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ORIGINAL ARTICLE

Hyperinsulinemia and Insulin Resistance in Newly Detected Non-Diabetic Hypertensives

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Abstract

Background: Hypertension is one of the most important cause of increased morbidity and mortality across the world and India alike. Research into newer pathophysiologic mechanisms such as hyperinsulinemia and Insulin resistance independent of obesity needs to be carried out extensively to address these potential therapeutic areas. ***Purpose:*** To measure the serum insulin levels and levels of insulin resistance in newly detected hypertensive patients and to check for any possible correlation between grades of hypertension and levels of insulin resistance. ***Material and Methods:*** 100 newly detected hypertensive cases and 100 age and sex matched normotensive controls were included in our study over 2 years at our hospital in Bhubaneswar. ***Results:*** The study revealed that newly detected hypertensive cases had higher mean serum fasting insulin levels and higher Insulin resistance as calculated by HOMA2-IR model as compared to controls ($p<0.001$). ***Conclusion:*** It was found in our study that there was a statistically significant increase in values of serum fasting insulin levels and Insulin resistance (HOMA2-IR) with severity (grades) of hypertension.

Key Words

Insulin resistance, HOMA IR, Grades of hypertension, Fasting serum insulin

Introduction

Globally, 71% of deaths are caused by non-communicable diseases (NCD) (1). Among NCDs, the four top killers that together account for more than 80% of all premature NCD deaths include cardiovascular diseases (17·9 million deaths annually), cancers (9·0 million), respiratory diseases (3·9 million), and diabetes (1·6 million) (2). It is expected that the global burden of NCDs will increase by 17% by 2025 (3). Hypertension (HTN) is the leading preventable risk factor for premature death and disability worldwide (2). Appropriate measures to control the levels will not only protect the individuals from hypertensive complications but also reduces the overall morbidity and mortality in the population.

An estimated 1.13 billion people worldwide have hypertension, most (two-thirds) living in low- and middle-income countries. In 2015, 1 in 4 men and 1 in 5 women had hypertension. Fewer than 1 in 5 people with hypertension have the problem under control (4). From 2005-2015, the death rate attributable to high Blood pressure (BP) increased by 10.5%, and the actual number of deaths attributable to high BP rose by 37.5% (5). Worldwide, raised blood pressure is estimated to cause 7.5 million deaths, about 12.8% of the total of all deaths. This accounts for 57 million disability adjusted life years (DALYS) or 3.7% of total DALYS indicating the huge mortality and morbidity of the disease (6). HTN is directly

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responsible for 57% of all stroke deaths and 24% of all coronary heart disease (CHD) deaths in India (7). A recent systematic review by Anchala *et al*. found the overall prevalence of hypertension in India to be 29.8% with significant urban-rural difference (8).

Hypertension progressively affects various organ systems leading to left ventricular hypertrophy, heart failure, peripheral arterial disease, coronary artery disease, albuminuria, retinopathy and stroke. The pathophysiology of essential hypertension has changed from the classical pathways to include hormonal, genetic and autacoids as new probable mechanisms. The role of insulin resistance (IR) with compensatory hyperinsulinemia leading to stimulation of sympathetic nervous system activity and renal tubular absorption have been proposed as one of the probable mechanisms (9,10). There are very few studies evaluating the role of insulin resistance and compensatory hyperinsulinemia in a hypertensive population in our country. This study intends to find if any correlation exists between hypertension and insulin resistance in our population. The aim of the study was to measure the serum insulin levels and levels of insulin resistance in newly detected hypertensive patients and to check for any possible correlation between grades of hypertension and levels of insulin resistance.

Materials and Methods

A case control study was conducted at Department of Medicine after obtaining approval from Institutional Ethics Committee. 100 patients fulfilling all inclusion and exclusion criteria were included as cases and 100 healthy age and sex matched non-hypertensive patients fulfilling the exclusion criteria were included as controls. Adults of age > 18 years and < 60 years with newly diagnosed hypertension (Systolic blood pressure (SBP) > 140 mm Hg or Diastolic blood pressure (DBP) > 90 mm Hg or both) were included as cases. Patients who were overweight a body mass index (BMI > 25 Kg/m2) had a past history of diabetes, hypertension, dyslipidemia, heart failure, chronic kidney disease, chronic liver disease, thyroid disorder, rheumatological disease or pregnancy were excluded from the study.

All the study participants filled a pre-determined questionnaire and detailed clinical examination was done. Height, weight, blood pressure, waist and hip circumference were measured and Waist-Hip ratio (WHR), BMI were calculated. At least 2 blood pressure measurements were done 5 minutes apart in sitting position and the average of the two was recorded. All precautions were taken prior to measurement of the blood pressure (11). The diagnosis and classification of hypertension was done according to 2018 ESC/ESH guidelines (11) (*Table 1*). Each of the blood pressure grades were further assigned a numerical category from 1 to 6 for easy comparison (*Table 1*). Baseline biochemical parameters like liver function test (LFT), renal function test (RFT), lipid profile, serum electrolytes, glycosylated haemoglobin (HbA1c), serum vitamin D levels and serum insulin levels where measured. The basal insulin resistance of the individual was calculated using the HOMA-2 IR calculator (homeostatic model assessment of insulin resistance) (12). A cut-off of 2.5 was considered as insulin resistance in adults (13). ECG, fundoscopy and complete clinical systemic examination was done in all study participants.

Categorical variables were presented in number (n) and percentage (%) whereas continuous variables where presented as mean ± standard deviation (SD) and median. Quantitative variables where compared using unpaired t-test / Mann-Whitney test between the two groups. Qualitative variables were compared using Chi-Square test/ Fisher's exact test. Spearman correlation coefficient was used to assess the association of HOMA IR with blood pressure levels. A value of < 0.05 was considered statistically significant. Analysis was done using SPSS Version 20.0.

Table 1: 2018 ESC/ESH Hypertension Classification Guidelines

Category	Systolic BP (mm Hg)		Diastolic BP (mm Hg)	Numerical Category
Optimal	< 120	and	< 80	1
Normal	120-129	and/or	80-84	2
High Normal	130-139	and/or	85-89	3
Grade 1 HTN	140-159	and/or	90-99	4
Grade 2 HTN	160-179	and/or	100-109	5
Grade 3 HTN	≥180	and/or	≥110	6
Isolated Systolic HTN	≥140	and	<90	–

Results

Baseline characteristics of 100 newly detected hypertensive cases and 100 age and sex matched controls were compared (*Table 2*). The mean age was 44.28 ± 12.48 years in cases and 47.26 ± 8.14 years in controls. The male to female ratio in the study group was similar in cases and in controls. The average BMI in cases was 23.82 ± 2.69 kg/m2 and in controls was 22.25 ± 2.43 kg/m2 (p= 0.102). The mean SBP was 159 ± 9.28 mm Hg and 118.46 ± 10.62 mm Hg among cases and controls respectively with a p value of <0.0001. Similarly, the mean DBP was 88.4 ± 12.26 mm Hg among cases and 74.26 ± 8.12 mm Hg among controls (p < 0.0001). 58% of cases had features suggestive of Left Ventricular Hypertrophy (LVH) as compared to 3% in controls (p<0.0001). Fundoscopy was normal in all the controls whereas 36 % of cases had retinopathy changes. 22% had grade II, 11 % had grade III hypertensive retinopathy and 2 had papilledema changes (grade IV).

The mean fasting serum insulin levels in the cases were 14.32 ± 3.75 µIU/ml with a median value of 12.97 µIU/ml (range 6.23 µIU/ml – 23.73 µIU/ml) as compared to 8.076 ± 1.37 µIU/ml in the controls with a median value of 7.93 µIU/ml (range 6.03 µIU/ml – 12.82 µIU/ml). The difference was statistically significant (p< 0.0001). The mean serum fasting insulin levels in cases were 12.16 ± 2.217, 15.974 ± 3.552, and 16.029 ± 5.746 in grade I, II and III hypertensions respectively which was significantly higher than controls who were

Table 2: Baseline Characteristics of Cases and Controls

Variable	CASES (n=100)	CONTROLS (n=100)	p value
Age (years)	44.28 ± 12.48	47.26 ± 8.14	0.026
Height (cms)	162.62 ± 6.48	163.61 ± 8.263	0.493
Weight (kgs)	62.8 ± 7.622	60.89 ± 8.86	0.101
BMI	23.82 ± 2.69	22.25 ± 2.43	0.102
Systolic BP (mm Hg)	159 ± 9.28	118.46 ± 10.62	<0.0001
Diastolic BP (mm Hg)	88.4 ± 12.26	74.26 ± 8.12	<0.0001
HbA1c (%)	5.83 ± 0.44	5.74 ± 0.42	0.968
Total cholesterol (mg/dl)	160.96 ± 21.24	176.76 ± 19.68	0.32
Triglyceride (mg/dl)	128.32 ± 17.41	133.65 ± 15.74	0.08
HDL (mg/dl)	45.22 ± 7.22	49.4 ± 7.68	0.022
LDL (mg/dl)	88.56 ± 16.62	86.28 ± 15.64	0.431
VLDL (mg/dl)	25.28 ± 5.62	22.4 ± 5.82	0.04
FBS (mg/dl)	88.63 ± 15.07	90.61 ± 18.45	0.684
Fasting serum insulin (µIU/ml)	14.32 ± 3.75	8.076 ± 1.37	<0.0001
HOMA IR	3.15 ± 1.225	1.822 ± 0.5	<0.0001

Table 3: Fasting Serum Insulin Levels with Various Categories of Hypertension

Category	1	2	3	4	5	6
Sample size	52	38	11	42	49	8
Mean ± SD	8.012 ± 1.287	8.155 ± 1.503	8.34 ± 1.564	12.16 ± 2.217	15.974 ± 3.522	16.029 ± 5.746
Median	7.745	7.930	8.04	12.30	15.24	17.45
Inter Quartile Range	6.932 - 9.017	7.025 - 9.112	7.19 - 9.65	10.787-12.772	12.965 - 18.825	10.942 - 21.432

Table 4: Insulin Resistance (HOMA2-IR) with Various Categories of Hypertension

Category	1	2	3	4	5	6
Sample size	52	38	11	42	49	8
Mean ± SD	1.792 ± 0.431	1.921 ± 0.596	1.657 ± 0.426	2.462 ± 0.708	3.724 ± 1.22	3.642 ± 1.313
Median	1.73	1.885	1.57	2.36	3.51	3.3
Inter Quartile Range	1.395 - 2.077	1.340 - 2.407	1.34 - 2.02	1.93 - 3.0	2.96 - 4.49	2.507 - 4.882

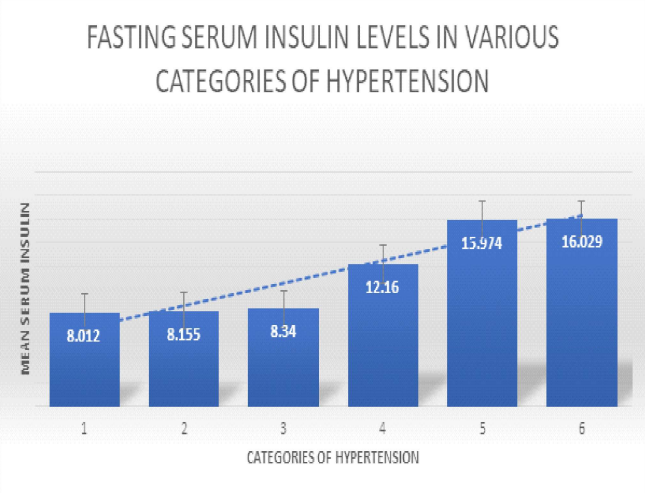

Figure 1: Bar Graph Showing Fasting Serum Insulin Levels in Various Categories of Hypertension

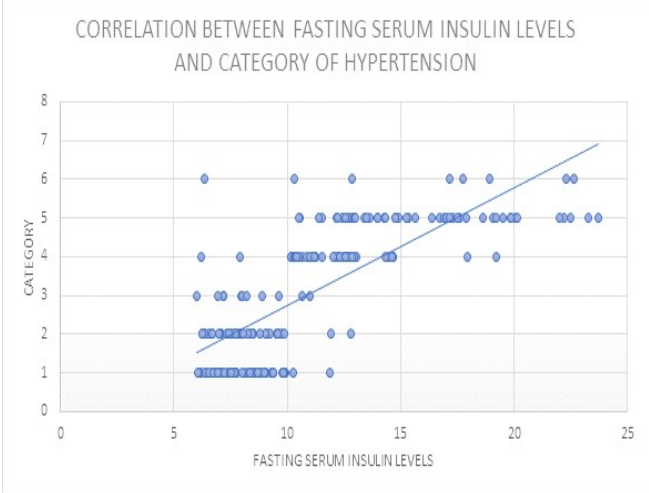

Figure 2: Scatter Diagram Showing Significant Positive Correlation Between Fasting Serum Insulin Levels and Categories of Hypertension (r=0.766, p <0.001)

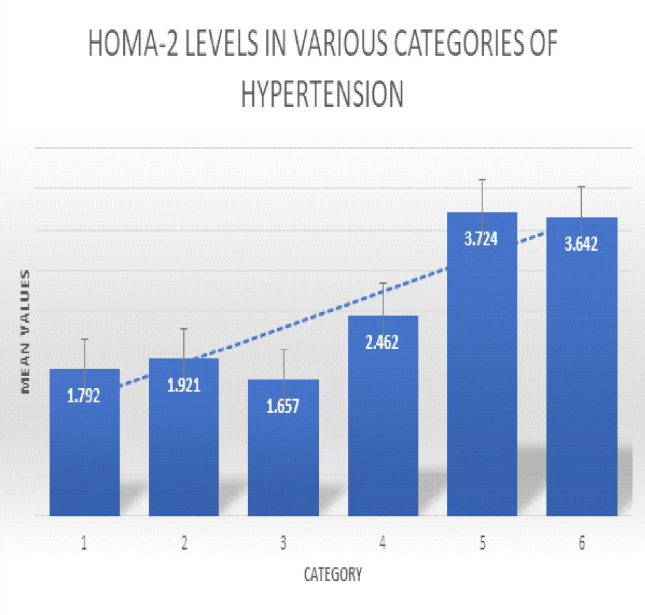

Figure 3: Bar Graph Showing HOMA2-IR Levels in Various Categories of Hypertension

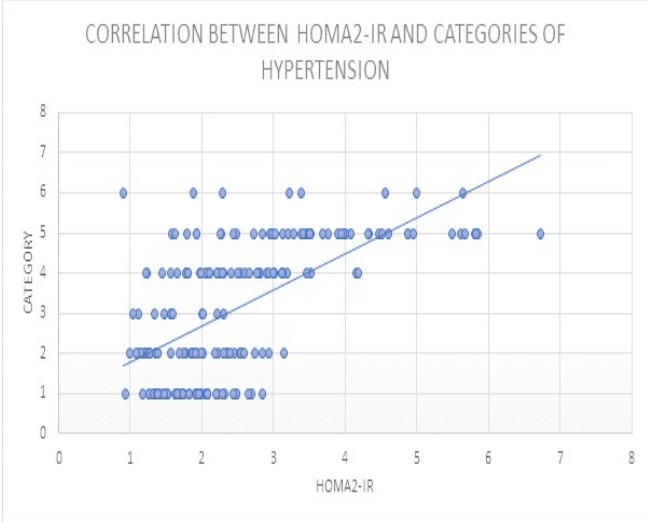

Figure 4: Scatter Diagram Showing Significant Positive Correlation Between HOMA2-IR and Categories of Hypertension (r=0.617, p <0.001)

normotensive (p < 0.0001). (*Table 3*) (*Figure 1*). There was also a significant positive correlation between categories of hypertension and fasting serum insulin levels (r= 0.766, p <0.001) (*Figure 2*).

The mean HOMA2-IR levels for cases and controls were 3.15 ± 1.225 and 1.822 ± 0.5 respectively, and the difference was statistically significant (p<0.005). The categories 4,5 and 6 (i.e. cases) had a mean HOMA2-IR values of 2.462 ± 0.708, 3.724 ± 1.22 and 3.642 ± 1.313 respectively whereas categories 1,2 and 3 (i.e. controls) had a mean HOMA2-IR values of 1.792 ± 0.431, 1.921 ± 0.596 and 1.657 ± 0.426 respectively (*Table 4*) (*Figure 3*). There was also a significant positive correlation between categories of hypertension and HOMA2-IR levels (r= 0.617, p <0.001) (*Figure 4*). A positive correlation was also found between HOMA2-

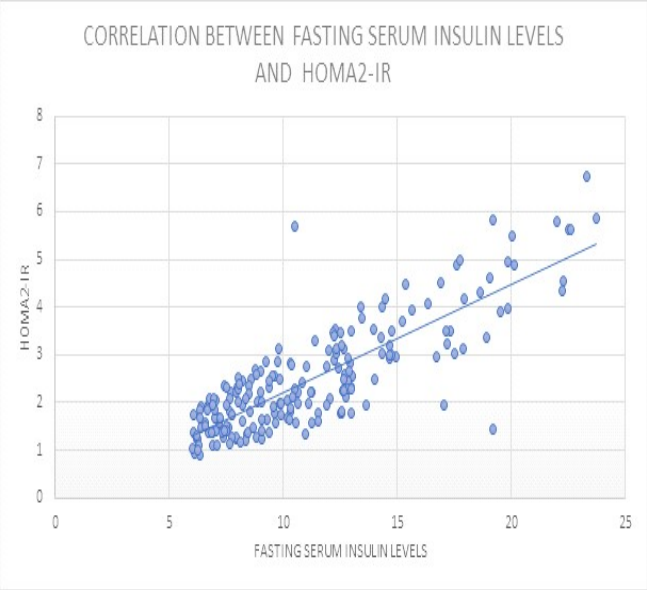

Figure 5: Scatter Diagram Showing Correlation Between Fasting Serum Insulin Levels and Insulin Resistance (HOMA2-IR) (r=0.830, p <0.001)

IR levels and fasting serum insulin levels which was statistically significant (r=0.830, p<0.001) (*Figure 5*).

Discussion

The mean serum fasting insulin in our study was 14.32 ± 3.75 µIU/ml in cases (hypertensive patients) and 8.076 ± 1.37 µIU/ml in controls. This is well supported by a study done by Tarray *et al*. where the mean serum fasting insulin levels were 15.32 ± 13.76 µIU/ml in patients and 8.01 ± 4.08 µIU/ml in controls (10). Serum fasting insulin levels in our study increased significantly with hypertension, with increased levels seen in higher grades of hypertension irrespective of age, weight, sex and serum glucose levels. There was also a significant positive correlation between various categories of hypertension and fasting serum insulin levels (r= 0.766, p <0.001). This observation was in tune with the findings from a study by Chaudhari *et al*. (14). These data do suggest that insulin resistance plays a major role in the regulation of blood pressure and also that insulin resistance might be one of the major etiological factors of hypertension in patients with or without obesity. However, in another study by Asch *et al*., hypertensive subjects had slightly but not significantly higher fasting plasma insulin levels than normotensive subjects (15).

In our study cases also had significantly higher mean HOMA2-IR levels as compared to controls (3.15 ± 1.225 vs 1.822 ± 0.5) (p<0.001). Tarray *et al*. in their study had HOMA2-IR levels of 3.81 ± 3.42 in cases and 1.76 ± 0.93 in controls which was in accordance with our study (10). The levels of HOMA2-IR increased with severity of hypertension in our study and the correlation was significantly positive (r= 0.617, p <0.001) supported by the landmark study from Ferrannini *et al*. (16). In a study by Mohammed F. Saad *et al*., they observed that insulin resistance but not hyperinsulinemia was related to hypertension without diabetes, but ethnic differences in these relations appear to exist (17).

In our study, insulin resistance and fasting insulin levels were significantly associated with hypertension. Ethnic differences were not analysed separately. Additionally, in our study we observed statistically significant correlation of serum fasting insulin levels and insulin resistance as measured by HOMA2-IR levels with various grades of hypertension which have not been previously observed in any other study to the best of our knowledge.

Limitations of our study include lesser number of study participants and lack of consideration of demographic, ethnical and regional variations in a large randomized population for better conclusions. It is possible that the pattern of associations with blood pressure might have been different if Insulin resistance was measured directly by the euglycemic insulin clamp technique or by frequently sampled intravenous glucose tolerance test rather than by HOMA-IR model.

Conclusion

To conclude, the mean fasting serum insulin levels in newly detected hypertensives in our study population was 14.32 ± 3.75 µIU/ml and the mean value of insulin resistance as detected by HOMA2-IR model in such patients is 3.15 ± 1.225 which are significantly higher than normotensive individuals. There is also a significant positive correlation between grades of hypertension and levels of insulin resistance suggesting role of hyperinsulinemia in the pathophysiology of essential hypertension which can be further investigated in a larger randomized population.

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Nil.

Conflicts of Interest
There are no conflicts of interest.

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