Prevalance of Insulin Resistance in Non-Diabetic Patients Suffering from Essential Hypertension using Homa-IR

Dr. Anjaneya Prasad[1], Dr. M. A. Sameena Farheen[2], Dr. Akif Ahamad Baig[3]

[1]Professor and Head of Department, Department of General Medicine, Dr. Pinnamaneni Siddhartha Institute of Medical Sciences, Chinnavutapalli, Vijayawada, Andhra Pradesh, India

[2]Postgraduate, Department of General Medicine, Dr. Pinnamaneni Siddhartha Institute of Medical Sciences, Chinnavutapalli, Vijayawada, Andhra Pradesh, India

[3]DM-Cardiology, Guntur, Andhra Pradesh, India

Abstract: <u>*Introduction*</u>*: Hypertension, a major cause of cardiovascular disease, often remains unmitigated by antihypertensive treatment, suggesting additional factors at play. Insulin resistance, a hallmark of metabolic syndrome, independently elevates cardiovascular risk. This study aims to assess insulin resistance prevalence in non-diabetic hypertensive individuals, potentially prompting routine screening to curb metabolic syndrome development and reduce cardiovascular disease incidence.* <u>*Objectives*</u>*: This study aims to investigate the prevalence of insulin resistance in non-diabetic patients with essential hypertension compared to a healthy population, with a focus on determining the association between insulin resistance and hypertension, BMI, age, sex, and family history of diabetes.* <u>*Materials and Methods*</u>*: A cross-sectional study was conducted at the Department of General Medicine, Dr. Pinnamaneni Siddhartha Institute of Medical Sciences, Andhra Pradesh. A total of 200 participants were included (100 hypertensive patients and 100 controls). Data on demographics, anthropometrics, and metabolic factors were collected. Insulin resistance was assessed using the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR). Statistical analysis was performed to compare variables between groups.* <u>*Results*</u>*: Hypertensive patients exhibited significantly higher mean fasting insulin levels and insulin resistance (HOMA-IR) compared to normotensive controls (p < 0.05). Insulin resistance was more prevalent in hypertensive individuals with BMI > 25. Age and sex did not show significant associations with insulin resistance. Similarly, there was no significant difference in insulin resistance based on family history of diabetes.* <u>*Conclusion*</u>*: Essential hypertension is associated with increased insulin resistance, especially in individuals with higher BMI. Early identification and management of insulin resistance in hypertensive patients may contribute to the prevention of metabolic syndrome and subsequent cardiovascular diseases.*

Keywords: Essential hypertension, insulin resistance, HOMA-IR, cardiovascular disease, BMI, metabolic syndrome

1. Introduction

Hypertension is one of the leading cause of Cardiovascular disease. It contributes to about 9.4 million deaths per year. It also doubles the risk of Cardiovascular disease like Coronary artery disease, Ischemic or hemorrhagic stroke, Heart failure or peripheral artery disease.

But epidemiological studies have not shown reduction in Cardiovascular disease even after treatment with Antihypertensives suggesting that some other factor along with Hypertension is leading to Cardiovascular disease.

Insulin resistance is defined as inability of Insulin to reduce blood glucose levels. Insulin resistance is a component of Metabolic syndrome and itself is a risk factor for many cardiovascular diseases. There are various methods to measure Insulin resistance. HOMA-IR is a simple and reliable measure of insulin resistance.

There are several mechanisms proposed by which Insulin resistance leads to Hypertension which includes an increase in plasma noradrenaline levels which augments Na+ H+ exchange and this results in increased intracellular accumulation of Na+ and Ca+ which increases the intracellular pH and also enhances the sensitivity of vascular smooth musculature to the vasopressor effects of nor-epinephrine, angiotensin and NaCl loading and effects of insulin like growth factor 1 (IGF-1) causing hypertrophy of the vessel walls and narrowing of the lumen of resistance vessels.

There is evidence that Essential hypertension patients who have Insulin resistance and other features of metabolic syndrome have an increased incidence of cardiovascular disease (CVD).

This study is being done to find out the prevalence of Insulin resistance in Non diabetic patients with Essential hypertension patient in comparison to healthy population and will help in recommending routine screening for Insulin resistance in hypertension patients, as early diagnosis and management of Insulin resistance may prevent development of Metabolic syndrome and thus will decrease the chances of cardiovascular disease.

2. Materials and Methods

This is an observational, cross-sectional study, conducted at Department of General Medicine, Dr. Pinnamaneni Siddhartha Institute of Medical Sciences, Andhra Pradesh. The sample size of this study was 200 (100 subjects and 100 controls). Subjects included hypertensive patients whereas controls included non-hypertensive patients.

Patient Eligibility
The inclusion and exclusion criteria for enrolling patients are as follows:

Inclusion criteria:
1) Age>18years
2) Patients recently diagnosed with Hypertension (As per JNC8 Guidelines) or already a known hypertension and on Lifestyle modification and on Anti-Hypertensive drugs.

Exclusion criteria:
1) Presence of Diabetes mellitus (FBS>126 or PPBS>200mg/dl)
2) Impaired glucose tolerance (FBS 100-125 , PPBS 140-199mg/dl)
3) Active systemic illness
4) Liver Disease
5) Renal Disease

3. Data Collection Methods

The patients were identified in the out-patient and in-patient department of general medicine. Patient's who fits into inclusion criteria were identified and detailed medical history was taken. The observations will be recorded on special Proforma designed for the study. Parameters to be analysed will be Age, Sex, Body Mass Index, Blood Pressure, duration of Hypertension, Medications for hypertension, family history of hypertension and Diabetes, other history of other medical illnesses and Drug history. Informed written consent was taken from all subjects.

Fasting serum glucose and Insulin test was done for all subjects. The test was processed in Radio-Immuno Assay lab by Chemoimmunoluscence method. The blood report of Fasting insulin was collected from laboratory after 24hrs or the next day and was noted on the proforma. Based on this report, HOMA-IR was calculated and Insulin Resistance was assessed.

$HOMA\text{-}IR(23) = Fasting\ Insulin(mU/L) \times Fasting\ glucose\ (mmol/L)\ /22.5$

OR

$Fasting\ Insulin(mU/L) \times Fasting\ glucose\ (mg/dl)/405$

Normal Insulin Resistance	HOMA SCORE <3
Moderate Insulin resistance	HOMA SCORE 3-5
Severe Insulin resistance	HOMA SCORE >5

Statistical Analysis
Results for Quantitative Variables like HOMA Score, Fasting Insulin, fasting blood sugar, age, BMI will be expressed as mean (±SD). Results for Qualitative Variables like gender, proportion of patients with family history of diabetes will be expressed as frequency and percentages. The comparison of normally distributed Quantitative variables between two independent groups will be performed using Wilcoxon signed Rank test . The comparison of normally distributed Quantitative variables between two groups will be performed using chi square method. Nominal categorical data between the groups will be compared using the $\chi 2$ test or Fisher's exact test (for expected frequencies <5) as appropriate. Non-normal distribution continuous variables will be compared using the Wilcoxon Rank Sum test of Mann Whitney U test as appropriate. The p<0.05 was considered significant.

4. Results

100 Hypertensive patients were compared with 100 non-hypertensives healthy subjects who served as controls. Out of 100 hypertensive patients, 63 were males and 37 were females whereas in non hypertensive group, 41 were males and 59 were females. Mean age in hypertensive group was 53.22±8.97 whereas in non hypertensive group it was 50.90±9.06. (Table 1)

Table 1: Demographic, anthropometric and metabolic profile of cases and control (Mean±SD).

Parameters	Hypertensive Mean ± SD	Non Hypertensive Mean ± SD	P value (Wilcoxon signed Rank test)
Age (years)	53.22±8.97	50.90±9.06	0.04999
BMI	27.84±4.26	26.50±4.47	0.04975
FBS	92.55±5.45	92.31±5.56	0.7512
Insulin	10.88±6.21	10.44±13.78	0.02938
HOMA-IR	2.50±1.45	2.13±1.40	0.03703

Mean Fasting Insulin in hypertensive patient was 10.88±6.21 whereas in non hypertensive patient it was 10.44±13.78 (Figure 1), indicating that fasting insulin level is significantly higher in Hypertensives when compared to normotensive group. (P <0.05)
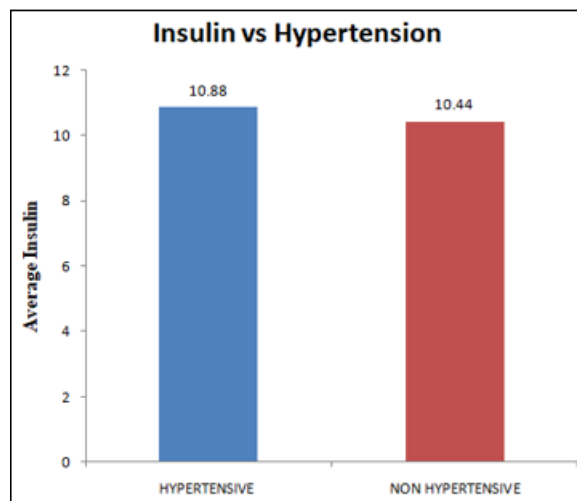
Figure 1: Fasting insulin in hypertensive versus normotensives

Insulin resistance was present in 28 out of 100 hypertensive patients (23 had moderate Insulin resistance and 5 had severe insulin resistance) whereas it was present in 20 out of 100 normotensive group (13 had moderate and 7 had severe insulin resistance). (Figure 2)
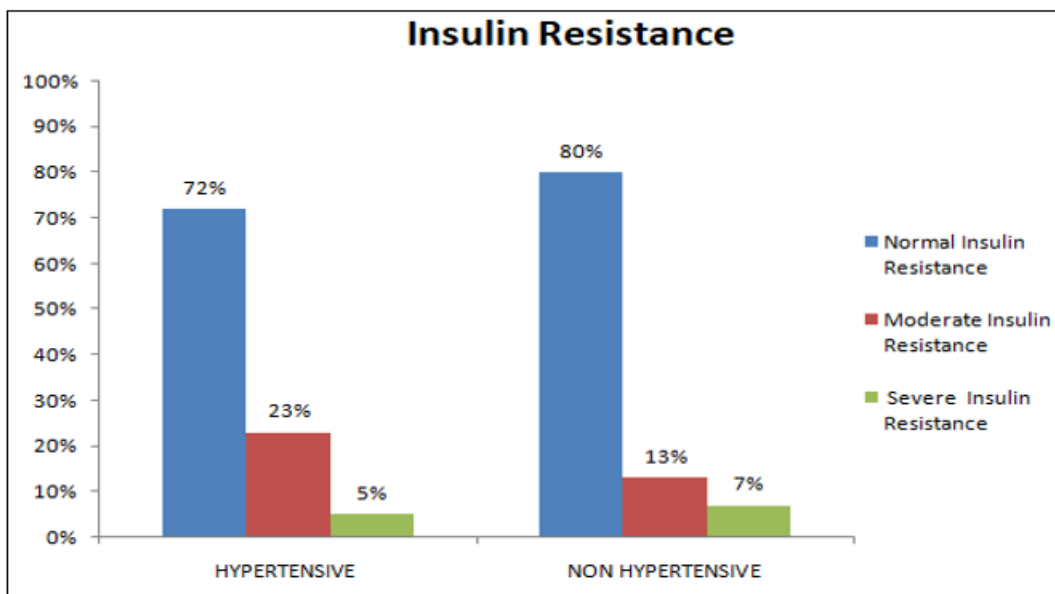
Figure 2: Hypertension vs normotensive in context of insulin resistance

The mean insulin resistance(HOMA-IR) in hypertensive subjects was 2.50+1.45, while same in control group was 2.13+1.40, indicating that insulin resistance in hypertensive subjects was significantly higher than in normotensive group. (P<0.05) (Figure 3)
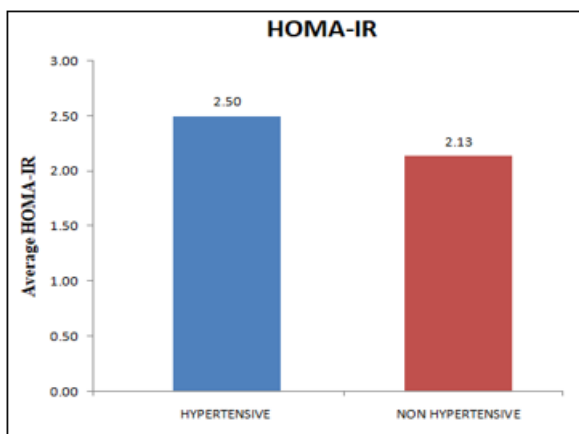

Figure 3: Hypertension vs normotensive in context of HOMA-IR

When age was compared with Insulin resistance, there was no significant difference between age >50 yrs group versus group of age <50years. (P > 0.05) (Table 2)

Table 2: Age vs HOMA-IR

Parameters	HOMA-IR>3 %(frequency)	HOMA-IR<3 %(frequency)	P value (Chi square)
Age<50	24.56% (28)	75.44% (88)	0.8309
Age >50	23.26% (20)	76.74% (66)	

When sex was compared with insulin resistance. There was no significant difference in HOMA-IR values in males when compared to females. (P >0.05). (Table 3)

Table 3: Comparison of gender with HOMA-IR

Parameters	HOMA-IR>3 %(frequency)	HOMA-IR<3 %(frequency)	P value (Chi square)
Male	26.92% (28)	73.08% (76)	0.3149
Female	20.83% (20)	79.17% (76)	

Mean BMI in hypertensive group was 27.84+4.26 whereas in non hypertensive group was 26.50+4.47. There were 59 patients with BMI< 25, out of which 7 had moderate to severe Insulin resistance(HOMA-IR>3) whereas 52 had normal insulin resistance (HOMA-IR <3). There were 93 patients with BMI between 25-30, out of which 24 had moderate to severe insulin resistance (HOMA-IR>3) whereas 69 patients had normal insulin resistance. There were 48 patients with BMI >30, out of which 17 had insulin resistance and 31 had normal insulin resitance. There was statistically significant difference in insulin resistance in patients with BMI <25 when compared to BMI >25. (P <0.05) (Table 4)

Table 4: BMI Vs Insulin Resistance in terms of HOMA-IR

Parameters	HOMA-IR<3 %(frequency)	HOMA-IR>3 %(frequency)	P value (Chi square)
BMI <25	88.14% (52)	11.86% (7)	0.0153
BMI 25-30	74.19% (69)	25.81% (24)	
BMI>30	64.58% (31)	35.42% (17)	

Family history of hypertension and insulin resitance was also compared in this study. There were 70 patients who had positive first or second degree family history of diabetes or impaired glucose tolerance, out of which 22 had moderate to severe insulin resistance (HOMA-IR >3) whereas 48 had normal insulin resistance (HOMA-IR <3) . There were 130 patients who had a negative family history of diabetes or impaired glucose tolerance, out of which 26 had moderate to severe insulin resistance (HOMA-IR>3) whereas 104 had normal insulin resistance (HOMA-IR <3). There was no significant difference in insulin resistance among both groups. (P >0.05). (Figure 4)
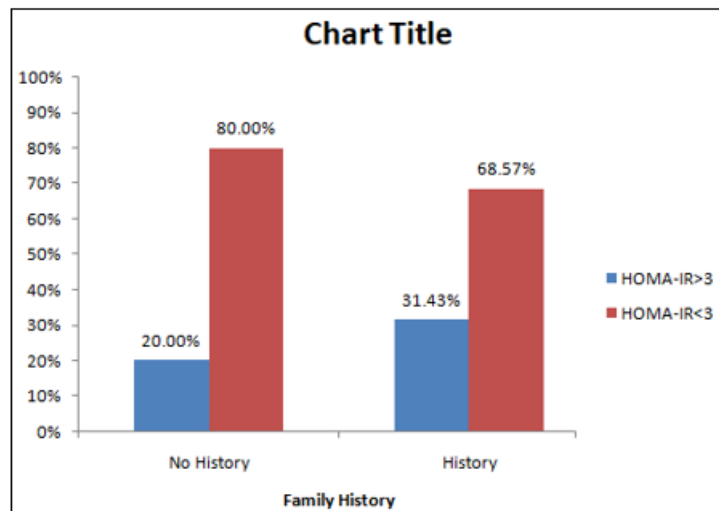
Figure 4: Insulin resistance Vs family history of diabetes in terms of HOMA-IR

5. Discussion

Insulin resistance is responsible for various metabolic disorders like hypertension, diabetes mellitus, coronary artery disease, dyslipidaemia and other abnormalities particularly obesity. This metabolic disorders increases cardiovascular mortality and morbidity. Since insulin resistance develops long before these metabolic disorders, early identification and treating insulin resistance can have great preventive value.[1] [3]

Insulin resistance should be ideally determined by euglycaemic insulin clamp technique. But this method is expensive, invasive and not available in clinical practice. Hence HOMA-IR which is a non- invasive, easily available and easily calculated using fasting insulin and glucose levels serves as the best alternate for it.

This study has examined the relationship between insulin resistance and hypertension and has also compared it with normotensive people. We have also studied the relationship between insulin resistance with BMI, age, sex and positive family history of diabetes. Although diabetes is very prevalent in India, there are very few studies in India on insulin resistance.[2] [4]

Earlier studies have also shown that insulin resistance is associated with hypertension patients in obese but not in lean subjects. In contrast, Ferrannini has showed in an earlier study that insulin resistance was associated with hypertension even among lean subjects.[5]

Our study included 100 hypertensives and 100 normotensive people and their demographic, arthropometric and metabolic factors are compared. The mean age of hypertenive group was 53.22 ± 8.97 and of controls was 50.90 ± 9.06. The mean BMI of hypertensive group was 27.84 ± 4.26 and that of controls was 26.50 ± 4.47. Both BMI and age was significantly higher in hypertensive group. ($P <0.05$) . There was male preponderance in hypertensive group whereas female preponderance was present in controls. The mean fasting glucose in hypertensive group was 92.55 ± 5.45 whereas in normotensive group it was 92.31 ± 5.56.

The study used HOMA-IR to measure insulin resistance. Among 100 hypertensives, 23 had moderate insulin resistance and 5 had severe insulin resistance. Among Normotensives, 13 had moderate insulin resistance and 7 had severe insulin resistance. The study showed a significantly higher fasting insulin and insulin resistance in hypertension group when compared to normotensives. HOMA-IR was significantly high in hypertension group (2.50 ± 1.45) when compared to controls (2.13 ± 1.40). ($P=0.03703$) and also Fasting insulin levels were significantly higher in hypertension group (10.88 ± 6.21 vs 10.44 ± 13.78). Increased insulin resistance results in increased insulin levels, which in turn leasds to blood pressure by activating sympathetic system and by increasing sodium reabsorption in kidneys. Our study also showed that patients with BMI>25 have increased insulin resistance (85.42% vs 14.58%) and mean fasting insulin levels was (11.17 ± 6.17 Vs 7.38 ± 4.93) when compared to patients who have BMI <25.

Similar results was also obtained in study done by Gurinder mohan et al in 2016 where he took 150 patients (75 hypertensives and 75 normotensives) and mean HOMA-IR in hypertensive group was (3.858 ± 1.840) whereas in controls was (2.093 ± 0.615) which was statistically significant. Also fasting serum insulin level was 17.09 ± 8.17 μIu/ml in hypertensives and 9.33 ± 2.67μIU/ml in controls (reference range 2-25 μIU/ml) and the difference was statistically significant. [3]

Zakir Hussain et al in Jabalpur in 2017 did a similar study in which the mean age of hypertensive patients was 49.79 ± 17.04 years and mean age of normotensive group was 51.94 ± 16.64 years. Male were more than females in both the groups. Out of 50 from each group, 19 (38%) of hypertensive patients and 7 (14%) of normotensive patients had insulin resistance with HOMA-IR >3. The mean fasting and post prandial blood sugar levels were almost similar in both groups ($p=0.03$). Mean HOMA-IR, waist size and waist hip ratio (WHR) was significantly ($p=0.02$) higher in hypertensive patients when compared to the normotensive group. [6]

Akande TO et al did a study in 2013 at Ibandan, Nigeria. He took 35 hypertensive and 35 normotensive patients without Diabetes mellitus. Insulin resistance was measured using HOMA-IR. They found that Hypertensives(31.4%) have significant Insulin resistance when compared to

Normotensives(8.6%) . They also noted that BMI has a linear correlation with the Insulin resistance.(7)

Nereida K.C. Lima et al did a study in America in 2008. The Aim of this study was to provide the prevalence of insulin resistance and associated CVD risk factors in treated and untreated patients with essential hypertension. In this study, they included 126 hypertension patients : 56 untreated and 70 treated patients. They measured Body mass Index, Blood pressure, blood glucose , Lipid profile and steady state plasma glucose concentrations using insulin suppression test. They showed that about 50% of essential hypertension both treated and untreated appeared to be Insulin Resistant and the risk of CVD was found to be very high in these patients.(8)

Mobin Mohteshamzadeh et al did a study in Liverpool, United Kingdom in 2005. They took 106 Hypertensive patients and 18 healthy controls. 21 out of 106 patients were found to be insulin resistant measured using HOMA-IR. They also found that one half of the patients with Insulin resistance developed Impaired Glucose tolerance after 1 year of follow up and 20% developed Type 2 Diabetes after 3 years of follow up.(9)

Our study results also suggest a need for larger studies to determine the mechanistic link between hypertension, insulin resistance and diabetes in the general population. Even though the actual mechanisms of insulin resistance in hypertensives patients in not clearly known but studies have demonstrated that early interventions may improve insulin sensitivity in these patients.

There were few limitations of our study. Firstly, HbA1C was not taken into consideration to label patient as Diabetes or impaired glucose intolerance or healthy due to infeasibility and cost issues.Second, Waist circumference was not taken into consideration due to infeasibility and inconvenience to the patient. Only BMI was compared with the insulin resistance.

6. Conclusion

Essential hypertension is associated with significantly higher mean fasting insulin levels and insulin resistance (HOMA-IR) . Insulin resistance increases with higher BMI (>25). Higher age was found to have no relationship with fasting insulin as well as insulin resistance (HOMA-IR). There was also no significant difference in insulin resistance between males and females. Patients who have a positive family history of diabetes were found to similar insulin resistance when compared to those without a positive family history of diabetes.

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