

## Original Research Article

# To study the prevalence of insulin resistance in non-diabetic hypertensive subjects

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## ABSTRACT

**Background:** Hypertension is an important medical and public health problem in both developed and developing countries. It is an important risk factor for morbidity and mortality from coronary heart disease, stroke and renal disease. It is well recognized that hypertension coexists in varying degrees with conditions of obesity, insulin resistance/hyperinsulinemia and dyslipidemia, the interrelated metabolic disorders characteristic of metabolic syndrome.

**Methods:** The study was carried out at Sri Guru Ram Das hospital, Amritsar, Punjab, India. A total of 150 patients were taken, out of which 75 were hypertensive and 75 healthy subjects more than 18 years of age were recruited. Serum insulin concentration was measured using a solid phase enzyme linked immunoassay based on the sandwich principle. Insulin resistance was determined by HOMA-IR (homeostasis model assessment of insulin resistance).

**Results:** Statistically, the mean fasting serum insulin level was  $17.09 \pm 8.17$   $\mu$ Iu/ml in cases and  $9.33 \pm 2.67$   $\mu$ IU/ml in controls (reference range 2-25  $\mu$ IU/ml); the difference was statistically significant ( $P < 0.001$ ). The mean value of HOMA-IR in cases was  $3.86 \pm 1.84$  as compared with controls with mean HOMA -IR value of  $2.01 \pm 0.62$ . This difference was statistically significant ( $P < 0.001$ ).

**Conclusions:** Essential hypertension is significantly associated with higher mean fasting insulin levels and insulin resistance. Hyperinsulinemia has a possible role in the pathophysiology of essential hypertension with insulin resistance being the likely predominant mechanism.

**Keywords:** Hypertension, Insulin resistance, Insulin

## INTRODUCTION

Hypertension is defined as the level of blood pressure at which the initiation of therapy reduces blood pressure related morbidity and mortality. Clinical criteria for defining hypertension generally are based on the average of two or more outpatient visits. A recent classification recommends blood pressure criteria for defining normal blood pressure, prehypertension, hypertension (stage I and II), and isolated systolic hypertension.<sup>1</sup>

The panel members appointed to the Eighth Joint National Committee (JNC 8) used rigorous evidence-

based methods, developing Evidence Statements and recommendations for blood pressure (BP) treatment based on a systematic review of the literature to meet user needs, especially the needs of the primary care clinician.

Hypertension is an important medical and public health problem in both developed and developing countries. It affects 25% of the adult population worldwide and its prevalence is predicted to increase by 60% by 2025, when a total of 1.56 billion people may be affected.<sup>2</sup> Epidemiological studies have shown that hypertension is present in 25% of urban and 10% of rural patients in India.<sup>3</sup>

Hypertension is an accepted risk factor for cardiovascular disease, but treatment for hypertension with antihypertensive agents does not decrease the risk of coronary heart disease as much as might be expected from epidemiological studies. A hypothesis which might explain this apparent discrepancy is that another abnormality, associated with hypertension and not corrected by anti-hypertensive treatment, may be involved in cardiovascular diseases.<sup>4</sup>

Reaven described the insulin resistance syndrome as the association of a number of abnormalities: insulin resistance, hyperinsulinaemia, glucose intolerance, increase of very low density lipoprotein, decrease of high density lipoprotein cholesterol and hypertension.<sup>5</sup>

There are several potential mechanism which have been proposed, by which elevated plasma insulin levels may lead to hypertension and these include increase in total body content of sodium, an increase in plasma nor epinephrine levels augmentation of  $\text{Na}^+$   $\text{H}^+$  exchange and resultant intracellular accumulation of  $\text{Na}^+$  and  $\text{Ca}^{+}$  thereby increasing the intracellular pH and enhancing the sensitivity of vascular smooth musculature to the pressor 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.<sup>6,7</sup>

Diminished tissue sensitivity to insulin is a characteristic of several diseases, including the metabolic syndrome, a complex cluster of symptoms that include abdominal obesity, hyperglycemia, dyslipidemia, hypertension, and insulin resistance.<sup>8,9</sup>

Obesity is frequently accompanied by peripheral insulin resistance, which in turn, results in secondary increase in insulin secretion to maintain euglycemia. Hypertension in insulin -resistance states is generally attributed to selective insulin resistance, chiefly by skeletal muscle, with preservation of renal and sympathetic nervous system sensitivity to insulin.

Accordingly, the hyperinsulinemia resulting from this selective insulin resistance causes increases sympathetic neural output and renal sodium retention and may thereby increase in blood pressure. However, accumulating body evidence indicates that insulin is a vasodilator and, through direct action on vascular smooth muscle calcium transport and levels, is an important regulator of vascular tone.<sup>13</sup>

Compensatory hyperinsulinemia seen in insulin resistance is suggested to play a causal role in development of hypertension because hyperinsulinemia has been associated with proliferation of vascular smooth muscle cells increased renin output increased renal sodium retention and increased catecholamine secretion.<sup>10-15</sup>

## METHODS

In this cross sectional study, a total of 150 patients was enrolled out of which 75 hypertensive subjects (as per JNC 8 blood pressure and cholesterol guidelines updates) and 75 healthy subjects aged more than 18 years attending the OPD/ Indoor of SGRDIMSAR for routine health check-up were enrolled.

According to JNC 8 hypertension and cholesterol guidelines updates on January 2014 hypertension is defined as Table 1. Healthy subjects without hypertension, diabetes mellitus, impaired glucose tolerance, impaired fasting glucose serve as control.

After fulfilling the following inclusion and exclusion criteria, the patient were enrolled in this study.

### Inclusion criteria

- Age > 18 years
- Hypertension (as per JNC 8 guidelines BP >140/90 or on antihypertensive drugs).

### Exclusion criteria

- Presence of diabetes mellitus (FBS > 126 or Post prandial >200)
- IGT (post Prandial >140-199)
- IFG (FBS 100-125)
- HbA1c > 5.6

After taking written consent, epidemiological / demographic data were taken from all patients. Detailed history and clinical examination was done in all patients. Height, weight, waist circumference, was measured by standard procedure. Waist circumference was measured as the smallest horizontal girth between costal margin and iliac crest. Blood sample was taken after 10 hours fasting for estimation of fasting lipid profile, fasting insulin levels and fasting plasma glucose.

Three or more of the following should be present to define metabolic syndrome according to NCEP: ATP III 2001:16

Central obesity: waist circumference > 102 cm(M), > 88 cm (F)

- Hypertriglyceridemia : triglyceride level  $\geq$  150 mg/dl or on specific medication
- Low HDL cholesterol : < 40 mg/dl and <50 mg/dl for men and women, respectively, or on specific medication
- Hypertension : blood pressure  $\geq$  130 mmHg systolic or  $\geq$  85 mmHg diastolic or on specific medication
- Fasting plasma glucose level  $\geq$  100 mg/dl or specific medication or previously diagnosed type 2 diabetes.

The DRG insulin enzyme immunoassay kit provides materials for the quantitative determination of insulin in serum and plasma (Heparin/Citrate-plasma). The DRG Insulin Kit is a solid phase enzyme linked immunoassay (ELISA) based on the sandwich principle.<sup>17</sup>

Insulin resistance can be estimated using several techniques. The euglycaemic hyperinsulinemic clamp technique is the gold standard method for evaluation.<sup>18</sup>

However this method is complex and expensive. HOMA-IR is a simple and reliable surrogate measure of insulin resistance.<sup>19,20</sup> HOMA model is derived from a mathematical assessment of the interaction between beta cell function and insulin resistance in an idealized model that is then used to compute steady state insulin and glucose concentrations.<sup>21,22</sup> An advantage of the HOMA method is that only a single venepuncture is required so it is simple and easy to use.

After obtaining insulin value, insulin resistance was calculated. Insulin resistance was calculated by HOMA-IR formula.<sup>21</sup>

Fasting insulin (uIU/ml)  $\times$  fasting glucose (mmol/l)/22.5 or fasting insulin (uIU/ml)  $\times$  fasting glucose (mg/dl)/405. After calculating insulin resistance, insulin resistance was categorized into normal, moderate and severe insulin resistance as follows Table 2.

## RESULTS

The study was conducted in Sri Guru Ram Das hospital, Amritsar, Punjab, India. 75 hypertensive patients were compared with 75 non hypertensive healthy subjects which served as controls. Out of 75 patients in each group, 56% (n = 42) were male and 44% (n = 33) were females, mean age of patients in hypertensive group was 53.93 $\pm$ 11.56 years, while in control group was 53.93 $\pm$ 10.40 years. Among the cases, 50.7% (n = 38)

patients belonged to rural background while in control group 53.3% (n = 40) subjects were from rural background which shows equal distribution of cases and controls according to demographic profile. Family history of hypertension in one or other first degree relatives was more common in hypertensive group than in the control group.

The demographic, anthropometric and metabolic profile of cases and controls are represented in Table 3. Cases and controls have been matched for age, gender, demographic profile, BMI, waist circumference, fasting plasma glucose and HbA1c. Mean BMI is higher in urban population, compared to their rural counterparts in hypertensive and control group. The mean BMI in hypertensive urban patients was 23.86 $\pm$ 2.07 kg/m<sup>2</sup> while in rural hypertensive patients mean BMI was 22.69 $\pm$ 1.59 kg/m<sup>2</sup> which was statistically significant (p = 0.008). 49.3% (n = 37) of hypertensive patients had metabolic syndrome in comparison to control group in whom only 12% (n = 9) had metabolic syndrome, suggesting that metabolic syndrome is more prevalent in hypertensive subjects.

**Table 1: According to JNC 8, hypertension may be defined as**

Patient characteristics	Blood pressure
Age <60 Diabetes CKD	>140/90
Age > 60	>150/90

**Table 2: Category of insulin resistance (HOMA-IR).**

Category	Homa score
Normal insulin resistance	< 3
Moderate insulin resistance	3– 5
Severe insulin resistance	> 5.0

**Table 3: Demographic, anthropometric and metabolic profile of cases and control (Mean $\pm$ SD).**

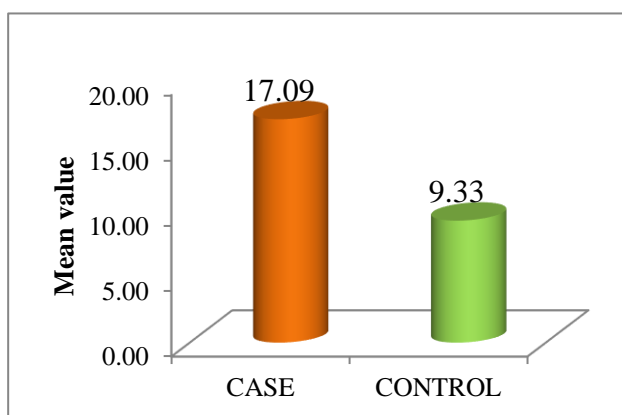
Parameter	Hypertensive subjects (n = 75)	Control (n = 75)	P-value
Age (years)	53.93 $\pm$ 11.56	53.93 $\pm$ 10.40	1.00
Waist circumference (cm)	88.72 $\pm$ 8.71	81.69 $\pm$ 4.73	< 0.001
BMI (kg/m <sup>2</sup> )	23.27 $\pm$ 1.92	22.70 $\pm$ 1.06	0.026
FBS (mg/dl)	91.27 $\pm$ 3.61	89.87 $\pm$ 3.89	0.024
HbA1c (%)	5.04 $\pm$ 0.21	5.047 $\pm$ 0.2029	0.779
Triglycerides (mg/dl)	193.91 $\pm$ 34.51	162.35 $\pm$ 30.33	< 0.001
High density lipoprotein (mg/dl)	45.13 $\pm$ 7.53	42.77 $\pm$ 8.90	0.081
Low density lipoprotein (mg/dl)	108.55 $\pm$ 17.06	104.84 $\pm$ 17.22	0.187
Cholesterol (mg/dl)	134.32 $\pm$ 22.30	131.00 $\pm$ 18.56	0.323
Fasting plasma insulin (uIU/ml)	17.09 $\pm$ 8.17	9.33 $\pm$ 2.67	< 0.001
Insulin resistance (HOMA-IR)	3.858 $\pm$ 1.840	2.093 $\pm$ 0.615	< 0.001

The mean fasting plasma insulin level in hypertensive subjects was  $17.09 \pm 8.169$   $\mu\text{IU/ml}$  while same in control group was  $9.33 \pm 2.674$   $\mu\text{IU/ml}$ , indicating that fasting plasma insulin level in hypertensive subjects was significantly higher than control group ( $P < 0.001$ ).

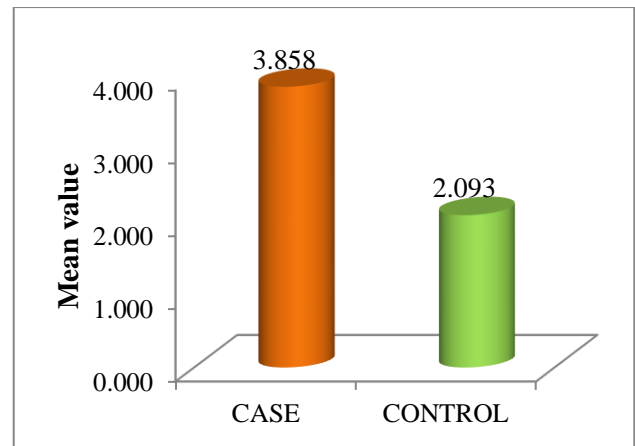
After obtaining fasting plasma insulin value, Insulin resistance was calculated by HOMA-IR formula.<sup>21</sup> Fasting plasma insulin ( $\mu\text{IU/ml}$ )  $\times$  fasting plasma glucose ( $\text{mmol/l}$ )/22.5 OR fasting plasma insulin ( $\mu\text{IU/ml}$ )  $\times$  fasting plasma glucose ( $\text{mg/dl}$ )/405.

The mean insulin resistance in hypertensive subjects was  $3.858 \pm 1.84$  and while same in control group was  $2.093 \pm 0.615$ , indicating that insulin resistance in hypertensive subjects was significantly higher than in control group ( $p < 0.001$ ). Mean fasting plasma insulin level in cases and control group was higher in urban population as compared to rural population. Insulin resistance was also higher in urban group of population which was statistically significant ( $p = 0.002$ ,  $0.001$  respectively). Hypertensive subjects with normal insulin resistance had mean waist circumference  $82.86 \pm 3.94$  cm and patient with moderate to severe insulin resistance had mean waist circumference  $88.20 \pm 6.04$  cm and  $96.77 \pm 9.56$  cm respectively.

The difference was statistically significant ( $p < 0.001$ ). The hypertensive subjects who had end organ damage in the form of hypertensive retinopathy or LVH or both had higher serum fasting insulin level  $23.04 \pm 4.34$   $\mu\text{IU/ml}$ ,  $22.45 \pm 7.139$   $\mu\text{IU/ml}$  and  $23.83 \pm 6.33$   $\mu\text{IU/ml}$  respectively and hence higher insulin resistance  $5.23 \pm 0.93$ ,  $5.07 \pm 1.57$  and  $5.39 \pm 1.36$  respectively. Hypertensive subjects with severe insulin resistance had higher systolic blood pressure, higher serum LDL levels, higher serum triglycerides levels and lower HDL levels as compared to healthy subjects which may be contributing to increased incidence of morbidity and mortality among them.



**Figure 1: Comparison of Mean fasting plasma insulin between hypertensive and control group.**



**Figure 2: Comparison of Mean insulin resistance between hypertensive and control group.**

## DISCUSSION

Insulin resistance can be linked to various metabolic disorders like hypertension, diabetes mellitus, coronary artery disease, dyslipidaemia and other abnormalities particularly obesity and this association increases cardiovascular mortality and morbidity.<sup>23</sup> Because insulin resistance develop long before these diseases appear; identification and treating insulin resistance have great preventive value.

Insulin resistance is determined ideally by euglycaemic insulin clamp technique. But this method is not available in clinical purpose. Although fasting plasma insulin concentrations are less accurate than the values obtained from euglycaemic insulin clamp technique, it provides a reasonable clinical alternative. Gupta and Jain concluded that measuring insulin level alone in a single fasting sample can serve as a simple, cheap, and convenient indirect qualitative index of insulin resistance.<sup>24</sup>

Both fasting and postprandial insulin is found to be high in Indians. Overall prevalence of insulin resistance in Indians ranges from 5-50%. The tremendous heterogeneity of Indians in terms of their insulin resistance relate to their different lifestyles, dietary habits and socio-economic strata.<sup>25</sup>

In this study, among the hypertensive subjects, 62.6% ( $n = 47$ ) cases had moderate to severe insulin resistance as compared to controls where only 12% ( $n = 9$ ) had moderate insulin resistance. Insulin resistance in hypertension had been reported and overall prevalence was around 50%. Chug et al have demonstrated relationship of insulin resistance and hypertension in north Indian subjects with a normal glucose tolerance. Similar findings were also observed in south Indian study by Mohan et al.<sup>26,27</sup> In a 8 year follow-up study initially normotensive but hyperinsulinaemic persons develop hypertension more often than normoinsulinaemic persons.<sup>28</sup>



End-organ damage, particularly hypertensive retinopathy and left ventricular hypertrophy, had been observed in patients with hypertension. Fundoscopic changes, which are observed as a complication in hypertension, and insulin resistance were strongly correlated in our subjects with hypertension. The importance of this finding was reinforced further by the finding that retinopathy may develop especially in those patients with hypertension who are insulin resistant.

In recent years, insulin resistance has gain importance as its role in the pathogenesis of many metabolic disorders. The insulin resistance syndrome includes hypertension, changes in atherogenic lipoproteins, diabetes, and hypercoaguability. Hypertensive subjects having all the four parameters of metabolic syndrome had higher mean insulin levels ( $25.9 \pm 6.98 \mu\text{IU/ml}$ ) and hence higher insulin resistance ( $5.85 \pm 1.46$ ) as compared to patients having three parameters. A similar study conducted by Salagre SB et al found that 49.07% of hypertensive subjects had metabolic syndrome.<sup>29</sup> A similar study conducted by Leila maria marchi-alves et al found that 60.7% (n = 102) hypertensive subjects had metabolic syndrome.<sup>30</sup>

Rural-urban difference of insulin resistance is also well documented. As seen in our study urban population had higher fasting serum insulin levels as compared to rural population and hence higher insulin resistance.

The Waist circumference, BMI, and dyslipidemia, metabolic syndrome and end-organ damage was higher in hypertensive subjects as compared to control group contributing to increased incidence of morbidity and mortality among them.

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