular ECGs and 11 without). These subjects' responses to plasma glucose and serum insulin were qualitatively comparable to those of every person examined in each group. In both groups of hypertension participants, specific insulin binding was considerably lower than in nonhypertensive subjects. In both groups of hypertensive people, Scatchard analysis found that the number of high affinity insulin receptors had decreased by about 51% without affecting the ligand's affinity for the receptor.

In order to comprehend the relationship between the incidence of ECG abnormalities and other hypertension-related factors, a model was predicted in which mean blood pressure, serum triglycerides, LDL

cholesterol, total cholesterol/HDL cholesterol, serum insulin at 50 minutes in the OGTT, therapy, family history of diabetes mellitus, CHD, and hypertension were considered as independent variables contributing to ECG changes in all 35 hypertensive participants.

In 84% of the cases, the classification of ECGs (as normal or abnormal) predicted by the aforementioned variables agreed with the observed alterations, according to multiple logistic regression analysis. The biggest contribution to ECG abnormalities among the many components thought to be involved came from the insulin levels at 60 minutes of the OGTT. In this investigation, this observation is crucial.

Discussion

The goal of the current investigation was to examine the association between insulin resistance and electrocardiographic alterations in an aged Indian subject population with hypertension. These participants had neither diabetes nor obesity, and they had not undergone any antihypertensive therapy known to have negative effects on insulin sensitivity. Only patients receiving calcium channel blockers or ACE inhibitors, known to have cardioprotective benefits (10), were taken into account when treated subjects were analysed. So, the most basic level of ECG abnormalities in these people could be secondary to high blood pressure or insulin resistance. This theory is supported by the data collected for this investigation.

Based on the following criteria, patients with abnormal ECGs were determined to have insulin resistance: I higher serum insulin levels (42% during OGTT); (ii) a lower ratio of AUC glucose to AUC insulin, which is a measure of insulin sensitivity; and (iii) a higher AUC insulin to AUC glucose, which is a measure of insulin secretion (insulin output) in response to a change in glucose. The number of subjects with fasting hyperinsulinemia (higher than mean levels of normotensive subjects of 19.8±4.0 pU/ml) was significantly higher (37%) compared to the group without ECG changes (26%), even though the mean fasting serum insulin levels of this group were only marginally (but not significantly) higher than the group without ECG changes.

15 (42% of the 35 hypertensive individuals examined) showed hyperinsulinemia. This is consistent with earlier research [11,12]. Manicardi *et al* [13] found that obese, untreated hypertension individuals also had hyperinsulinemia and glucose intolerance. The incidence of insulin resistance is notably higher (41%) than expected, despite the fact that some of our subjects were receiving antihypertensive medication, which is known to increase insulin sensitivity [10]. and that they were not obese compared to participants in previous research. Comparisons of patients receiving ACE inhibitor medication in both groups of hypertension patients show no appreciable variation in the quantity or length of treatments (1-2 years).

Both groups of hypertension patients received calcium channel blocker medication for a comparable amount of time. It is challenging to compare the two groups with hypertension for statistical analysis due to the limited numbers of participants in each category. But it seems that the incidence of insulin resistance in hypertension in the current study is comparatively higher than in earlier studies, pointing to the involvement of additional factors. Age-related blood pressure rise is greatly influenced by race and ethnicity [14]. Also, different racial and ethnic populations exhibit varied trends in the link between blood pressure and insulin resistance [15]. As the incidence of CHD is higher in our participants' ethnic groups than in the general population [16], it is possible that racial differences will have an impact.

Plasma glucose response was somewhat higher in hypertension patients compared to nontensive subjects, despite the fact that they do not exhibit obvious glucose intolerance. Given that both groups of hypertensive participants responded similarly to the OGTT for plasma glucose, it suggests that the rise in blood pressure alone may be to blame. The presence of fewer insulin receptors in both groups of hypertensive participants could be explained by higher blood pressure and plasma glucose levels. This finding is in line with the decrease in the number and expression of insulin receptors in the liver of spontaneously hypertensive rats used as a model for human hypertension [17]. However, hypertensive people with hyperinsulinemia do not exhibit a significant decline in the amount of insulin that binds to erythrocytes, indicating that the postreceptor site in lU3C is where insulin resistance is.

As only participants with hyperinsulinemia had the highest observed levels, the elevation in serum LDL cholesterol, a significant risk factor for CHD [18], reported in the current investigation is connected to hyperinsulinemia. A total cholesterol/HDL cholesterol ratio of more than 5.0 has been linked, independently, to an increased risk of CHD [18]. The hypertension group with abnormal ECG had a greater ratio. This might also contribute to alterations in the ECG.

The link between insulin resistance and electrocardiographic alterations, a readily available non-invasive biomarker of heart disease, is a significant finding in the current investigation. Multiple logistic regression analysis was used to compare individuals with and without ECG abnormalities, and the results showed that 84% of the time, the ECG changes were correctly classified using independent risk variables for CHD. High significance of the goodness of fit for this model was demonstrated by chi-square analysis. Insulin levels in GTT were one of the factors that had the biggest impact on the aberrant ECG. In a group of Chinese hypertensive people who also had insulin resistance, Sheu *et al* [19] reported ECG abnormalities. The subjects in that study, however, had a higher body mass index than our subjects did [Table 1].

The correlation of family history across all subject categories is another finding. Although the existence of FH in the hypertensive group with ECG changes may have caused some of the ECG abnormalities, this seems improbable at the moment given that this group has fewer people with positive family histories than other groups. Our data do not currently indicate a mechanism through which the elevated insulin levels (hyperinsulinemia) of hypertensive people could result in aberrant ECG readings. According to Rowe a, hyperinsulinemia may cause the sympathetic nervous system (SNS) to become more active and lead to a further rise in blood pressure [20]. This raised blood pressure may have a more significant effect on the heart's output, leading to hypertrophy (or LVH).

Conclusion

In conclusion, the present investigation showed that 41% of Indian hypertension participants exhibited insulin resistance hyperinsulinemia and no other confounding factors other high blood pressure. While elevated blood pressure may be the cause of metabolic abnormalities such as insulin binding to receptors and plasma glucose response, hyperinsulinemia may also be the cause of ECG abnormalities and elevated serum LDL cholesterol levels. The logistic regression analysis implies that there is a connection between hyperinsulinemia and ECG abnormalities. According to the research, electrocardiographic alterations in Asian Indian hypertension people who are not obese or have diabetes may be partially correlated with insulin levels in the OGTT.

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