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Association of Insulin Resistance and Blood Pressure in Newly Diagnosed Patients of Essential Hypertension: A Cross-Sectional Study

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Abstract

Objective: To find correlation of insulin resistance with blood pressure in newly diagnosed hypertensive patients without comorbidity.

Material and methods: The study was conducted in LLRM Medical College Meerut (UP). Newly diagnosed hypertensive and prehypertensive patients were selected from Outdoor Patient Department (OPD) and Indoor Patient Department (IPD). A total of 150 patients were enrolled in the study. They were devided into 3 groups as per stages of hypertension in JNC8 guidelines. It was a cross-sectional observational study. Insulin resistance was accessed by HOMA-IR. To establish correlation between two quantitative variables Pearsons correlation coefficient was used.

Results: Mean serum insulin levels and mean HOMA-IR increasesd with increasing stages of hypertension with statistically significant difference (p value < 0.05). Also, Pearson's correlation co-efficient of SBP with HOMA IR and insulin level was 0.311 and 0.292, respectively and for DBP the value ofcorrelation co-efficient with HOMA IR and insulin level was 0.278 and 0.267, respectively, signifying weak positive correlation.

Conclusion: On the basis of our observations, we concluded that even without other co-morbidities and obesity, insulin resistance was positively correlated with essential hypertension, especially with higher stages of hypertension, for both systolic and diastolic blood pressure.

Key words: Insulin resistance, hypertension.

Introduction

The new generation is plagued by a sedentary lifestyle and abundance of food rich in carbohydrates and salt. During the course of evolution we have shifted from a low salt, low sugar society to high salt, high sugar society.The thrifty genotypes[1] required for survival in low sodium, low calorie society and physical stress are an inherent part of us and are no longer advantageous but maladaptive and characteristic of diseased phenotype having hypertension, obesity and insulin resistance.

Insulin resistance and hypertension are essential components of metabolic syndrome[2] and are proven risk factors for cardiovascular diseases.

The aim of our study was to study the prevalence of insulin resistance in individuals of essential hypertension after ruling-out co-morbidities such as diabetes mellitus (DM) and metabolic syndrome.

Material and methods

Study population

The study was conducted in LLRM Medical College, Meerut (UP). Newly diagnosed hypertensive and prehypertensive patients (as per JNC8)[3] guidelines were selected from Outdoor patient department (OPD)/Indoor patient department (IPD). A total of 150 patients were enrolled in the study.Written informed consent was taken from all the patients. Ethical clearance was taken from the institutional Ethics Committee.

Inclusion criteria

Patients newly diagnosed with systolic blood pressure (SBP) > 120 mmHg or diastolic blood pressure (DBP) > 80 mmHg (as per JNC8 guidelines) with age more than 18 years were included in the study. The subjects were not on antihypertensive drugs previously.

Exclusion criteria

Patients with DM/kidney disease/thyroid disorders/acute infection were excluded.Patients with increased BMI (WHO criteria)[4] and metabolic syndrome (NCEP-ATPIII criteria)[5] were also excluded from the study.

Study design: It was a cross-sectional, observational study.

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The study population was divided in 3 groups, as per stages of JNC8 guidelines[3], i.e., group A (pre-hypertension stage), group B (stage 1 hypertension) and group C (stage 2 hypertension).

Study procedure

Detailed history taking and clinical examination, including BMI and fundus examination was done in all patients.

BP was measured according to JNC8 guidelines[3] and insulin resistance was assessed by using surrogate marker of insulin resistance, HOMA-IR[6]. The value of HOMA-IR index increases with increase in Insulin resistance. It was quantified by using the formula:-

HOMA-IR = fasting insulin (miu/L) x fasting blood sugar mmol/l/22.5

All Patients were also subjected to kidney function tests, liver function tests, thyroid profile, fasting lipid profile, blood sugar profile, including HBA1C and haemogram. Other investigations were done as per requirement.

Statistical analysis

The data was tabulated in Microsoft Excel and was analysed by IBM-SPSS version 21. For parametric quantitative, data was depicted as mean and standard deviation and comparison between more than two groups was made by ANOVA. p value was considered significant at $p < 0.05$. To establish correlation between two quantitative variables, Pearson's correlation co-efficient was used and was considered significant at p value < 0.01.

Observations

Out of 150 patints enrolled, 50 subjects were prehypertensive (SBP- 139 mmHg and DBP- 80-89 mmHg), 48 were in stage 1 hypertension (SBP- 140-159 mmHg) and DBP - 90-99 mmHg) and 52 subjects were in stage 2 hypertension (SBP - 160 mmHg and DBP ≥ 100 mmHg as per JNC8 guidelines[3].

Baseline characteristics

The gender distribution in our study was 31 males and 19 females in prehypertensive group, 30 males and 18 females in stage 1 hypertension group and 34 males and 18 females in stage 2 hypertension group (Fig. 1).

Other baseline characteristics i.e age, BMI, FBS and HBA1C were also comparable in all the three groups .The patients included in all the three groups were non-obese, non diabetic and there was no overt metabolic syndrome (Table I).

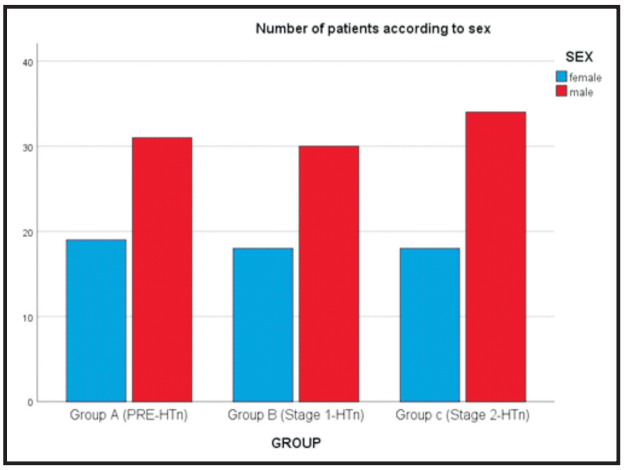

Fig. 1: *Distributions of patients according to gender in different groups.*

Table I: Baseline characterstics.

S. no.	Parameter	Pre-hypertension	Stage-1 hypertension	Stage-2 hypertension	p-value
1.	Mean Age (in years)	52.12 ± 6.01	52.60 ± 13.68	54.40 ± 13.54	0.58
2.	Mean BMI Kg/m^2	22.23 ± 1.40	22.08 ± 1.28	21.96 ± 1.4	0.622
3.	Mean FBS* (mg/dl)	89.50 ± 8.56	89.72 ± 8.35	88.29 ± 8.01	0.630
4.	Mean HBA1C (%)	5.38 ± 0.80	5.53 ± 0.37	5.48 ± 0.36	0.079
5.	Mean SBP (mmHg)	134	151	173	-
6.	Mean DBP (mmHg)	70	91	108	-

**FBS = Fasting blood sugar.*

Table II shows the insulin levels and HOMA-IR values in the three study groups. It was seen that as the stage of hypertension progressed, mean insulin levels and mean HOMA-IR also increased with significant difference among the groups (p - value < 0.05).

Table II: Insulin level and HOMA-IR in different study groups.

Parameters	Pre-hypertension	Stage-1 hypertension	Stage-2 hypertension	P-value
Insulin levels (mIU/L)	4.90 ± 2.96	8.08 ± 4.96	9.83 ± 7.28	< 0.001
HOMA-IR	1.09 ± 0.69	1.82 ± 1.12	2.14 ± 1.67	< 0.001

In all 3 groups, when the correlation was established between systolic blood pressure with insulin levels and HOMA-IR there was weak, but, significant positive correlation.

Similarly, with diastolic blood pressure we found weak but, significant positive correlation with insulin levels and HOMA-IR (Table III).

Table III: Correlation of blood pressure with insulin resistance and HOMA-IR.

Parameters	Systolic blood pressure		Diastolic blood pressure	
	Pearson's correlation co-efficient	P-value	Pearson's correlation co-efficient	P-value
Insulin level (ulU/ml)	0.311	< 0.001	0.278	0.001
HOMA-IR	0.292	< 0.001	0.267	0.001

Level of significance at p value < 0.01.

The Scatter plots depict weak significant correlation for both insulin resistance and HOMA-IR with blood pressure (systolic and diastolic) in Figs. 2, 3, 4, and 5.

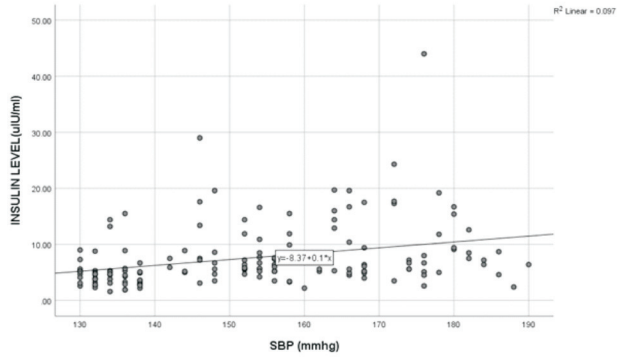

Fig. 2: *Scatter plot between SBP and insulin level.*

Pearson's correlation co-efficient r (0.311) between SBP and insulin level with p value < 0.001; depicting weak significant positive correlation.

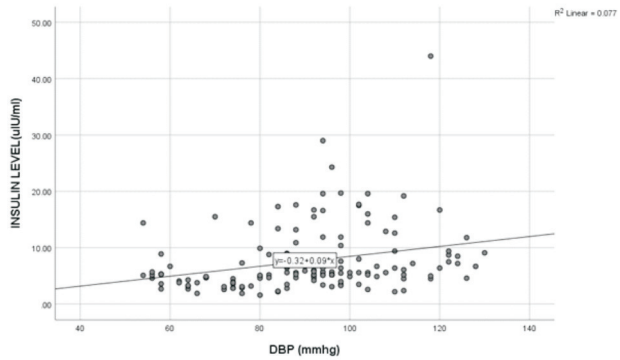

Fig. 3: *Scatter plot between DBP and insulin level.*

Pearson's correlation co-efficient r (0.278) between DBP and insulin level with p value of 0.001 suggesting weak positive significant correlation.

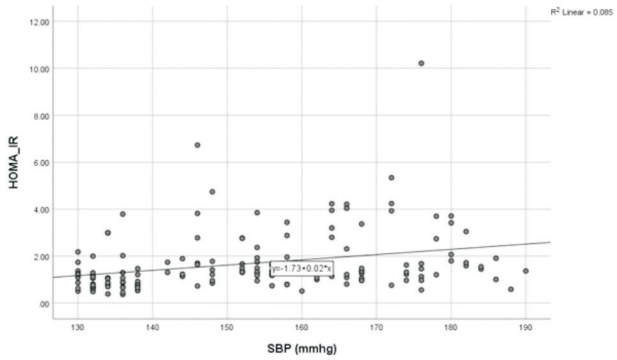

Fig. 4: *Scatter plot between SBP and HOMA-IR.*

Pearson's correlation co-efficient (0.292) between SBP and HOMA-IR with p value of < 0.001 suggesting positive correlation that too significant.

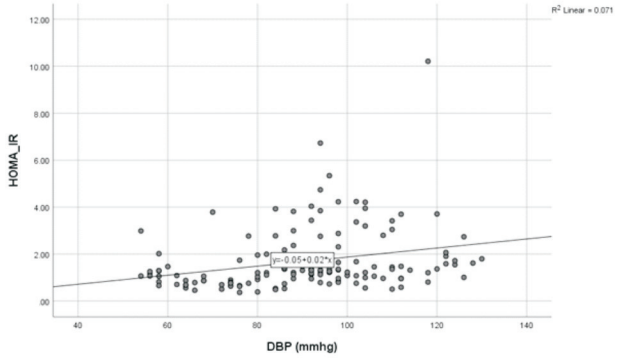

Fig. 5: *Scatter plot between DBP and HOMA-IR.*

Pearson's correlation co-efficient (0.267) between DBP and HOMA-IR with p value 0.001 suggesting significant positive correlation.

Discussion

Insulin resistance and hypertension are components of the metabolic syndrome and often co-exist. The pathogenesis of essential hypertension is not clearly understood; many environmental and genetic factors have been found to contribute towards it and insulin resistance is one of them. Independent of metabolic effects, insulin regulates sodium homeostasis by enhancing sodium reabsorption in the kidney[7]. The elevated insulin level also affects sympathetic nervous system thereby, contributing to the regulation of blood pressure. Normally insulin stimulates production of nitric oxide from the endothelium and thereby contributing to vasorelaxation. Therefore, in insulin resistant state, vasoconstriction takes place[8]. The above mechanisms may contribute to the development of hypertension in pre-existing insulin resistant state.

Also, the essential hypertensive subjects have been shown to have significant defects in activating the insulin receptor. There is decreased insulin action on insulin receptor (IR) which reduces the activation of receptor tyrosine kinase. As a result,

there is decrease in receptor autophosphorylation and tyrosine phosphorylation of insulin resistance substrate (IRS-1), there is decrease in activation of phosphatidyl inositol kinase,a subunit of IRS-1. This IRS-1 causes decreased glucose transport to skeletal muscle, resulting in impaired glucose uptake. As a compensatory response, hyperinsulinaemia ensues to maintain normal blood glucose levels[9].

Thus, co-existence of insulin resistance and hypertension can be seen as a cause-effect relationship (insulin resistance as a cause of hypertension or vice versa) or a non-causal relationship.

Certain previous studies suggest the correlation of essential hypertension with insulin resistance in favour of the above mentioned hypothesis and pathophysiological pathways.

S Demissie *et al,* in 2006, studied oxidative stress correlation with insulin resistance, hypertension and telomere length in men. Telomere length in leukocytes inversely related to age and also shorter telomere length was found in inflammation and oxidative stress. They measured leukocyte telomere terminal restriction fragment (TRF) length in 327 caucasian men with a mean age of 62.2 years (range 40 - 89 years) from the offspring cohort of the Framingham Heart Study. TRF length was found to be inversely correlated with age ($r = -0.41$, $P < 0.0001$) and age-adjusted TRF length was inversely correlated with the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) ($r = -0.16$, $P = 0.007$) and urinary 8-epi-PGF2α ($r = -0.16$, $P = 0.005$) an index of systemic oxidative stress. When compared with their normotensive peers, hypertensive subjects exhibited shorter age-adjusted TRF length (hypertensives = 5.93 ± 0.042 kb, normotensives = 6.07 ± 0.040 kb, $P = 0.025$). Collectively, they found that hypertension, increased insulin resistance and oxidative stress are associated with shorter leukocyte telomere length and that shorter leukocyte telomere length in hypertensives is largely due to insulin resistance. When compared with their normotensive peers, subjects with hypertension had a shorter age-adjusted TRF length (5.93 ± 0.042 kb vs 6.07 ± 0.040 kb, $P = 0.025$) and a higher HOMA-IR (5.25 ± 0.26 vs 3.78 ± 0.20, $P < 0.001$)[10].

Sinha *et al,* in 2012, studied insulin resistance in essential hypertension among male volunteers from Bangladesh. They compared healthy males with hypertensive subjects and a correlation was set between essential hypertension and insulin resistance. They concluded that incidence of insulin resistance is higher in essential hypertensive subjects in comparison to the controls, i.e., normotensive subjects[11]. Elevated insulin levels may alter blood pressure as it has effects on the sympathetic nervous system and renal sodium reabsorption. It has been suggested that sympathetic overactivity may lead to structural changes in the microvasculature, which ultimately increases blood pressure and decreases peripheral glucose uptake[12].

Haffner *et al*[12] (1998) Welborn *et al*[13] (2002) and Penesova *et al*[14] (2004) also found a similar positive correlation between insulin resistance and essential hypertension.

In the present study, we studied three categories of patients; prehypertensive, grade I hypertensive and grade II hypertensive, as per JNC8 guidelines. All three groups were age and sex matched. Patients of metabolic syndrome as per NCEP: ATPIII guidelines were excluded. All subjects were non-obese with BMI < 25 Kg/m^2 and the mean BMI was comparable in all three groups.

Similarly, fasting blood sugar levels and HBA1c in all three groups were comparable, with p values 0.630 and 0.079, respectively.

Similar to the above mentioned studies, we found increasing fasting serum insulin levels with increase in the stage of hypertension and the results were statistically significant $p < 0.05$. The fasting serum insulin levels were positively and significantly correlated with systolic and diastolic blood pressure.

Similar to serum insulin levels, HOMA-IR also increased with increasing stages of hypertension.

However, Baba *et al*[15] 1991 and Every *et al*[16] 1993 did not find an association between serum insulin levels and blood pressure in middle-aged, non-obese subjects.

Thus, although the positive relationship between insulin resistance and hypertension has been found in several longitudinal studies, but results are not entirely consistent.

Whether insulin resistance predicts the subsequent development of hypertension or higher blood pressure predicts hyperinsulinaemia and increased insulin resistance during follow-up is uanswered till now. Because insulin resistance and hypertension share common dietary and lifestyle risk factors and similar pathophysiological pathways, including chronic inflammation and endothelial dysfunction, lifestyle and pharmacological interventions that improve insulin sensitivity possibly may also reduce risk of hypertension, metabolic syndrome and cardiovascular disease.

Conclusion

On the basis of our observations, we conclude that even without other co-morbidities and obesity, insulin resistance is positively correlated with essential hypertension especially with higher stages of hypertension (for both systolic and diastolic BP).

Therefore, we advocate effective lifestyle and pharmacological interventions to prevent and treat insulin resistance and hypertension, whichever is present or detected earlier.

Limitation of the study: As our study was done at a single centre, involving one ethnic group above results should can be further explored for prophylactic measures and treatment in patients of essential hypertension without co-morbidity and obesity from developing metabolic syndrome, dyslipidaemia and diabetes mellitus by a multiple centre study, and meta analyses on a larger group of population.

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